藥 學 博 士 學 位 論 文

Studies on Drug Discovery and Development for Central Nervous System

Part I : (+)-3-Hydroxymorphinan [(+)-3-HM] derivatives as neuroprotectants
Part II : Arylpiperazine-containing pyrimidine 4-carboxamide derivatives as a potential antidepressant

중추신경계에 작용하는 약물 발굴과 개발에 관한 연구

파트 Ⅰ: 신경보호제로써의 (+)-3-하이드록시모르피난 [(+)-3-HM] 유도체

파트 Ⅱ: 항우울증 약물로써의 아릴피페라진 함유 피리미딘 4-카르복스아미드 유도체

2013年 8月

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Abstract

Parkinson's disease is a neurodegenerative disorder that is represented by destruction of dopaminergic neurons. While the materials with neuroprotective activity have been actively developed, (+)-3-HM shows the neuroprotective effect in an animal model of Parkinson's disease. (+)-3-HM, a metabolite of DM which has been used as an antitussive for a long time, is a promising substance to be developed as a drug for Parkinson's disease, but there was no efficacy in case of oral administration because of low absorption. In order to solve this problem, prodrug of (+)-3-HM, GCC1290K was researched and US.FDA Pahse II clinical trial is underway.

After obtaining the indicator of neuroprotective effect with glutamate toxicity in HT-22 cell, derivatization of (+)-3-HM was accomplished using Suzuki-Miyaura cross-coupling reaction and Buchwald-Hartwig cross-couplig reaction. DF derivatives were prepared by Suzuki-Miyaura cross-coupling reaction, and polycycle derivatives were synthesized by the electrophilic aromatic substitution reaction followed by cyclization reaction.

Depression (major depressive disorder) is a disease of the overall mental functioning in a degrade state accompanied by cognitive impairment. Antidepressant is a drug acting on receptor or transporter of neurotransmitter. The arylpiperazine containing pyrimidine 4-carboxamide derivatives were synthesized for the development

of SARI (serotonin antagonist/reuptake inhibitor) compounds. These derivatives were made through the change of the pyrimidine ring substituent or phenyl ring substituent, and the size of the linker. The lead compound was found by binding assay, forced swimming test, and spontaneous locomotor activity test.

Keywords : Parkinson's disease, Neuroprotective effect, (+)-3-HM, GCC1290K, Cross-coupling, Glutamate toxicity, Antidepressant, Serotonin, Pyrimidine, Forced swimming test, Locomotor activity

Student Number : 2008-30479

Contents

Part I . (+)-3-Hydroxymorphinan [(+)-3-HM] derivatives as neuroprotectants

1. Introduction

1.1 Parkinson's Disease

As an expansion of the human's life span and a progression of an aging society, brain diseases such as Alzheimer and Parkinson's disease (PD) are raised. The brain diseases feature that death or degeneration of certain brain cells is progressed temporarily or for a long time. Since the dead brain cells are not restored, the death of brain cells leads to mortal damage of brain function. In particular, the incompletion of brain function accompanying the progressive weakness of cognitive function, sensory function, movement function and whole body function causes change of characteristics and behavior.[1)]

There are approximately 100 million people in the world and 800,000 people in the United States alone with Parkinson's disease. Parkinson's disease is a result of chronic progressive degeneration of neurons, the cause of which has not yet completely been clarified. While the primary cause of Parkinson's disease is not known, it is characterized by degeneration of dopaminergic neurons of the substantia nigra (SN). The substantia nigra is a portion of the lower brain, or brain stem that helps control voluntary movements. The shortage of dopamine in the brain caused by the loss of these neurons is believed to cause the observable disease symptoms. Clinically, it

manifests in the form of the cardinal symptoms resting tremors, rigor, bradykinesia, and postural instability.[2)]

Levodopa, dopamine agonists such as rotigotine, pramipexol, bromocriptine, ropinirol, cabergoline, pergolide, apomorphine and lisuride, anticholinergics, NMDA antagonists, β-blocker as well as the MAO-B inhibitor selegiline and the COMT inhibitor entacapone are used as medicines for relief from the motor symptoms.[3)] Most of these agents intervene in the dopamine and/or choline signal cascade and thereby symptomatically influence the Parkinson-typical movement disorders.

In the present therapy for the Parkinson's disease, treatment is initiated after the appearance of the cardinal symptoms. In general, Parkinson's disease is said to be clinically evident if at least two of the four cardinal symptoms (bradykinesia, resting tremors, rigor, and postural instability) are detected and respond to L-dopa.[4)] Unfortunately, the motor function disorders in Parkinson patients become apparent only after about 70-80% of the dopaminergic neurons in the substantia nigra (SN) are irreparably damaged.[5)] Chances of a therapy with lasting effects are very bleak at that point. Hence, it is desirable to initiate the therapy as early as possible.

Current clinical observations as well as anatomical and genetic research show that diagnosis of Parkinson patients at an early stage and identification of high risk patients is possible. With that an opportunity arises for influencing the disease process at a point of time when more neurons are still there, rather than at the time of

appearance of several cardinal motor symptoms of the Parkinson's disease, and thereby for protecting a quantitatively greater number of neurons. One can expect that the administration of an effective neuroprotective agent at an early stage will significantly delay the process of the development of the disease: The sooner the therapy is initiated, the higher are the chances of a long lasting prevention of the onset of symptoms, which degrade the quality of life.

Hence, such remedies are needed that not only influence the dopaminergic transmission and alleviate the symptoms of the Parkinson's disease in advanced stages, but also reverse, prevent, or at least significantly delay the dopaminergic neuron extinction in the early, to a great extent motor-asymptomatic, Parkinson stages.[6)]

1.2. Neuroprotection

The concept of neuroprotection was applied to chronic diseases of the brain as well as acute neurological conditions, since some of the basic mechanisms of damage to the central nervous system (CNS) are similar in these conditions. Neurodegenerative disorders include Parkinson’s disease, Alzheimer’s disease (AD), Huntington’s disease (HD) and amyotrophic lateral sclerosis (ALS). Neuroprotection has been regarded to be the mechanism of action of some of the drugs used in the treatment of these conditions.

Neurodegeneration in PD, AD, and other neurodegenerative diseases seems to be

multifactorial, in that a complex set of toxic reactions including inflammation, glutamatergic neurotoxicity, increases in iron and nitric oxide, depletion of endogenous antioxidants, reduced expression of trophic factors, dysfunction of the ubiquitin-proteasome system, and expression of proapoptotic proteins leads to the death of neurons. Gangliosides are the major class of glycoconjugates on neurons and carry the majority of the sialic acid within the CNS. Ganglioside synthesis is essential for the development of a stable CNS. Interruption of ganglioside synthesis produces CNS degeneration and modified axon-glial interactions.[7] Thus, the fundamental objective in neurodegeneration and neuroprotection research is to determine which of these factors embodies the primary event, the sequence in which these events occur, and whether they act in concurrence in the pathogenic process. This has resulted in the concept that drugs addressed against a single target will be ineffective and instead a single drug with multiple pharmacological properties or a cocktail of drugs may be more appropriate. Among the many factors involved, apoptosis and glutamate toxicity play an important role.

Apoptosis mediated by genetic programs intrinsic to the cell is being implicated in neurodegenerative disorders. During the normal development of the vertebrate nervous system, approximately 50% of the different types of neurons usually die right after they establish synaptic connections with their target cells. It has been hypothesized that this death is due to failure of these neurons to obtain adequate amounts of survival specific

neurotrophic factors from target cells. The mechanism of death is postulated to be deprival of extracellular survival signals, which normally suppress apoptosis.

Many neurodegenerative disorders are distinguished by conformational alteration in proteins that result in misfolding, aggregation and intra- or extra-neuronal accumulation of amyloid fibrils. Molecular chaprones provide a first line of defence against misfolded, aggregation-prone proteins and are among the most potent suppressors of neurodegeneration known for animal models of human disease. A better understanding of the molecular basis of chaperon-mediated protection against neurodegeneration may result in the development of therapies for neurodegenerative disorders that are associated with protein misfolding and aggregation.

1.3. (+)-3-Hydroxymorphinan [(+)-3-HM]

(+)-3-Hydroxymorphinan [(+)-3-HM)] is a metabolite of dextromethorphan (DM) which has been used as an antitussive for a long time. The chemical name of (+)-3-HM is (4b*S*,8a*S*,9*S*)-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthren-3-ol. (+)-3-HM has potent neuroprotective and neurotrophic effects in lipopolysaccharide (LPS) and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated dopaminergic neurons of the nigrostriatal pathway,[8)] but notably without producing any neuropsychotoxic side effects (e.g., dissociation or hallucinations) or having any

anticonvulsant actions.[9] In this animal model, daily injections with (+)-3-HM showed that dopamine (DA) neurons in substantia nigra pars compacta have been protected and DA levels in striatum has been restored.[10] It does not seem to bind to the NMDA receptor,[9] and instead, its neuroprotective properties appear result from inhibition of glutamate release via the suppression of presynaptic voltage-dependent Ca^{2+} entry and protein kinase C activity.[11] (+)-3-HM offer poteintially potent neuroprotection in multiple inflammatory disease models both by exerting a neurotrophic effect and by inhibiting microglial activation associated with the production of a host of pro-inflammatory and neurotoxic factors, including nitric oxide (NO), tumor necrosis factor-α (TNF-α), prostaglandin E_2 (PGE_2), extracellular superoxide, and intracellular reactive oxygen species (iROS).[12] In any case, as such, the compound has been investigated as a potential antiparkinsonian agent. However, (+)-3-HM is efficacious only if they are administered intraperitoneally or intravenously.[10]

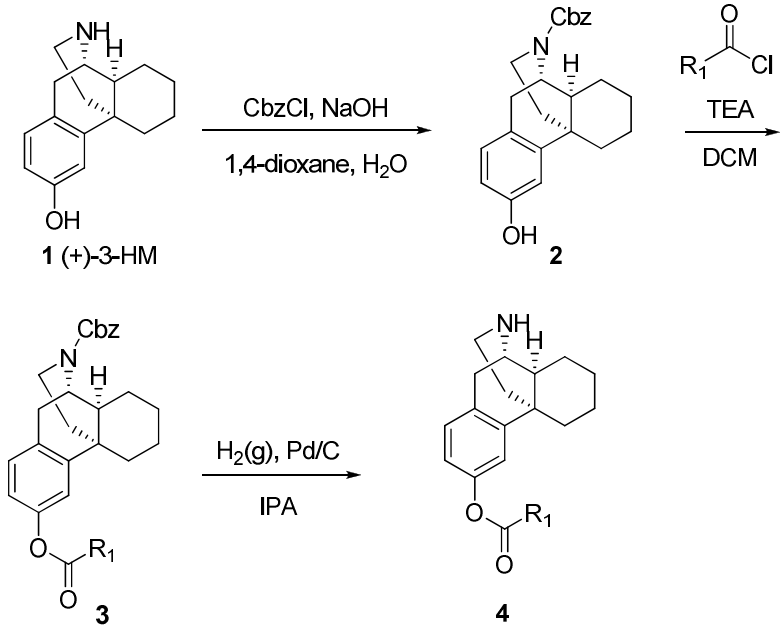
2. Results and Discussion

2.1. Prodrug approach to (+)-3-HM

It is well known that extensive first-pass metabolism occurs to a large number of

phenolic drugs like morphinans, steroids and salicylates, resulting in a low and variable bioavailability after oral administration. This is often due to pronounced first-pass metabolism and not limited absorption from the gastrointestinal tract. First-pass metabolism of phenolic drugs occurs in the gut mucosa and/or the liver by sulphation, methylation or glucuronidation of the phenolic moieties. The prodrug principle may be a useful approach to protect the vulnerable phenol group against first-pass metabolism. However, traditional esterification of the phenol group has only met with limited success at preventing first-pass metabolism. The reason for this is most likely that enzymatic hydrolysis of the ester group occurs in the intestinal tract and/or the liver during first-pass. As a consequence, the phenolic drug will thereby be released within organs with high enzymatic activity and, therefore, no protection of the phenolic group will be achieved. A more promising approach to prevent or depress the first-pass metabolism of phenolic drugs may be the use of prodrug derivatives where the prodrug-to-drug conversion mainly occurs at the target organ or in the blood stream after passage of the intestinal wall and the liver. Derivatives where the conversion to the parent phenol occurs by non-enzymatic means, e.g., via chemical hydrolysis or an intramolecular reaction occurring with an appropriate rate at physiological pH (7.4) and at 37°C might be useful. To ensure passage of the prodrug in largely intact form through the stomach and the upper intestine, suitable prodrug forms should preferably be more stable at lower pH values.[13)]

To enhance the oral bioavailability of (+)-3-HM, which is approximately 18%, prodrug approach was considered and 3-hydroxy group of (+)-3-HM was chosen for chemical modification by making ester or ether bond.

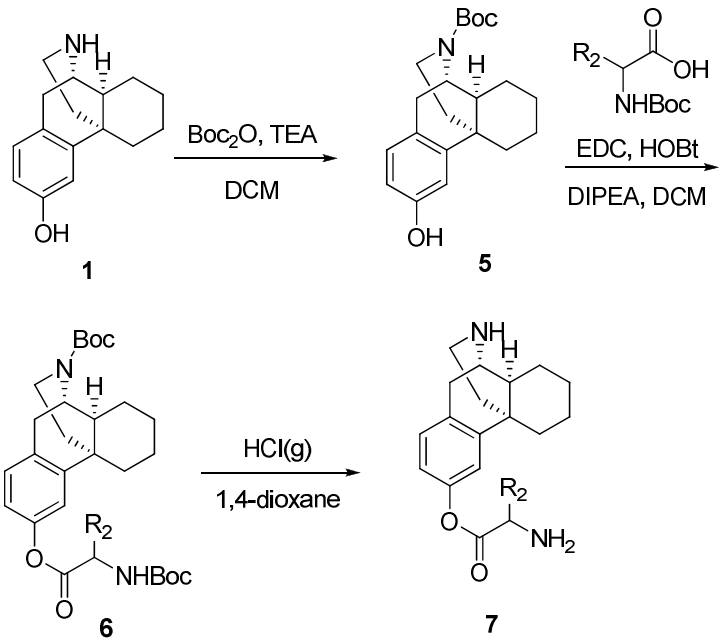


Scheme 1. Preparation of ester derivatives **4**

2.1.1. Ester and amino acid derivatives

At the first round of trial, ester-type prodrugs are made, but they are unacceptably labile or resistant toward cleavage. The ester derivatives are prepared by reacting a (+)-3-HM (**1**) with benzyl chloroformate in aqueous NaOH to provide *N*-17-protected (+)-

3-HM (**2**) and acylating the resulting product with acid chloride in the presence of triethylamine to yield ester intermediate **3**, and finally deprotecting *N*-17-Cbz group of the resulting product to obtain a compound of formula **4**, as shown in scheme 1.



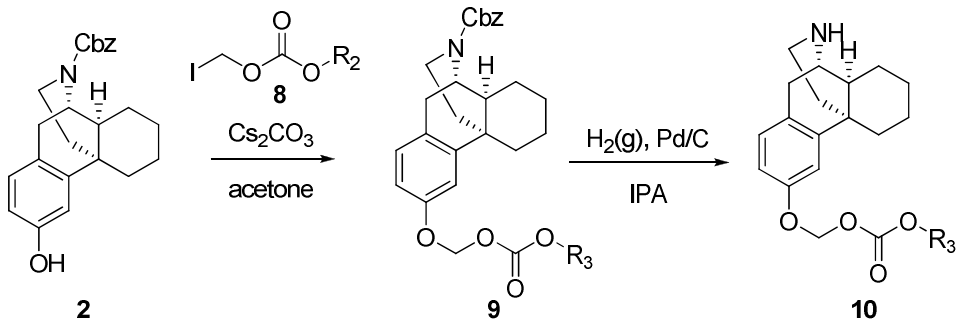
Scheme 2. Preparation of amino acid derivatives **7**

Another round of trial involved amino acid-type prodrugs which showed instability in low pH media. The amino acid derivatives are prepared by reacting a (+)-3-HM (**1**) with Boc_2O in triethylamine in DCM to provide *N*-17-protected (+)-3-HM (**5**) and EDC coupling of the resulting product with Boc-protected amino acid to yield α-amino ester intermediate **6**, and finally deprotecting *N*-17-Boc group of the resulting

product to obtain a compound of formula **7**, as shown in scheme 2.

2.1.2. Methylene linker derivatives

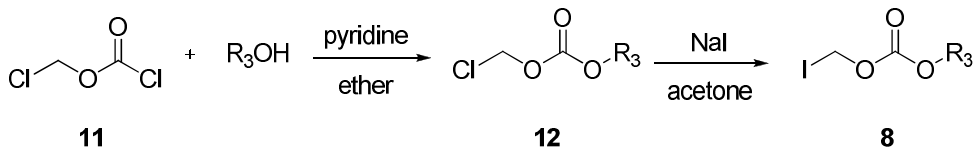
The compound of formula **10** may be prepared by alkylating the intermediate **2** with iodomethyl alkyl carbonate (**8**) in the presence of cesium carbonate to yield alkyl phenoxymethyl carbonate of formula **9**, and deprotecting *N*-17-Cbz group of the resulting product to obtain a compound of formula **10**, as shown in scheme 3.



Scheme 3. Preparation of methylene linker derivatives **10**

The iodomethyl alkyl carbonate derivative (**8**) used as a starting material in preparing the compound of formula **10** may be prepared by treating an chloroformic acid chloromethyl ester (**11**) with an alcohol in anhydrous ether with pyridine to produce a corresponding chloromethyl alkyl carbonate (**12**), reacting the resulting product with

sodium iodide in acetone to provide a corresponding iodomethyl alkyl carbonate (**8**)[14] as shown in scheme 4.



11 **12** **8**

Scheme 4. Preparation of iodomethyl alkyl carbonate derivatives **6**

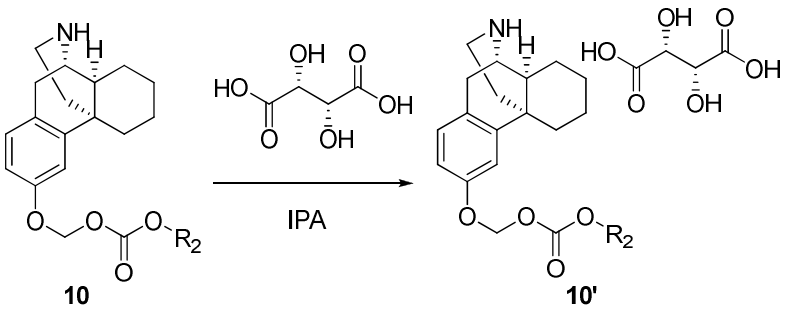
Formation of a salt form of these compounds may be obtained as illustrated in scheme 5. To the IPA solution of deprotected compound **10** may be added L-(+)-tartaric acid. After thorough mixing these ingredients by stirring at 40 ^{o}C for 30 min, IPA may be switched to EtOAc in order to give better solid state characteristics. The solid may be then filtered and washed with EtOAc to give the drug substance **10'** with minimal impurities.

2.2. Synthesis of Dimemorfan (DF) derivaitves

2.2.1. DF as a neuroprotectant

A DM analog, dimemorfan (DF) has been recognized as an effective non-narcotic antitussivewith a low incidence of adverse events since 1975. It does not induce any

significant physical or psychological dependence, and its antitussive action is not affected by the opioid receptor–blocker levallorphan.The antitussive efficacy of DF is approximately equal to that of DM. As with DM, DF has potent anticonvulsant activity, although its precise mechanism remains unknown. Its other possible beneficial effects have been evaluated using diverse models of neurodegeneration. Interestingly, the evidence indicates that the recognition sites for DM and DF are identical or overlapping. As DF has an established safety record in humans at antitussive doses and it is not metabolized to dextrorphan, which causes phencyclidine (PCP)-like behavioral effects, it is a promising compound deserving further study of its anticonvulsant and neuroprotective properties.[15)]



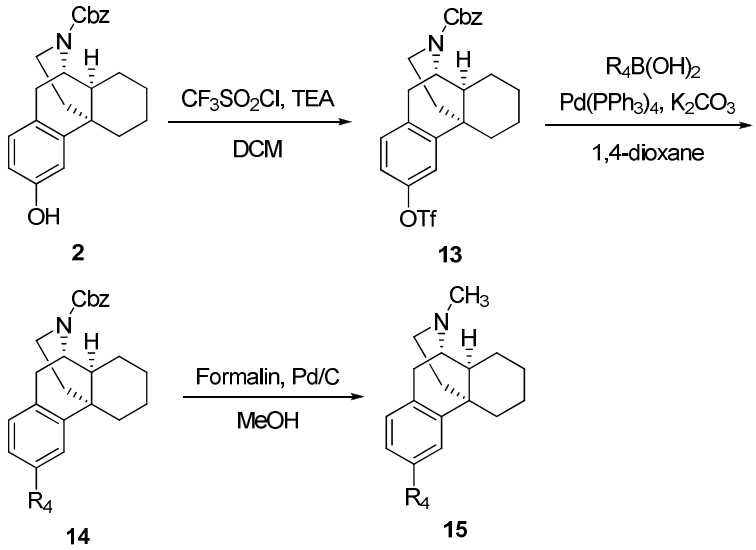
Scheme 5. Salt formation of methylene linker derivatives **8'**

2.2.2. Preparation of DF derivatives

Because of our interest in discovering and developing a neuroprotective agent for the treatment of Parkinson's disease, we were attracted to morphinan analogs such as DF as a potential target. There is only one synthesis of DF reported in 1972. The overall yield for preparation of DF was only 15% and it took 70 hours to cyclize the requisite ring system by phosphoric acid.[16] We envisioned that this compound might be more readily prepared by using *N*-17-Cbz-(+)-3-HM (**2**) as a starting material (Scheme 1). The 3-alkyl or 3-aryl group would be introduced by palladium-catalyzed Suzuki-Miyaura cross-coupling reaction if 3-hydroxy group of (+)-3-HM is appropriately converted into the corresponding triflate. Subsequently, nitrogen would be prone to undergo facile reductive alkylation, thereby resulting in DF in a straightforward manner.

The synthesis of DF derivatives commences with the conversion of commercially available (+)-3--HM into the *N*-17-Cbz-(+)-3-HM **(2)**. Treatment of this compound with trifluoromethanesulfonyl chloride in the presence of triethylamine generated an intermediate triflate **13** (Scheme 6).

The stage is now set for the key palladium-catalyzed Suzuki-Miyaura cross-coupling reaction.[17] In the event, a mixture of triflate **13**, alkylboronic acid or arylboronic acid, tetrakis (triphenylphosphine)palladium (0), and potassium carbonate in 1,4-dioxane is reacted to furnish **14**. Only a trace amount of reduced product is isolated under these conditions.

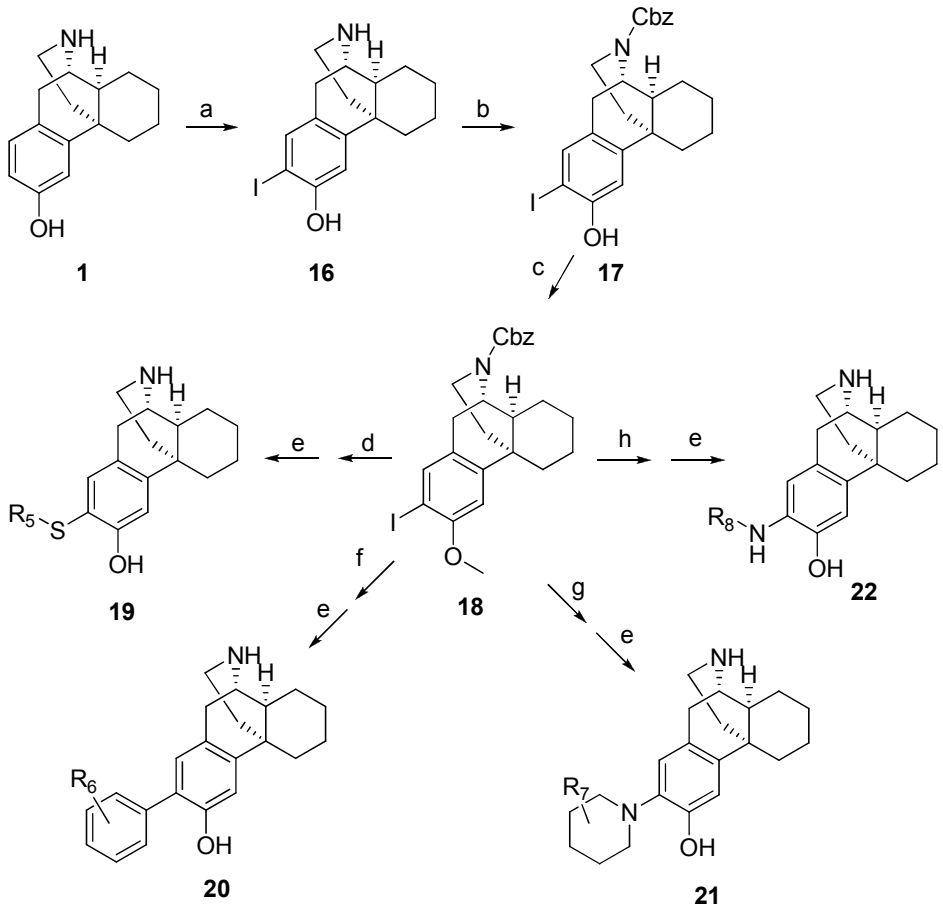


Scheme 6. Preparation of DF derivatives **13**

At this stage, we briefly consider the possibility of converting **14** into **15** in order to make DF derivatives in a stepwise fashion. However, we are also intrigued by the more attractive possibility of transforming **14** directly into DF derivatives (**15)**. Indeed, subjecting a MeOH solution of **14** under hydrogen gas in the presence of palladium on charcoal and formalin produce DF derivatives (**15**).[18)]

2.3. Synthesis of 2-substituted (+)-3-HM derivaitves

During the course of the investigation to synthesize (+)-3-HM derivatives with



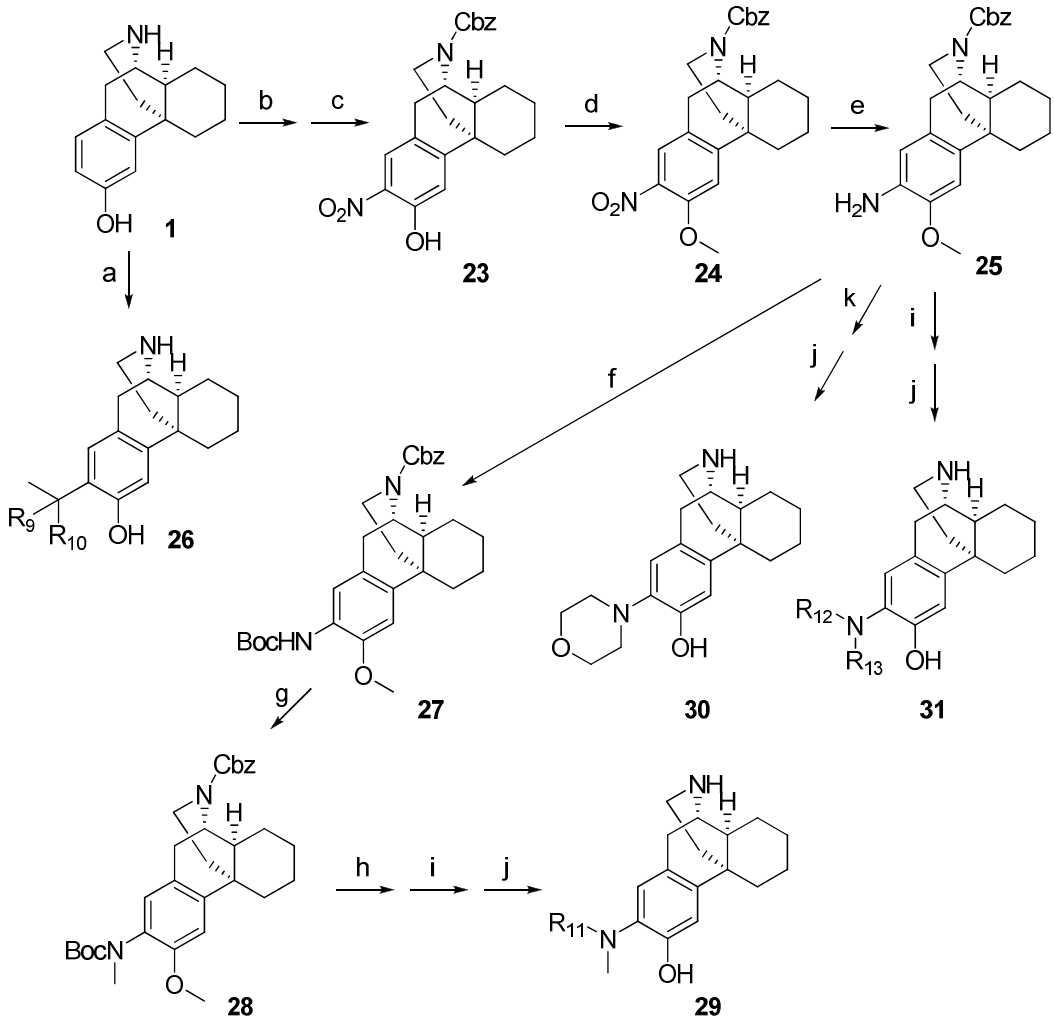
(a) KI, I_2, NaOH, H_2O
(b) CbzCl, NaOH, 1-4-dioxane, H_2O
(c) MeI, K_2CO_3, acetone
(d) R_5SH, $Pd(PPh_3)_4$, Na*t*BuO, EtOH
(e) BBr_3, DCM
(f) Arylboronic acid, $Pd(PPh_3)_4$, K_2CO_3, 1,4-dioxane
(g) Cyclicamine, $Pd_2(dba)_3$, BINAP, Na*t*BuO, 15-crown-5, THF
(h) Arylamie or alkylamine, $(dppf)PdCl_2.CH_2Cl_2$, dppf, Na*t*BuO, THF

Scheme 7. Preparation of 2-substituted derivatives using 2-iodo intermediate **18**

neuroprotective effect, functionalization of 2-position of (+)-3-HM was attempted as part of the meidicinal chemistry approach.

2.3.1. Preparation using 2-iodo intermediate

As shown in the following scheme 7, (+)-3-HM (**1**) undergoes iodination under conditions of the mixure of iodine and potassium iodide in aqueous sodium hydroxide to give iodide **16**.[19] Protection of the iodide **16** with CbzCl, and subsequent methylation produce a key intermediate **18**. Treatment of the key intermediate **18** with various thiols in the presence of $Pd(PPh_3)_4$ and NaO*t*Bu in EtOH, and subsequent demethylation using BBr_3 provides a compound of formula **19**. On the other hand, palladium-catalyzed Suzuki-Miyaura cross-coupling reaction of the key intermediate **18** with arylboronic acid, followed by demethylation using BBr_3 smoothly affords the diaryl compounds **20**. The key intermediate **18** is coupled with cyclicamine in the presence of $Pd_2(dba)_3$, racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), NaO*t*Bu and 15-crown-5 in a suitable solvent such as THF.[20] The resulting coupled product is treated with BBr_3 to generate a compound of formula **21**. Likewise, aniline or alkylamine is coupled with the key intermediate **18** in the presence of $(dppf)PdCl_2.CH_2Cl_2$, dppf, and NaO*t*Bu in THF.[21] The resulting coupled product is treated using the same method as described above to provide a compound of formula **22**.



(a) 3° alcohol
(b) HNO_3, formic acid
(c) CbzCl, NaOH, 1,4-dioxane, H_2O
(d) MeI, K_2CO_3, acetone
(e) $H_2NNH_2.H_2O$, Raney Ni, MeOH
(f) $(BOC)_2O$, THF
(g) MeI, NaH, THF
(h) TFA, DCM
(i) Aldehyde or ketone, $NaBH(OAc)_3$, DCE
(j) BBr_3, DCM
(k) 2-Chloroethylether, $NaHCO_3$, DMF

Scheme 8. Preparation of 2-substituted derivatives using 2-amino intermediate **25**

2.3.2. Preparation using 2-amino intermediate

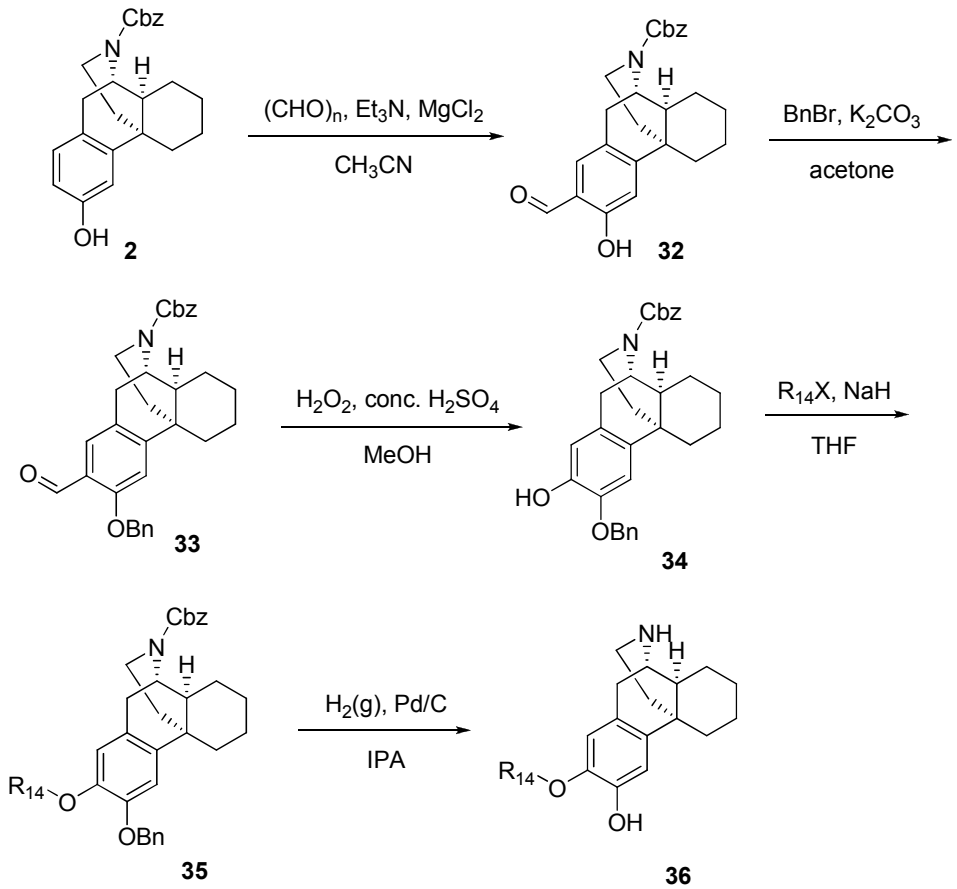
As shown in the following scheme 8, 2-*t*-butyl type compound **26** is obtained by treating (+)-3-HM with tertiary alcohol such as *t*-butanol in the presence of conc. sulfuric acid.[22)]

Preparation of amino-morphinans is described in the following scheme 8. Thus, (+)-3-HM is treated with HNO_3/formic acid to give 2-nitro-3-hydroxymorphinan, which is converted to the compound of formula **23** after amino protection by employing a protective group of cbz.[23)] Methylation of the compound of formula **23**, followed by selective reduction using hydrazine in the presence of a catalyst Raney Ni in MeOH, generate the critical intermediate, aniline **25**.[24)]

Protection of aniline **25** with di-tert-butyl-dicarbonate ($(BOC)_2O$) generates the compound of formula **27**, which is alkylated to provide the compound of formula **28**. After deprotection of BOC group of the compound of formula **28** using TFA, the corresponding aniline derivative is utilized for reductive alkylation, leading to the target aniline analogue **29**.

Another way of preparing aniline derivatives is a reaction of the aniline **25** with 2-chloroethyl ether in the presence of sodium bicarbonate in DMF to obtain the resulting compound. Demethylation the resulting compound using BBr_3 in methylene chloride provides the compound of formula **30**. On the other hand, reductive alkylation of

aniline **25**, followed by demethylation using BBr_3 provides a compound of formula **31**.



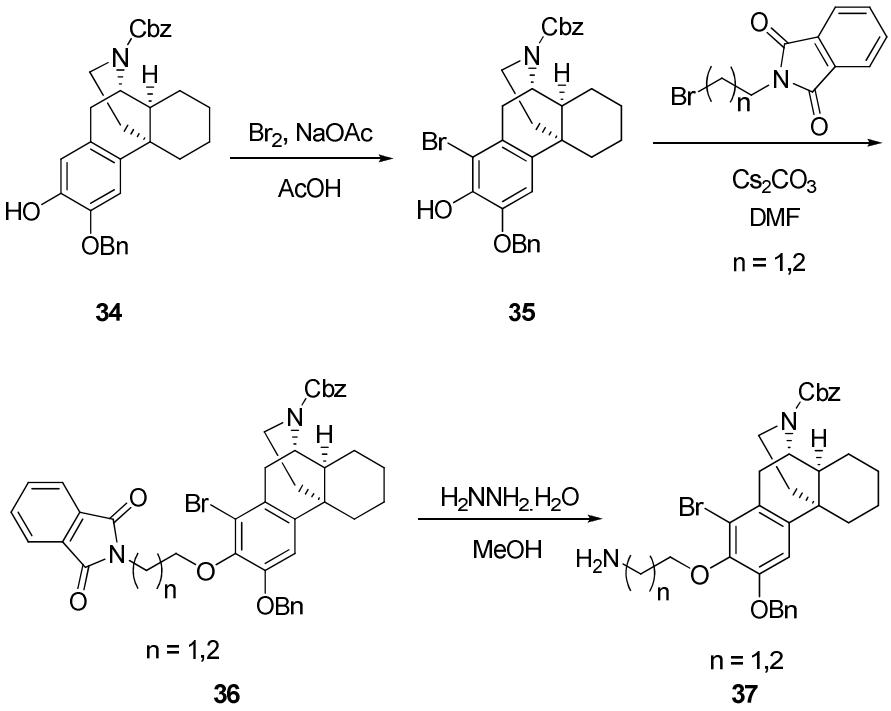
Scheme 9. Preparation of 2-substituted derivatives using 2-hydroxy intermediate **34**

When formylation of **2** is conducted by using paraformaldehyde with $MgCl_2$-TEA in butyronitrile, ortho-formylation occurrs exclusively at the 2-position.[25] After benzyl protection of 3-hydroxyl group, the acid-catalyzed oxidation of benzaldehyde to phenol

with hydrogen peroxide in methanol is performed to yield the corresponding alcohol **34**.[26] Alkylation of 2-hydroxyl group followed by deprotection of cbz and benzyl group by hydrogenation provides a compound of formula **36** (Scheme 9).

2.4. Synthesis of polycycle derivaitves

To improve neuroprotection activity and pk profile of (+)-3-HM, we investigated to expand the scope of morphinan structure to polycycle derivatives.



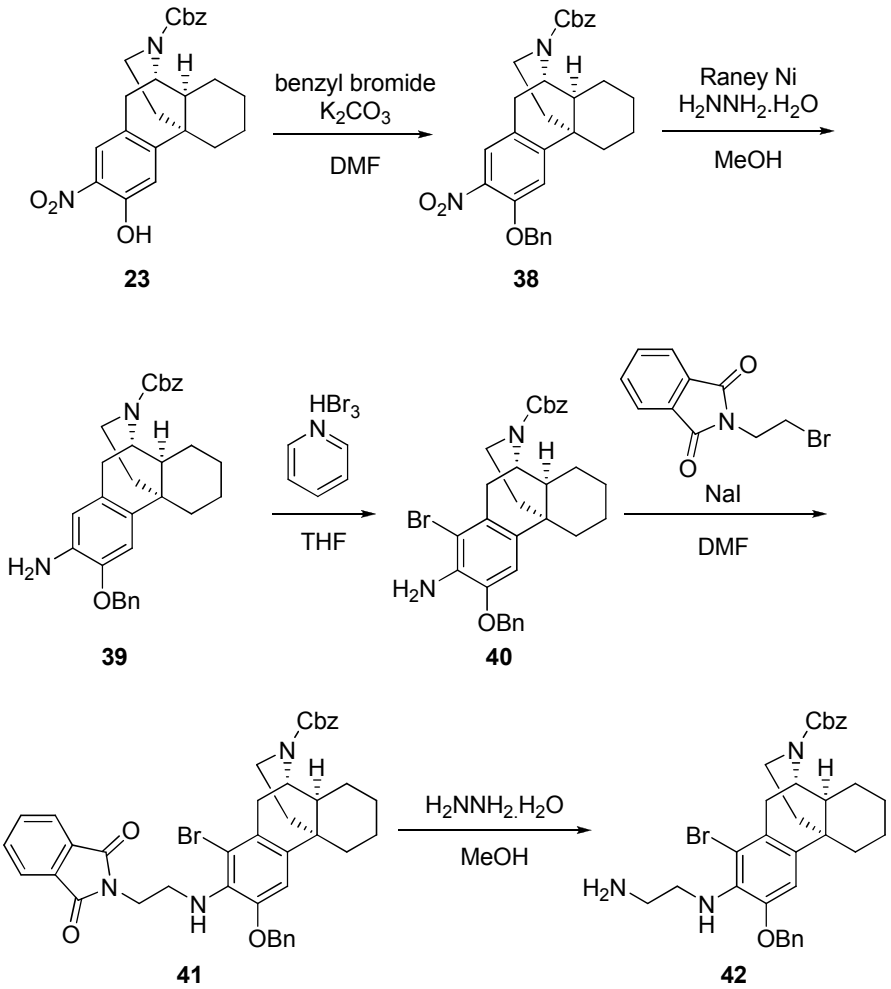
Scheme 10. Preparation of intermediate **37**

Bromination of 1-position is accomplished by using bromine in the presence of sodium acetate in acetic acid. Alkylation of 2-hydroxyl group followed by hydrazinolysis of phthalimide group provided the precursor **37** for cyclization reaction as shown is scheme 10.

Benzyl protection of 3-hydroyl group and subsequent reduction with hydrazine hydrate and catalytic Raney Ni in methanol provide the corresponding aniline **39**. Intermediate **42** was prepared by consecutive bromination, alkylation, and hydazinolysis as above described (Scheme 11).

The intermediates **44**, **46** are prepared by alkylation of phenol or aniline derivatives, and reduction of ester group with lithium borohydride (Scheme 12).

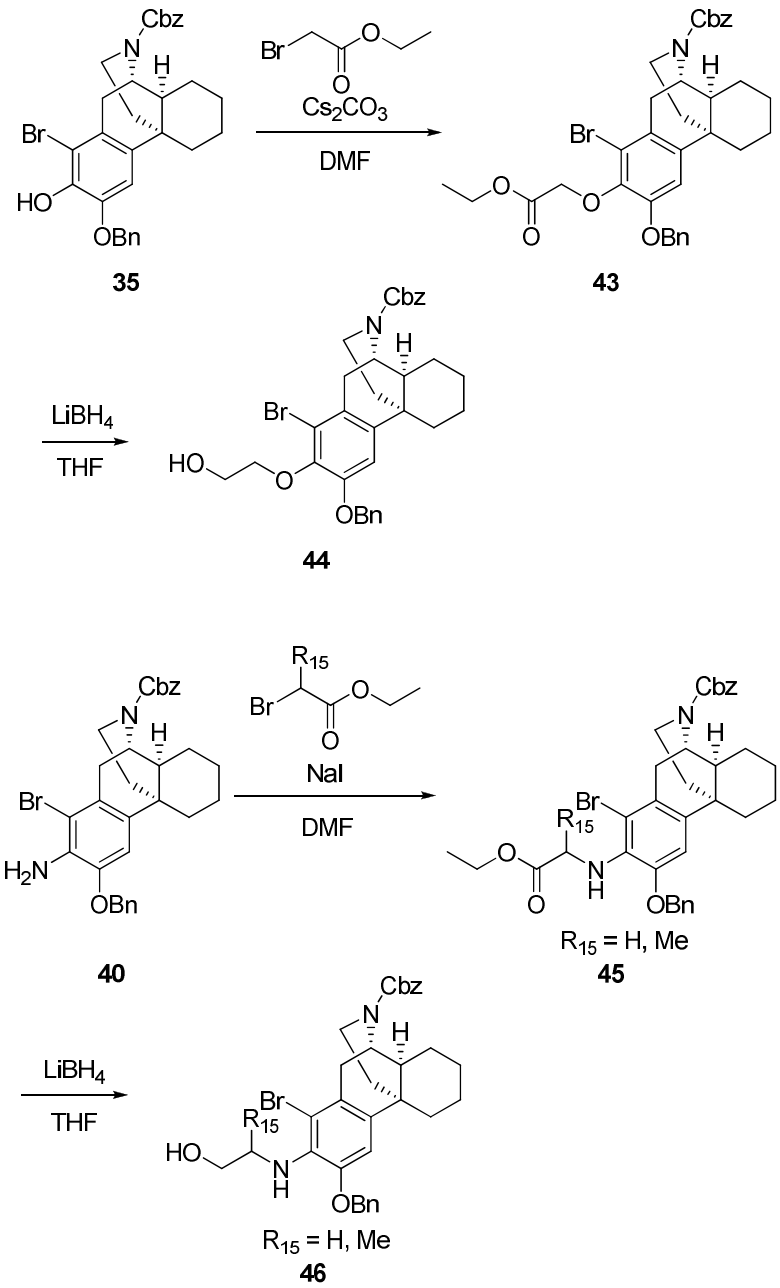
Intramolecular cyclization of amino intermediate **37** or **42** by use of sodium *tert*-butoxide in the presence of a catalytic amount of $Pd_2(dba)_3$, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) in THF gives rise to the corresponding pentacycle **47** or **49**. Hydrogenation of compound **47** or **49** with Pd on carbon in the presence of isopropyl alcohol generates the target product **48** or **50**. The quinoxaline type product of **50** is formed by way of concurrent oxidation toward aromaticity (Scheme 13).



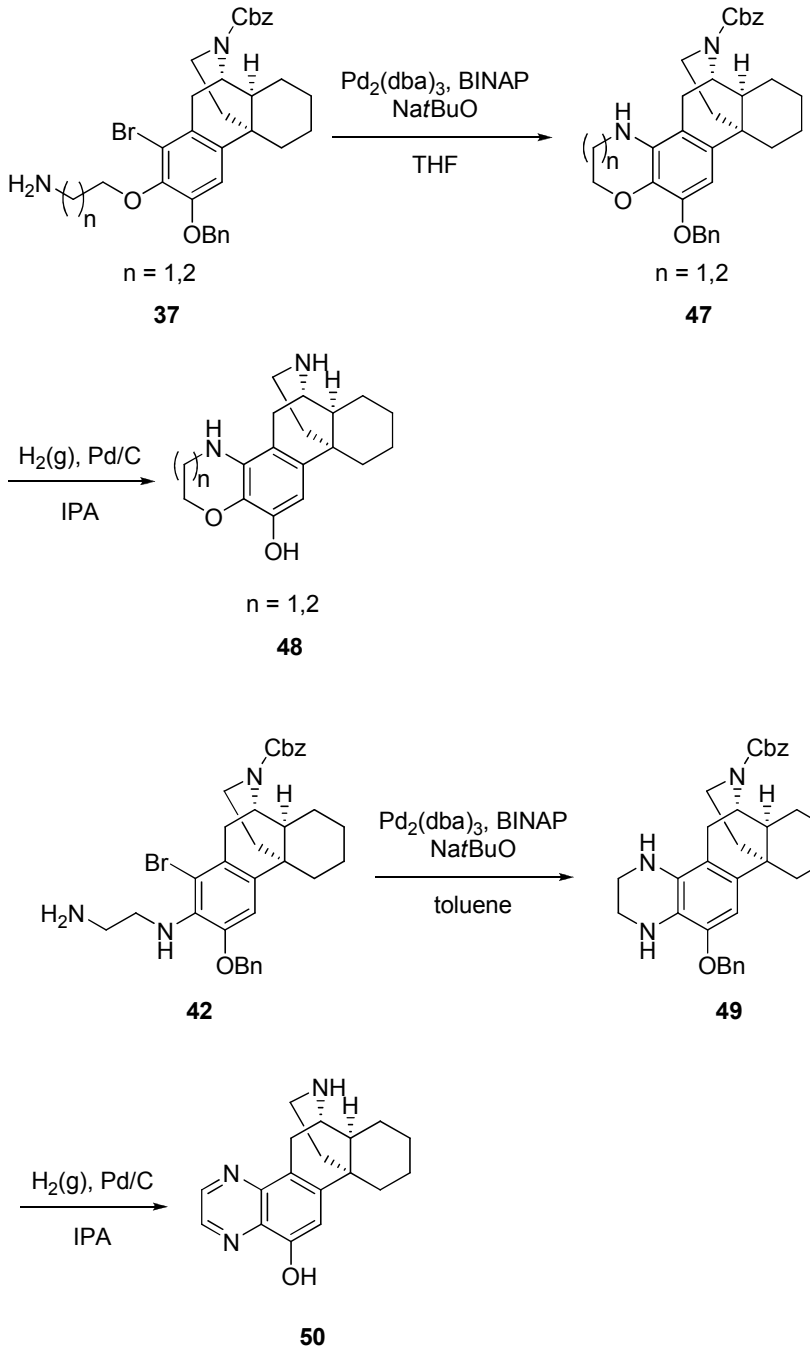
Scheme 11. Preparation of intermediate **42**

The attempts to gain the cyclized compound of hydroxyl intermediate **44** or **46** using the same condition of amino derivatives fail along with simple debromination. On the other hand, the Buchwald-Hartwig cross-coupling reaction with compound **24** as ligand provides the pentacycle **52** or **54**. Hydrogenation of compound **52** with Pd on

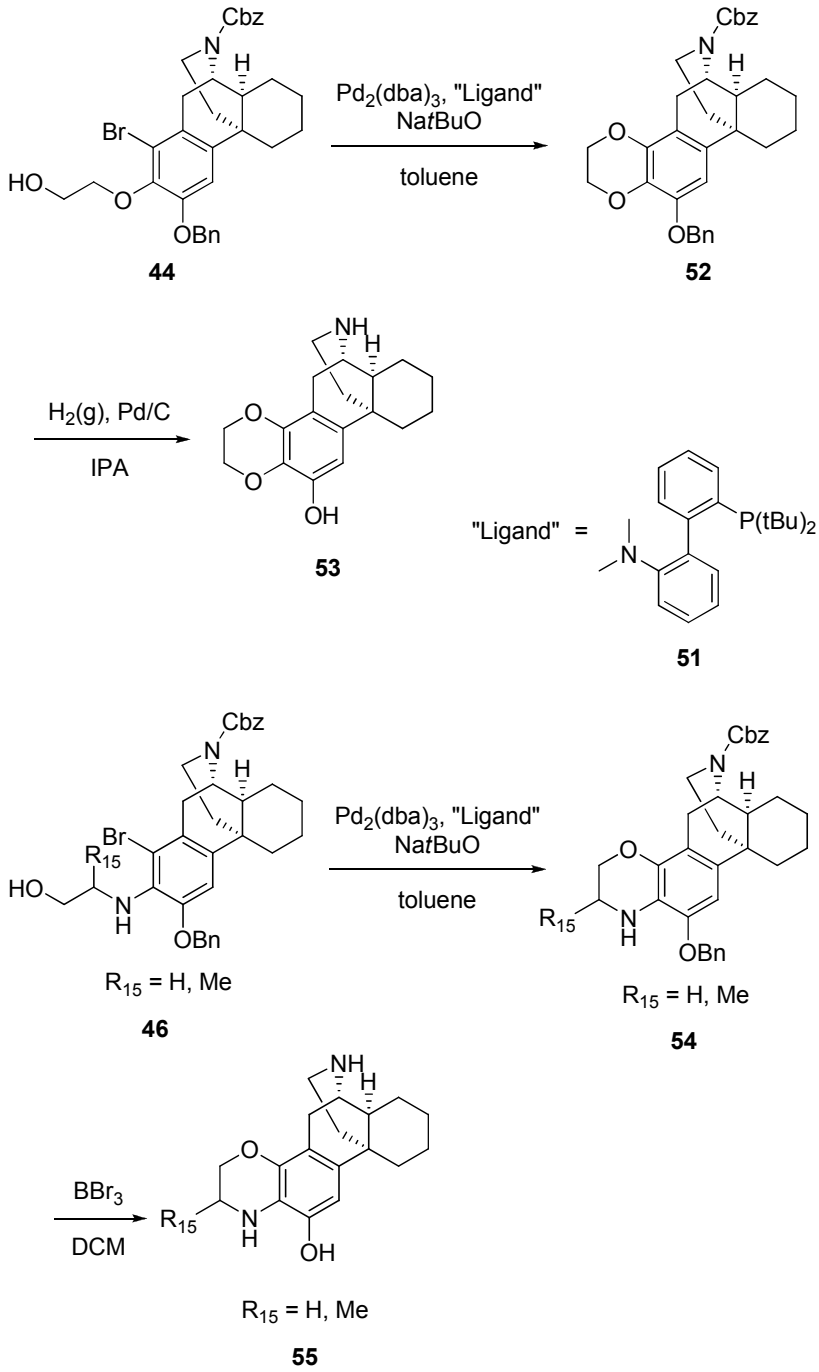
carbon produces a target compound **53**. And the treatment of compound **54** with boron tribromide produces another target compound **55**. (Scheme 14)



Scheme 12. Preparation of intermediates **44** and **46**



Scheme 13. Buchwald-Hartwig cross-coupling reaction with BINAP



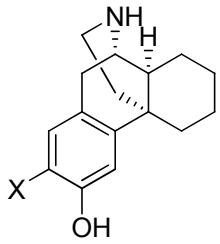
Scheme 14. Buchwald-Hartwig cross-coupling reaction with Ligand **51**

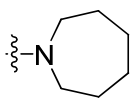
2.5. Biological assay

2.5.1. Cell cytotoxicity test

HT22 cells (mouse hippocampal neuron, Salk Institute and KRIBB) are placed in a 96-well plate 3 x 10^3 cells/well for 16 h before treatment. Five millimolar glutamate and the inventive compounds are co-treated and incubated for 24 h in growth media (DMEM with 10% FBS and 1% penicillin streptomycin). MTT (3-(4,5-dimethylthazol-2-yl)-2,5-diphenyltetrazolium bromide, Sigma®) is treated for 4 h and detected with a plate reader at a wavelength = 450 nm.[27)]

The EC_{50} values are statistically analyzed using Prism® (GraphPad Software Inc., San Diego, CA). The results of the cell cytotoxicity test are summarized in Table 1 and Table 2. (EC_{50}: neuroprotective effect against glutamate toxicity, and CC_{50}: cytotoxicity of compound)



X	EC_{50} (μM)	CC_{50} (μM)
	24.4	-
	11.6	-
	86.3	-
	>100	-
	0.579	12.2
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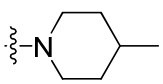
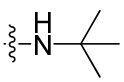
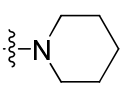
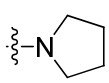
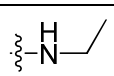
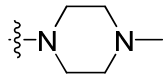
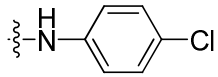
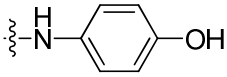
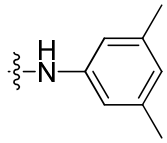
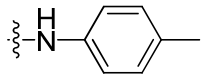
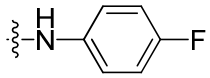
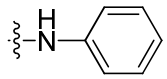
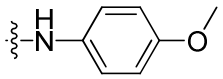
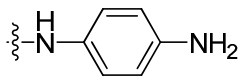
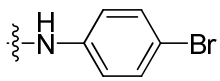
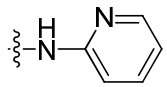
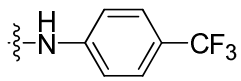
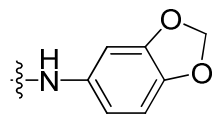
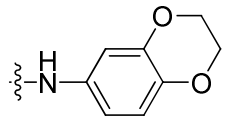
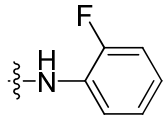
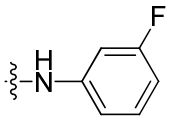
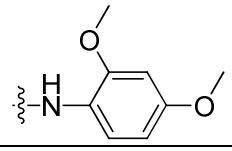
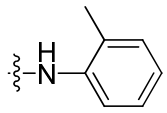
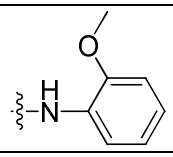
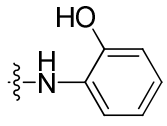
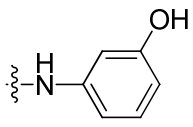
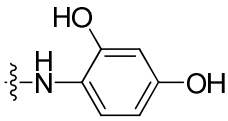
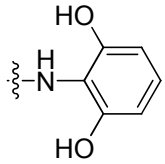
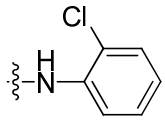
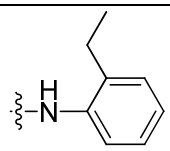
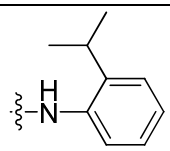
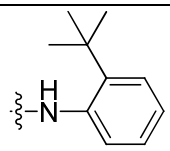
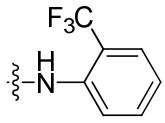
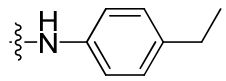
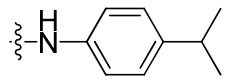
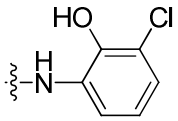
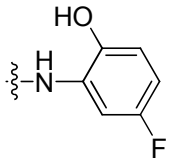
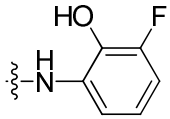
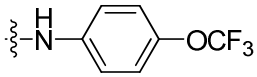
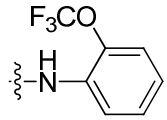
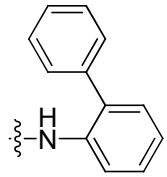
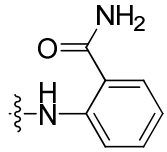
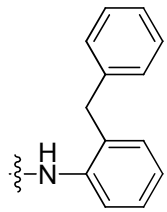
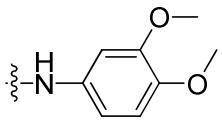
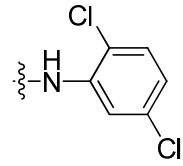
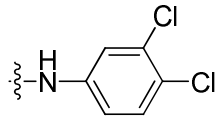
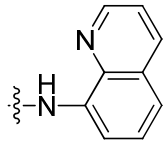
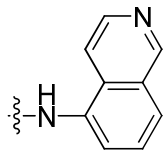
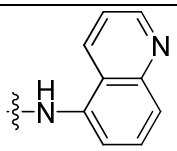
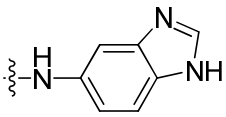
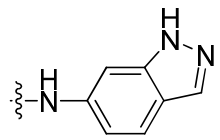
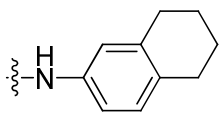
	0.272	8.04
	0.423	>100
	0.482	63.5
	0.638	80.5
	1.10	49.1

	3.10	14.4
	0.610	1.87
	0.00459	2.31
	0.0273	1.52
	0.0325	1.84
	0.0335	19.9
	0.0358	7.79
	0.0404	7.50
	0.0431	14.1
	0.0697	1.67
	2.34	41.5
	2.59	52.8

	0.301	84.5
	0.140	14.2
	0.211	11.8
	0.145	13.8
	0.0330	7.20
	0.0178	6.90
	0.0959	11.4
	0.00271	10.4
	0.802	75.0

	0.0731	40.9
	0.275	9.00
	0.0991	2.70
	0.0328	1.10
	0.0430	1.00
	0.0360	1.40
	0.0249	1.50
	0.0402	1.60
	0.0598	1.50
	0.101	9.20

	0.354	12.6
	0.199	5.50
	0.131	1.40
	0.0693	1.70
	0.0190	1.40
	1.79	50.0
	0.0524	1.60
	0.0289	10.1

	0.464	1.90
	0.314	1.60
	0.0213	2.90
	0.107	12.5
	1.72	8.50
	1.02	48.0
	2.51	54.6
	0.0362	1.60
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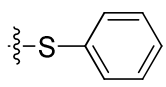
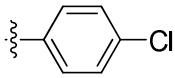
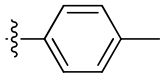
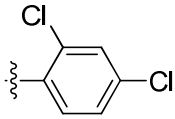
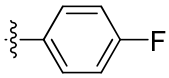
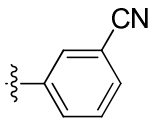
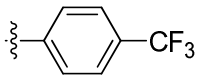
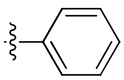
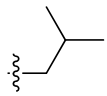
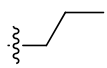
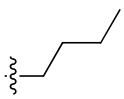
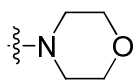
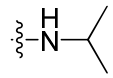
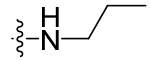
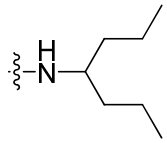
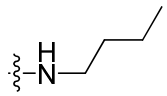
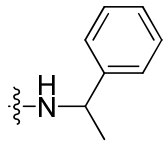
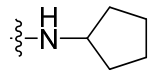
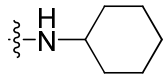
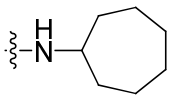
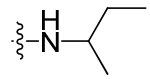
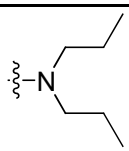
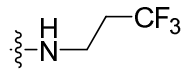
	1.67	5.57

	0.796	-
	1.66	9.40
	2.97	4.40
	3.11	8.30
	4.60	21.0
	6.10	11.0
	9.10	-
	1.43	11.3
	1.02	28.2
	2.07	51.5
	6.71	-
	8.39	-
	1.55	>100

	0.0354	39.5
	0.0416	37.2
	0.0740	1.94
	0.0747	35.0
	0.0813	15.0
	0.0927	37.8
	0.0986	13.8
	0.102	7.55
	0.131	66.4
	0.178	3.49
	0.183	67.0
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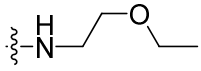
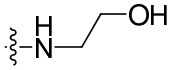
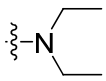
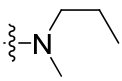
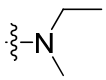
	10.4	>100
	11.7	>100
	14.0	>100
	0.548	29.6
	1.59	>100
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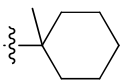
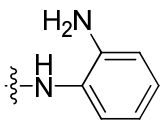
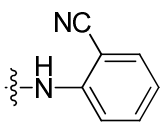
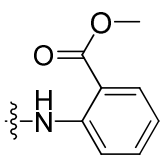
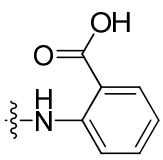
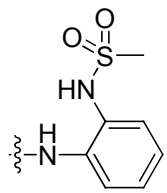
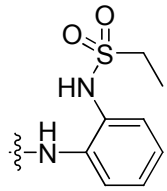
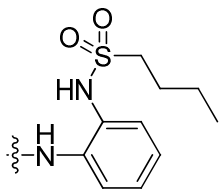
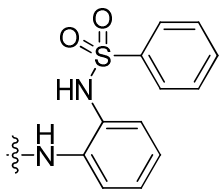
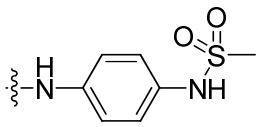
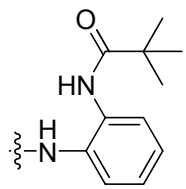
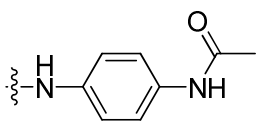
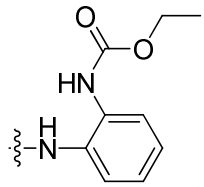
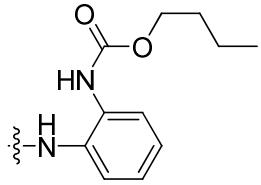
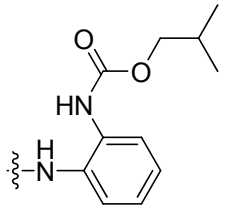
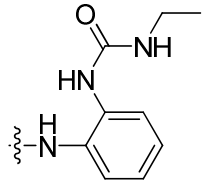
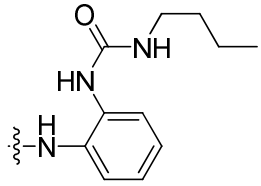
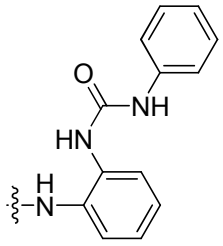
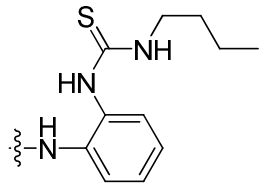
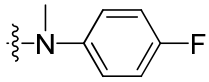
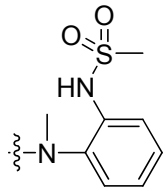
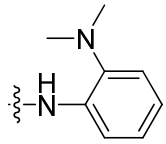
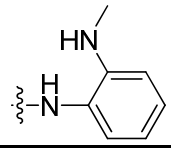
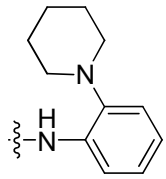
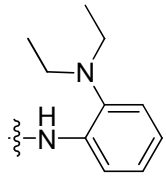
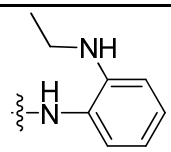
	0.594	2.24
	0.0366	21.8
	0.557	5.80
	7.96	>100
	14.1	>100

	0.00453	7.55
	0.475	36.5
	0.0556	20.0
	0.0272	3.01
	0.0329	11.4
	2.50	53.6
	2.84	36.5

	1.08	36.5
	0.891	-
	0.211	8.70
	8.85	36.5
	>100	23.1
	3.70	33.8

	0.459	-
	0.371	6.40
	10.9	45.9
	0.0121	6.10
	0.0621	1.30
	0.0356	1.60
	0.0439	1.60
	0.0112	1.60

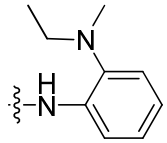
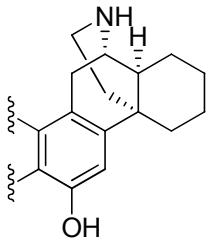
	0.0177	1.50
(+)-3-HM	31.3	>100

Table 1. Cell cytotoxicity of 2-substituted derivatives



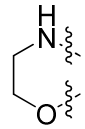
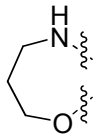
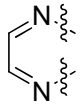
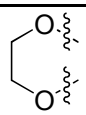
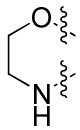
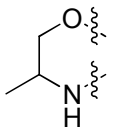
Compound	EC_{50} (μM)	CC_{50} (μM)
	26.9	> 100
	27.7	> 100
	16.3	44.8
	4.97	> 100
	0.650	13.5
	0.314	> 100
(+)-3-HM	31.3	>100

Table 2. Cell cytotoxicity of polycycle derivatives

2.5.2. ROS measurement

HT22 cells (1 x 10^4) plated in a 96-well plate are treated with 5 mM glutamate in the absence or presence of (+)-3-HM, and incubated for 8 hrs. After washing with PBS, cells are stained with 10 μM 2,7-dichlorodihydrofluorescein diacetate (DCFDA) in HBSS (Hank's balanced salt solution, Gibco) for 30 min in the dark. Then the cells are washed with PBS twice and extracted with 1% Triton X-100 in PBS for 10 min at 37℃. Fluorescence is recorded with the excitation wavelength of 490 nm and the emission wavelength of 525 nm (Infinite M200, TECAN).[27] The EC_{50} values are analyzed statistically using Prizm® (GraphPad Software Inc., San Diego, CA, USA). Fig. 1 shows the results of ROS measurement using DCFDA.

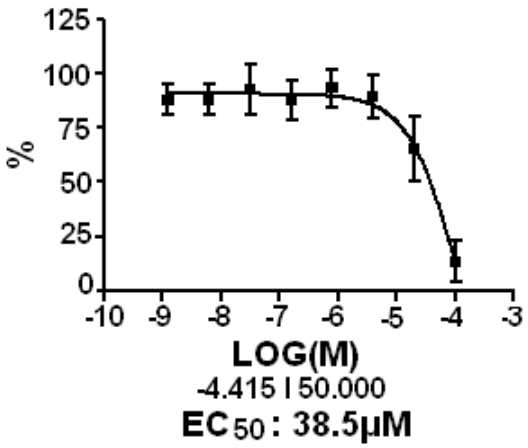


Figure 1. ROS measurment of (+)-3-HM

2.5.3. Identifying target gene using RT-PCR analysis

HT22 cells (1.5 x 10^7) plated in a 100 mm dish are treated with 10 mM glutamate in the absence or presence of (+)-3-HM, and incubated for 18 h. Oligonucleotide primers used for the PCR amplification are DJ-1 (PARK7), LRRK2 (Leucine-rich repeat kinase 2), PINK1 (PTEN induced putative kinase 1), SirT1 (silent mating type information regulation 2 homolog 1 (*S. cerevisiae*)), SirT2 (silent mating type information regulation 2 homolog 2 (*S. cerevisiae*)), and others. PCR products are electrophoresed on 2 % agarose gels and detected by ethidium bromide.[28)]

Fig. 2 shows the results of reverse transcription polymerase chain reaction.

In Fig. 2, Lane 1 is mock, Lane 2 is the group treated with 10 mM Glutamate, and Lane 3 is the group treated with 10 mM Glutamate and 100 μM (+)-3-HM.

2.5.4. Western blotting analysis

HT22 cells (1.5 x 10^7) plated in a 100 mm dish are treated with 10 mM glutamate in the absence or presence of (+)-3-HM, and incubated for 18 h. The cells are collected by scraping in a sample buffer (3 % SDS, 1 % glycerol, 0.5 % 2-mercaptoethanol, 0.05 % bromophenol blue, and 80 mM Tris-HCl buffer, pH 6.8, with complete protease inhibitors). The resulting suspention is centrifuged and the pellets thus obtained are re-

suspended in the sample buffer. The samples are heated for 3 min in boiling water, fractionated on 4-20 % polyacrylamide gels, and electroblotted onto membranes. SirT1 affinity purified polyclonal antibody is used as the primary antibody. Immunoreactive bands are detected with the ECL (Amersham Pharmacia Biotech, Arlington Heights, IL) Western blotting detection reagents.[28)]

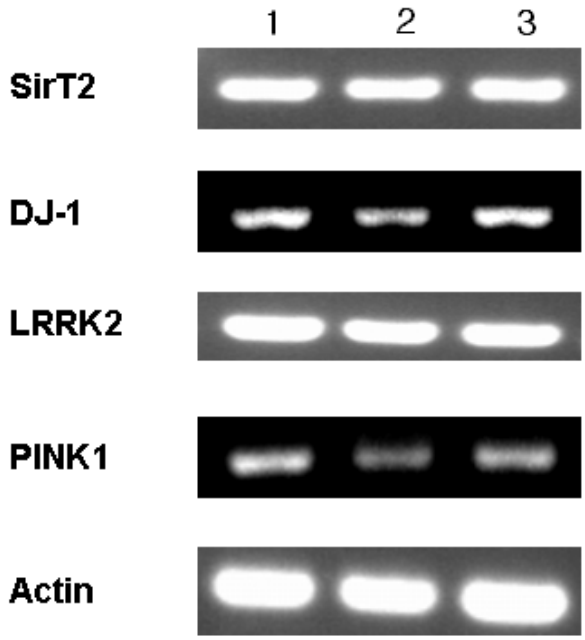


Figure 2. RT-PCR analysis of (+)-3-HM

Fig. 3 shows the results of western blotting analysis.

In Fig. 3, Lane 1 is Mock, Lane 2 is the group treated with 10 mM Glutamate, Lane 3 is the group treated with 10 mM Glutamate and 100 μM (+)-3-HM, Lane 4 is

the group treated with 10 mM Glutamate and 10 μM (+)-3-HM, Lane 5 is the group treated with 10 mM Glutamate and 1 μM (+)-3-HM, Lane 6 is the group treated with 10 mM Glutamate and 100 nM (+)-3-HM.

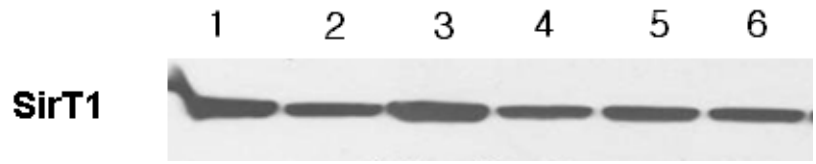


Figure 3. Western blotting analysis of (+)-3-HM

2.5.5. Total antioxidant activity assay

Briefly, 1 mL of reaction mixture including 2.5 μM metmyoglobin, 150 μM 2,2'-azinobis(3-ethylbenzoline 6-sulfonate), 75 μM H_2O_2, and 0.84 % sample or Trolox (for standard) in PBS is incubated for 7.5 min at 30 ℃; then the absorbance at 734 nm is measured. The data are normalized to 1 mM Trolox (TEAC activity).[27] The EC_{50} values were analyzed statistically using Prizm® (GraphPad Software Inc., San Diego, CA, USA).

Fig. 4 shows the results of total antioxidant activity assay.

As can be seen from Fig. 4, the EC_{50} of Trolox was 47.5 μM, (+)-3-HM shows 22.4 % of inhibition at 100 μM.

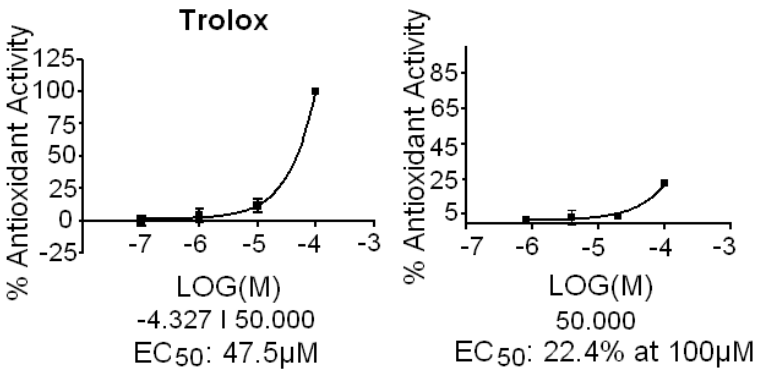


Figure 4. Total antioxidant activity assay of (+)-3-HM

3. Conclusion

(+)-3-HM has potent neuroprotective and neurotrophic effects in animal models of Parkinson's disease but, it is efficacious only if they are administered intraperitoneally or intravenously. To enhance the oral bioavailability of (+)-3-HM, which is approximately 18%, prodrug approach was considered and 3-hydroxy group of (+)-3-HM was chosen for chemical modification. At the first round of trial, ester and amino-acid prodrugs were made, but they are unacceptably labile or resistant toward cleavage. Another round of trial involved methylene linker-type prodrug which showed improved bioavilability. A residrual issue was instability originated from the free amine character

of prodrug compound, thus we attempted to make optimal salt form of GCC1290A. Among the salt prodrug compounds tested, we were able to choose tartaric acid salt with reasonably good physicochemical properties. Finally, we found the compound of GCC1290K, a novel prodrug of (+)-3-HM. Thorough pre-formulation studies of GCC1290A culminated in discovery of GCC1290K, which is developed as an antiparkinsonian drug under clinical trial of US FDA phase II.

After obtaining the indicator of neuroprotective effect with glutamate toxicity in HT-22 cell, we have achieved a convenient synthesis of DF by adopting Suzuki-Miyaura cross-coupling reaction. This concise synthesis of DF clearly exemplifies the utility of the Suzuki-Miyaura cross-coupling reaction, thereby providing DF in a sequence of only four steps starting from the commercially available (+)-3-HM.

To improve the efficacy of glutamate toxicity in HT-22 cell, derivatization of (+)-3-HM was accomplished as part of our commitment. At the beginning of our medicinal chemistry approach to SAR study, we discovered that 2-methylamino substituted derivative showed favorable activity against HT-22 cell assay. A variety of 2-amino substituted derivatives of (+)-3-HM was easily prepared by using palladium-based cross-coupling reactions. As a further study, we investigated a series of 2-amino substituted derivatives and 4-hydroxyphenylamino and 2-hydroxyphenylamino substituted derivatives showed favorable biological activity. Current (+)-3-HM derivatives on 2-position are synthesized from (+)-3-HM within maximum 5 steps.

To improve neurorotection activity an pK profile of (+)-3-HM, we expanded scope of morphinan structure to polycycle derivatives. Buchwald-Hartwig cross-coupling reaction of amino group was conducted by use of BINAP, and the same type reaction on hydroxyl group was also carried out successfully by use of 2-di-*t*-butylphosphino-2'-(*N,N*-dimethylamino)biphenyl. Deprotection and subsequent purification of cross-coupled compounds yielded 1,2-fused (+)-3-HM derivatives. Nitrogen analogs on 2-position of (+)-3-HM turned out to be more active than oxygen analogs.

4. Experimentals

^{1}H NMR spectra were recorded on either a Jeol ECX-400, or a Jeol JNM-LA300 spectrometer. Chemical shifts were expressed in parts per million (ppm, δ units). Coupling constants are in units of hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d(doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), br (broad).

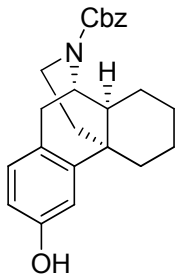
Mass spectra were obtained with either a Micromass, Quattro LC Triple Quadrupole Tandem Mass Spectometer, ESI or Agilent, 6110 Quadrupole LC/MS, ESI.

For preparative HPLC, *ca* 100 mg of a product was injected in 1 mL of DMSO onto a SunFire^{TM} Prep C18 OBD 5 um 19x100mm Column with a 10 min gradient from

10% CH_3CN to 90% CH_3CN in H_2O. Flash chromatography was carried using Merck silica gel 60 (230-400 mesh). Most of the reactions were monitored by thin-layer chromatography on 0.25 mm E. Merck silica gel plates (60F-254), visualized with UV light using a 5% ethanolic phosphomolybdic acid or p-anisaldehyde solution.

4.1. Examples of (+)-3-HM prodrugs

Example 1 : Preparation of (+)-3-hydroxy-*N*-(benzyloxycarbonyl)morphinan



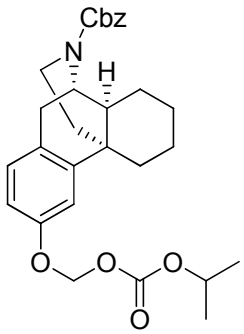
To (+)-3-HM hydrobromide (50.0 g, 154.2 mmol), sodium hydroxide (12.3 g, 308.4 mmol) in a mixture of 1,4-dioxane (200 mL) and water (200 mL) was added Cbz-Cl (24.2 mL, 169.6 mmol) dropwise at room temperature. The reaction mixture was stirred vigorously at room temperature overnight. After the reaction was completed, water (200 mL) was added. The mixture was extracted with diethyl ether (500 mL X 2). The combined organics were dried over $MgSO_4$, filtered, and evaporated under vacuum.

Standing under high vacuum provided the title compound (57.7 g, 99 %) as a light yellow solid. The compound was used for the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.31 (m, 5H), 6.70-6.91 (m, 1H), 6.77 (d, *J* = 2.4 Hz, 1H), 6.65-6.61 (m, 1H), 5.18-5.13 (m, 2H), 4.36 (br d, *J* = 42.0 Hz, 1H), 3.94-3.83 (m, 1H), 3.12-3.03 (m, 1H), 2.72-2.57 (m, 2H), 2.32 (d, *J* = 11.2 Hz, 1H), 1.71-1.24 (m, 9H), 1.11-1.02 (m, 1H).

MH+ 378.

Example 2 : Preparation of (+)-[*N*-(benzyloxycarbonyl)morphinan-3-yloxy]methyl isopropyl carbonate



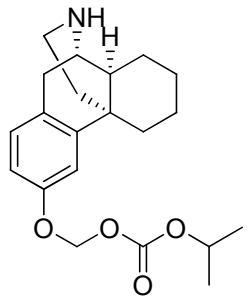
To (+)-3-hydroxy-*N*-(benzyloxycarbonyl)morphinan (33.0 g, 87.4 mmol) and cesium carbonate (28.5 g, 87.4 mmol) in acetone (450 mL) was added iodomethyl isopropyl carbonate (21.3 g, 87.4 mmol) at room temperature. The reaction mixture was stirred vigorously at room temperature overnight. The acetone was then removed by

rotary evaporation under vacuum. To the residue was added saturated $NaHCO_3$ solution. The mixture was extracted with EtOAc (300 mL X 2). The combined organics were washed with 1*N* HCl solution (300 mL), dried over $MgSO_4$, filtered, and evaporated under vacuum to provide the title compound (42.0 g, 97 %) as a yellow gum.

$[\alpha]_D^{27}$ +112.0° (c=1.0, MeOH); IR (KBr) ν_{max} 2931, 1754, 1695, 1496, 1422, 1270, 1234, 1218, 1185, 1044 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.32 (m, 5H), 7.03 (t, *J* = 8.4 Hz, 1H), 6.96 (s, 1H), 6.88 (dd, *J* = 8.4, 2.4 Hz, 1H), 5.75 and 5.70 (ABq, *J* = 6.8 Hz, 2H), 5.21-5.09 (m, 2H), 4.93 (m, 1H), 4.37 (br d, *J* = 43.2 Hz, 1H), 3.96-3.84 (m, 1H), 3.17-3.05 (m, 1H), 2.76-2.56 (m, 2H), 2.34 (d, *J* = 10.8 Hz, 1H), 1.72-1.43 (m, 6H), 1.43-1.26 (m, 9H), 1.08-0.99 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 155.4, 153.7, 140.8, 136.9, 130.9, 130.7, 129.3, 129.2, 128.4, 127.9, 127.8, 114.0, 113.4, 88.6, 72.9, 66.9, 49.8, 43.7, 41.5, 38.3, 37.6, 36.4, 31.3, 26.4, 26.3, 22.3, 22.0, 21.7.

MH+ 494.

Example 3 : Preparation of (+)-isopropyl (morphinan-3-yloxy)methyl carbonate

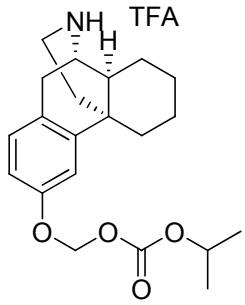


(+)-Isopropyl [*N*-(benzyloxycarbonyl)morphinan-3-yloxy]methyl carbonate (42.0 g, 84.1 mmol) was subjected to hydrogenation (balloon) on 10 % Pd/C (6.3 g) in EtOH (250 mL) at room temperature. After the reaction was completed, the reaction mixture was filtered through a Celite, and washed with EtOH (400 mL). The combined EtOH solution was evaporated under vacuum. The residue was further purified by prep reverse-phase HPLC to provide the title compound (5.82 g, 19 %) as a yellow solid.

$[\alpha]_D^{27}$ +27.9° (c=1.0, MeOH); IR (KBr) ν_{max} 2980, 2929, 2856, 1753, 1610, 1496, 1271, 1218, 1112, 1045 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, *J* = 8.4 Hz, 1H), 6.94 (d, *J* = 2.6 Hz, 1H), 6.87 (dd, *J* = 8.4, 2.6 Hz, 1H), 5.77 and 5.71 (ABq, *J* = 6.4 Hz, 2H), 4.93 (m, 1H), 3.16-3.05 (m, 2H), 2.94-2.54 (m, 4H), 2.29 (d, *J* = 11.9 Hz, 1H), 1.78-1.74 (m, 1H), 1.66-1.50 (m, 3H), 1.41-1.20 (m, 10H), 1.07-0.99 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 153.7, 141.8, 132.2, 128.8, 113.9, 113.1, 88.7, 72.6, 65.9, 50.9, 46.8, 42.2, 38.9, 38.2, 36.8, 33.1, 26.7, 26.6, 22.0, 21.7.

MH+ 360.

Example 4 : Preparation of (+)-isopropyl (morphinan-3-yloxy)methyl carbonate TFA

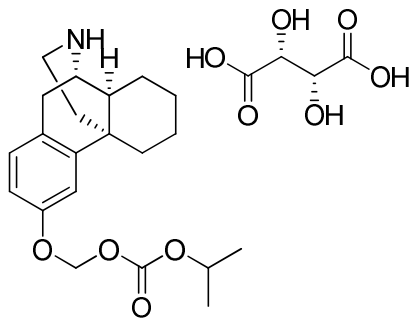


(+)-Isopropyl [(benzyloxycarbonyl)morphinan-3-yloxy]methyl carbonate (16.9 g, 34.2 mmol) was subjected to hydrogenation (balloon) on 10 % Pd/C (1.7 g) in 1,4-dioxane (100 mL) at room temperature. After the reaction was completed, the reaction mixture was filtered through a Celite, and washed with 1,4-dioxane (50 mL). The combined 1,4-dioxane solution was evaporated under vacuum. The residue was further purified by prep reverse-phase HPLC with 0.1 % TFA to provide the title compound (8.86 g, 55 %) as a colorless gum.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (br, 2H), 7.12 (d, *J* = 8.4 Hz, 1H), 6.95-6.93 (m, 2H), 5.76 and 5.70 (ABq, *J* = 6.4 Hz, 2H), 4.95-4.89 (m, 1H), 3.68 (br, 1H), 3.23-3.11 (m, 3H), 2.75 (br, 1H), 2.35 (d, *J* = 13.6 Hz, 1H), 2.08 (d, *J* = 12.0 Hz, 1H), 1.98-1.90 (m, 1H), 1.66 (d, *J* = 12.8 Hz, 1H), 1.58-1.37 (m, 5H), 1.30 (d, *J* = 6.0 Hz, 6H), 1.27-1.24 (m, 1H), 1.07-1.03 (m, 1H).

MH+ 360.

Example 5 : Preparation of (+)-isopropyl (morphinan-3-yloxy)methyl carbonate L-(+)-tartaric acid



Method 1: (+)-Isopropyl (morphinan-3-yloxy)methyl carbonate TFA (300 mg, 0.634 mmol) was dissolved in EtOAc (20 mL) and washed with saturated $NaHCO_3$ solution (20 mL X 2). To the EtOAc layer was added L-(+)-tartaric acid (95.2 mg, 0.634 mmol). The mixture was stirred at 40 °C for 10 min. and cooled to room temperature. The precipitated solution was filtered and washed with EtOAc (10 mL) to provide the title compound (268 mg, 83 %) as a white solid.

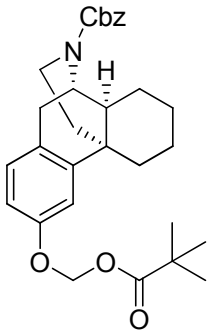
Method 2: (+)-Isopropyl [*N*-(benzyloxycarbonyl)morphinan-3-yloxy]methyl carbonate (1.72 g, 3.48 mmol) was subjected to hydrogenation (balloon) on 10 % Pd/C (170 mg) in IPA (25 mL) at room temperature. After the reaction was completed, the reaction mixture was filtered through a Celite, and washed with IPA (20 mL). To the combined IPA solution was added L-(+)-tartaric acid (522 mg, 3.48 mmol). The mixture was stirred at 40 °C for 30 min. The mixture was evaporated under vacuum. To the

residue was added EtOAc (20 mL). The solution was filtered and washed with EtOAc (10 mL) to provide the title compound (1.61 g, 91 %) as a white solid.

$[\alpha]_D^{27}$ +24.0° (c=1.0, MeOH); mp 159 °C; IR (KBr) ν_{max} 3525, 3179, 2933, 2456, 1760, 1455, 1431, 1271, 1219, 1043 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.18 (d, *J* = 8.4 Hz, 1H), 7.03 (d, *J* = 2.4 Hz, 1H), 6.95 (dd, *J* = 8.4, 2.4 Hz, 1H), 5.75 and 5.72 (ABq, *J* = 6.8 Hz, 2H), 4.89-4.82 (m, 1H), 4.39 (s, 2H), 3.70-3.68 (m, 1H), 3.25 (d, *J* = 6.0 Hz, 1H), 3.11 (dd, *J* = 13.6, 4.0 Hz, 1H), 2.99 (br d, *J* = 18.8 Hz, 1H), 2.74-2.66 (m, 1H), 2.45 (d, *J* = 14.4 Hz, 1H), 1.96 (d, *J* = 11.6 Hz, 1H), 1.88-1.80 (m, 1H), 1.70 (d, *J* = 12.8 Hz, 1H), 1.59-1.42 (m, 5H), 1.34-1.28 (m, 1H), 1.26 (d, *J* = 6.4 Hz, 6H), 1.14-1.04 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 176.1, 156.5, 153.9, 139.5, 129.4, 128.9, 114.8, 113.5, 88.4, 73.1, 72.5, 51.3, 41.2, 38.4, 37.6, 36.6, 35.5, 27.7, 25.9, 25.6, 21.7, 20.7; HR-FAB-MS *m/z*: 360.2173 $[M+H]^+$ (Calcd for $C_{21}H_{30}NO_4$: 360.2175).

MH+ 360.

Example 6 : Preparation of (+)-[*N*-(benzyloxycarbonyl)morphinan-3-yloxy]methyl pivalate

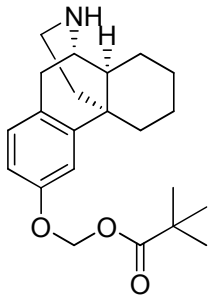


To (+)-3-hydroxy-*N*-(benzyloxycarbonyl)morphinan (12.0 g, 31.8 mmol) and cesium carbonate (11.4 g, 35.0 mmol) in acetone (150 mL) was added iodomethyl pivalate (8.46 g, 35.0 mmol) at room temperature. The reaction mixture was stirred vigorously at room temperature overnight. The acetone was then removed by rotary evaporation under vacuum. To the residue was added saturated $NaHCO_3$ solution. The mixture was extracted with EtOAc (150 mL X 2). The combined organics were washed with 1*N* HCl solution (100 mL), dried over $MgSO_4$, filtered, and evaporated under vacuum to provide the crude product, which was further purified by prep reverse-phase HPLC to afford the title compound (13.2 g, 84 %) as a yellow gum.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.32 (m, 5H), 7.02 (t, *J* = 8.8 Hz, 1H), 6.97 (s, 1H), 6.84 (dd, *J* = 8.4, 2.4 Hz, 1H), 5.76 and 5.72 (ABq, *J* = 6.4 Hz, 2H), 5.20-5.09 (m, 2H), 4.37 (br d, *J* = 43.6 Hz, 1H), 3.95-3.84 (m, 1H), 3.15-3.05 (m, 1H), 2.72-2.59 (m, 2H), 2.34 (d, *J* = 12.0 Hz, 1H), 1.73-1.42 (m, 6H), 1.39-1.25 (m, 3H), 1.21 (s, 9H), 1.11-1.00 (m, 1H).

MH+ 492.

Example 7 : Preparation of (+)-(morphinan-3-yloxy)methyl pivalate

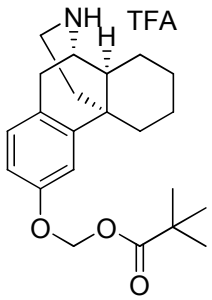


(+)-[*N*-(Benzyloxycarbonyl)morphinan-3-yloxy]methyl pivalate (13.2 g, 26.8 mmol) was subjected to hydrogenation (balloon) on 10 % Pd/C (2.0 g) in EtOH (100 mL) at room temperature. After the reaction was completed, the reaction mixture was filtered through a Celite, and washed with EtOH (300 mL). The combined EtOH solution was evaporated under vacuum. The residue was further purified by reverse-phase prep HPLC to provide the title compound (4.31 g, 45 %) as a light yellow gum.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (d, *J* = 8.4 Hz, 1H), 6.94 (d, *J* = 2.7 Hz, 1H), 6.83 (dd, *J* = 8.4, 2.7 Hz, 1H), 5.76 and 5.71 (ABq, *J* = 6.4 Hz, 2H), 3.16-3.08 (m, 2H), 2.80-2.54 (m, 4H), 2.28 (d, *J* = 13.2 Hz, 1H), 1.81-1.76 (m, 1H), 1.66-1.50 (m, 3H), 1.42-1.26 (m, 4H), 1.21 (s, 9H), 1.09-1.00 (m, 1H).

MH+ 358.

Example 8 : Preparation of (+)-(morphinan-3-yloxy)methyl pivalate TFA

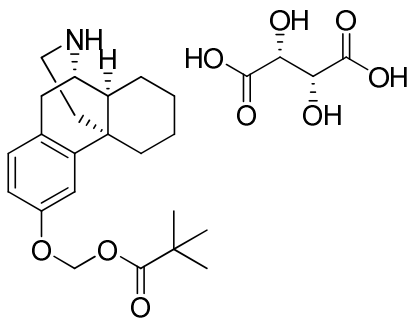


(+)-[*N*-(Benzyloxycarbonyl)morphinan-3-yloxy]methyl pivalate (4.66 g, 9.48 mmol) was subjected to hydrogenation (balloon) on 10 % Pd/C (470 mg) in IPA (40 mL) at room temperature. After the reaction was completed, the reaction mixture was filtered through a Celite, and washed with IPA (20 mL). The combined IPA solution was evaporated under vacuum. The residue was further purified by prep reverse-phase HPLC with 0.1 % TFA to provide the title compound (3.79 g, 85 %) as a colorless gum.

^{1}H NMR (400 MHz, CD_3OD) δ 7.18 (d, *J* = 8.4 Hz, 1H), 7.06 (d, *J* = 2.8 Hz, 1H), 6.95 (dd, *J* = 8.4, 2.8 Hz, 1H), 5.79 and 5.73 (ABq, *J* = 6.8 Hz, 2H), 3.70-3.68 (m, 1H), 3.33-3.26 (m, 1H), 3.10 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.95 (br d, *J* = 19.2 Hz, 1H), 2.74-2.67 (m, 1H), 2.46 (d, *J* = 14.0 Hz, 1H), 1.94 (d, *J* = 12.0 Hz, 1H), 1.87-1.78 (m, 1H), 1.71 (d, *J* = 12.8 Hz, 1H), 1.60-1.40 (m, 5H), 1.34-1.25 (m, 1H), 1.17 (s, 9H), 1.15-1.07 (m, 1H).

MH+ 358.

Example 9 : Preparation of (+)-(morphinan-3-yloxy)methyl pivalate L-(+)-tartaric acid



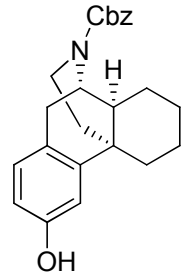
^{1}H NMR (400 MHz, CD_3OD) δ 7.18 (d, *J* = 8.0 Hz, 1H), 7.04 (d, *J* = 2.0 Hz, 1H), 6.93 (dd, *J* = 8.4, 2.4 Hz, 1H), 5.79 and 5.73 (ABq, *J* = 6.8 Hz, 2H), 4.32 (s, 2H), 3.68 (br, 1H), 3.29-3.22 (m, 1H), 3.12-3.08 (m, 1H), 2.99 (br d, *J* = 19.2 Hz, 1H), 2.70-2.63 (m, 1H), 2.44 (d, *J* = 13.6 Hz, 1H), 2.00-1.96 (m, 1H), 1.89-1.81 (m, 1H), 1.70 (d, *J* = 13.6 Hz, 1H), 1.59-1.40 (m, 4H), 1.32-1.21 (m, 2H), 1.17 (s, 9H), 1.13-1.06 (m, 1H).

MH+ 358.

4.2. Examples of Dimemorfan (DF) derivaitves

Example 1 : 3-(4-(Trifluoromethyl)phenyl)-*N*-(benzyloxycarbonyl)morphinan

Step 1: 3-Hydroxy-*N*-(benzyloxycarbonyl)morphinan

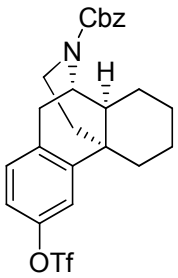


To 3-hydroxymorphinan (HM) hydrobromide (50.0 g, 154.2 mmol), sodium hydroxide (12.3 g, 308.4 mmol) in a mixture of 1,4-dioxane (200 mL) and water (200 mL) was added Cbz-Cl (24.2 mL, 169.6 mmol) dropwise at rt. The reaction mixture was stirred vigorously at rt overnight. After the reaction was completed, water (200 mL) was added. The mixture was extracted with diethyl ether (500 mL X 2). The combined organics were dried over $MgSO_4$, filtered, and evaporated under vacuum. Standing under high vacuum provided the title compound (57.7 g, 99%) as a light yellow solid. The compound was used for the next step without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.32 (m, 5H), 6.91 (m, 1H), 6.76 (s, 1H), 6.62 (m, 1H), 5.17-5.12 (m, 2H), 4.35 (d, *J* = 29.25 Hz, 1H), 3.92-3.82 (m, 1H), 3.11-3.03 (m, 1H), 2.72-2.56 (m, 2H), 2.31-2.28 (m, 1H), 1.63-1.26 (m, 10H), 1.11-1.00 (m, 1H).

MH+ 378.

Step 2: 3-(Trifluoromethanesulfonyloxy)-*N*-(benzyloxycarbonyl)morphinan

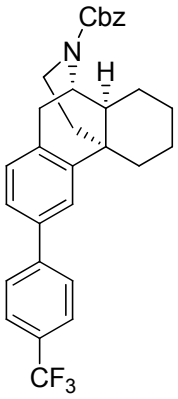


TEA (4.43 mL, 31.8 mmol) was added to a solution of 3-hydroxy-*N*-(benzyloxycarbonyl)morphinan (10.0 g, 26.5 mmol) and trifluoromethanesulfonyl chloride (5.36 g, 31.8 mmol) in DCM (100 mL) at 0°C. The reaction mixture was warmed up to r.t. and stirreded for 12h at r.t. H_2O (25 mL) was added to the reaction mixture and then extracted with DCM (50mL). The organic extract was dried over anhydrous $MgSO_4$, filtered, and concentrated in *vacuo*. Purification by silica gel column chromatography (Biotage, Eluent : 4% EtOAc / Hexane→ 32% EtOAc / Hexane (Gradient)) provided 11.8 g (87 %) of desired product as a liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.29 (m, 5H), 7.18-7.13 (m, 2H), 7.05 (dd, *J* = 8.4, 2.8 Hz, 1H), 5.12, (s, 2H), 4.40 (d, *J* = 44.0 Hz, 1H), 3.98-3.86 (m, 1H), 3.18-3.11 (m, 1H), 2.78-2.73 (m, 1H), 2.64-2.53 (m, 1H), 2.31 (d, *J* = 14.0 Hz, 1H), 1.76-1.50 (m, 6), 1.42-1.30 (m, 2H), 1.23-1.16 (m, 1H), 0.99-0.96 (m, 1H).

MH+ 510.

Step 3: 3-(4-(Trifluoromethyl)phenyl)-*N*-(benzyloxycarbonyl)morphinan

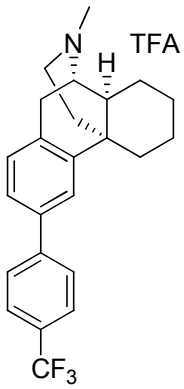


To a solution of 3-(trifluoromethanesulfonyloxy)-*N*-(benzyloxycarbonyl)morphinan (500 mg, 0.98 mmol) in dioxane (10 mL) / H_2O (1 mL) was added 4-(trifluoromethyl)phenylboronic acid (370 mg, 2.0 mmol), K_2CO_3 (540 mg, 3.9 mmol) and tetrakis(triphenylphosphine)palladium(0) (110 mg, 0.098 mmol). The reaction mixture was irradiated in a microwave reactor (Biotage) for 1hr at 180°C. Purification by silica gel column chromatography (Biotage, Eluent : 4% EtOAc / Hexane→ 32% EtOAc / Hexane (Gradient)) provided 320 mg (65 %) of desired product as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.63 (m, 4H), 7.48 (s, 1H), 7.38-7.30 (m, 6H), 7.20-7.18 (m, 1H), 5.21-5.13 (m, 2H), 4.42 (d, *J* = 41.2 Hz, 1H), 3.99-3.88 (m, 1H), 3.23-3.17 (m, 1H), 2.82-2.62 (m, 2H), 2.49 (d, *J* = 12.8 Hz, 1H), 1.75-1.23 (m, 9H), 1.10-1.07 (m, 1H).

MH+ 506.

Example 2 : 3-(4-(Trifluoromethyl)phenyl)-*N*-methylmorphinan TFA salt

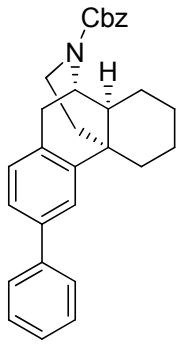


3-(4-(Trifluoromethyl)phenyl)-*N*-(benzyloxycarbonyl)morphinan (310 mg, 0.61 mmol) from Example 1 and formalin (140 μL, 1.8 mmol, 37 wt%) were subjected to hydrogenation (balloon) on 10% Pd/C (31 mg) in MeOH (20 mL) at rt. After the reaction was completed, the reaction mixture was filtered through a Celite, and washed with MeOH (40 mL). The combined MeOH solution was evaporated under vacuum. The residue was further purified by prep reverse-phase HPLC (0.1 % TFA added) to provide the title compound (260 mg, 84 %) as a liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.23 (s, 1H), 7.66 (dd, *J* = 25.6, 8.0 Hz, 4H), 7.51-7.43 (m, 2H), 7.31-7.25 (m, 1H), 3.68 (s, 1H), 3.37-3.24 (m, 2H), 3.10 (d, *J* = 20 Hz, 1H), 2.87 (s, 3H), 2.65-2.51 (m, 2H), 2.25 (d, *J* = 12 Hz, 1H), 2.17-2.13 (m, 1H) 1.76-1.1.41 (m, 6H), 1.37-1.23 (m, 1H), 1.18-1.07 (m, 1H).

MH+ 386.

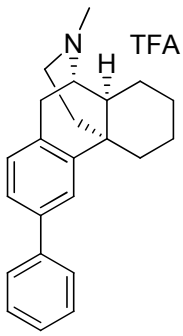
Example 3 : 3-Phenyl-*N*-(benzyloxylcarbonyl)morphinan



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.2 Hz, 2H), 7.48-7.30 (m, 10H), 7.17-7.13 (m, 1H), 5.18-5.13 (m, 2H), 4.40 (d, *J* = 42.4 Hz, 1H), 3.99-3.85 (m, 1H), 3.24-3.13 (m, 1H), 2.81-2.66 (m, 2H), 2.50 (d, *J* = 10.8 Hz, 1H), 1.74-1.25 (m, 9H), 1.12-1.09 (m, 1H).

MH+ 438.

Example 4 : 3-Phenyl-*N*-methylmorphinan TFA salt

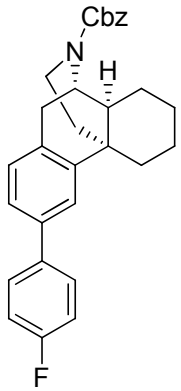


^{1}H NMR (400 MHz, $CDCl_3$) δ 11.68 (s, 1H), 7.54-7.43 (m, 6H), 7.38-7.33 (m, 1H), 7.28-7.22 (m, 1H), 3.62 (s, 1H), 3.34-3.23 (m, 2H), 3.07 (d, *J* = 19.6 Hz, 1H), 2.85 (s,

3H), 2.70-2.52 (m, 2H), 2.36-2.16 (m, 2H) 1.71-1.25 (m, 7H), 1.18-1.12 (m, 1H).

MH+ 318.

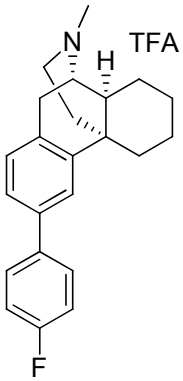
Example 5 : 3-(4-Fluorophenyl)-*N*-(benzyloxycarbonyl)morphinan



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.49 (m, 2H), 7.42-7.13 (m, 7H), 7.16-7.08 (m, 3H), 5.18-5.13 (m, 2H), 4.40 (d, *J* = 42.4 Hz, 1H), 3.99-3.85 (m, 1H), 3.24-3.13 (m, 1H), 2.80-2.72 (m, 2H), 2.49 (d, *J* = 12 Hz, 1H), 1.74-1.25 (m, 9H), 1.11-1.08 (m, 1H).

MH+ 456.

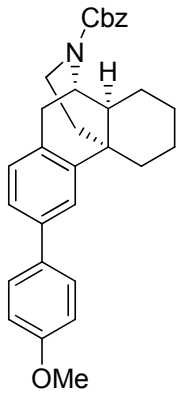
Example 6 : 3-(4-Fluorophenyl)-*N*-methylmorphinan TFA salt



^{1}H NMR (400 MHz, $CDCl_3$) δ 11.70 (s, 1H), 7.50-7.38 (m, 4H), 7.26-7.22 (m, 1H), 7.15-7.11 (m, 2H), 3.64 (s, 1H), 3.32-3.05 (m, 3H), 2.85 (s, 3H), 2.60-2.50 (m, 2H), 2.32-2.14 (m, 2H) 1.71-1.25 (m, 7H), 1.18-1.12 (m, 1H).

MH+ 336.

Example 7 : 3-(4-Methoxyphenyl)-*N*-(benzyloxycarbonyl)morphinan

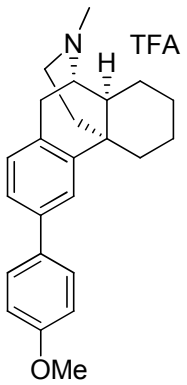


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.8 Hz, 2H), 7.43 (s, 1H), 7.39-7.31 (m, 6H), 7.14-7.12 (m, 1H), 7.97 (d, *J* = 8.8 Hz, 2H), 5.18-5.13 (m, 2H), 4.40 (d, *J* = 41.2

Hz, 1H), 3.94-3.84 (m, 4H), 3.21-3.18 (m, 1H), 2.79-2.73 (m, 2H), 2.49 (d, *J* = 10.8 Hz, 1H), 1.70-1.25 (m, 9H), 1.15-1.09 (m, 1H).

MH+ 468.

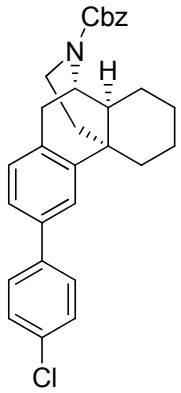
Example 8 : 3-(4-Methoxyphenyl)-*N*-methylmorphinan TFA salt



^{1}H NMR (400 MHz, $CDCl_3$) δ 11.68 (s, 1H), 7.53-7.38 (m, 4H), 7.25-7.20 (m, 1H), 6.98 (d, *J* = 8.4 Hz, 2H), 3.85 (s, 3H), 3.67 (s, 1H), 3.35-3.08 (m, 3H), 2.87 (s, 3H), 2.64-2.50 (m, 2H), 2.35-2.16 (m, 2H) 1.68-1.16 (m, 8H).

MH+ 348.

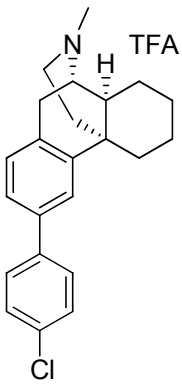
Example 9 : 3-(4-Chlorophenyl)-*N*-(benzyloxycarbonyl)morphinan



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.4 Hz, 2H), 7.43 (s, 1H), 7.39-7.31 (m, 8H), 7.15 (d, *J* = 6.0 Hz, 1H), 5.18-5.13 (m, 2H), 4.41 (d, *J* = 39.2 Hz, 1H), 3.91-3.88 (m, 1H), 3.21-3.17 (m, 1H), 2.80-2.68 (m, 2H), 2.48 (d, *J* = 12.8 Hz, 1H), 1.76-1.25 (m, 9H), 1.13-1.07 (m, 1H).

MH+ 472.

Example 10 : 3-(4-Chlorophenyl)-*N*-methylmorphinan TFA salt

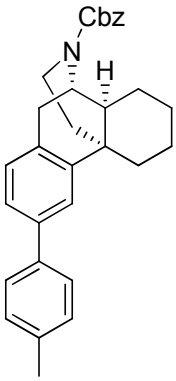


^{1}H NMR (400 MHz, $CDCl_3$) δ 11.39 (s, 1H), 7.48-7.39 (m, 6H), 7.27-7.25 (m, 1H),

3.65 (s, 1H), 3.33-3.26 (m, 2H), 3.22 (d, *J* = 5.6 Hz, 1H), 2.85 (s, 3H), 2.62-2.50 (m, 2H), 2.24 (d, *J* = 12.4 Hz, 1H), 2.15-2.07 (m, 1H) 1.71-1.37 (m, 6H), 1.37-1.25 (m, 1H), 1.17-1.07 (m, 1H).

MH+ 352.

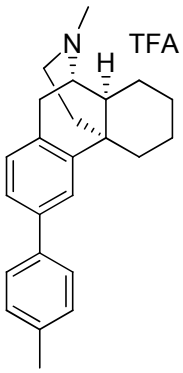
Example 11 : 3-(4-Methylphenyl)-*N*-(benzyloxycarbonyl)morphinan



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.0 Hz, 2H), 7.38-7.29 (m, 7H), 7.24-7.22 (m, 2H), 7.15-7.11 (m, 1H), 5.18-5.13 (m, 2H), 4.40 (d, *J* = 42.8 Hz, 1H), 3.97-3.87 (m, 1H), 3.22-3.15 (m, 1H), 2.80-2.68 (m, 2H), 2.49 (d, *J* = 10.8 Hz, 1H), 2.38 (s, 3H), 1.76-1.25 (m, 9H), 1.12-1.09 (m, 1H).

MH+ 452.

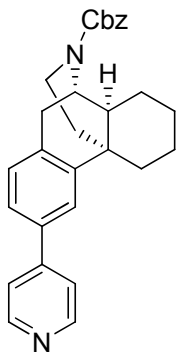
Example 12 : 3-(4-Methylphenyl)-*N*-methylmorphinan TFA salt



^{1}H NMR (400 MHz, $CDCl_3$) δ 11.54 (s, 1H), 7.51-7.41 (m, 4H), 7.26-7.21 (m, 3H), 3.63(s, 1H), 3.35-3.21 (m, 3H), 2.85 (s, 3H), 2.66-2.51 (m, 2H), 2.39 (s, 3H), 2.26 (d, *J* = 12 Hz, 1H), 2.17-2.07 (m, 1H), 1.70-1.40 (m, 6H), 1.34-1.25 (m, 1H), 1.19-1.09 (m, 1H).

MH+ 332.

Example 13 : 3-(Pyridin-4-yl)-*N*-(benzyloxycarbonyl)morphinan

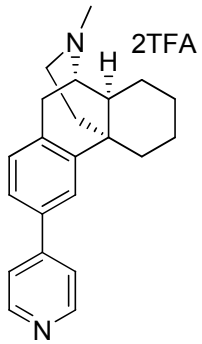


^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, *J* = 4.4 Hz, 2H), 7.54-7.52 (m, 3H), 7.47-7.34 (m, 6H), 7.25-7.19 (m, 1H), 5.18-5.13 (m, 2H), 4.42 (d, *J* = 43.2 Hz, 1H), 3.98-

3.88 (m, 1H), 3.25-3.15 (m, 1H), 2.83-2.63 (m, 2H), 2.49 (d, *J* = 13.2 Hz, 1H), 1.79-1.25 (m, 9H), 1.11-1.05 (m, 1H).

MH+ 439.

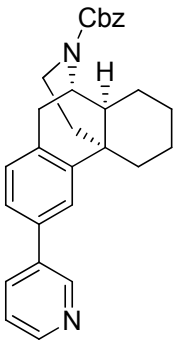
Example 14 : 3-(Pyridin-4-yl)-*N*-methylmorphinan 2TFA salt



^{1}H NMR (400 MHz, $CDCl_3$) δ 11.41 (s, 1H), 8.94 (d, *J* = 5.6 Hz, 2H), 8.05 (d, *J* = 5.6 Hz, 2H), 7.84 (br, 1H), 7.69 (s, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 3.72 (s, 1H), 3.36-3.30 (m, 2H), 3.07 (d, *J* = 4.8 Hz, 1H), 2.88 (d, *J* = 4.4 Hz, 3H), 2.56-2.52 (m, 2H), 2.43 (d, *J* = 12.4 Hz, 1H), 2.33-2.27 (m, 1H), 1.74-1.44 (m, 6H), 1.34-1.17 (m, 1H), 1.13-1.01 (m, 1H).

MH+ 319.

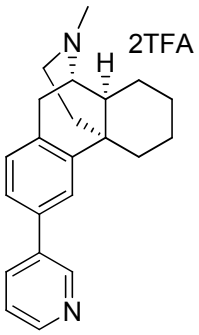
Example 15 : 3-(Pyridin-3-yl)-*N*-(benzyloxycarbonyl)morphinan



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 8.60 (d, *J* = 4.4 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.47-7.08 (m, 9H), 5.21-5.13 (m, 2H), 4.42 (d, *J* = 42 Hz, 1H), 3.99-3.88 (m, 1H), 3.25-3.16 (m, 1H), 2.83-2.61 (m, 2H), 2.48 (d, *J* = 13.2 Hz, 1H), 1.79-1.25 (m, 9H), 1.11-1.03 (m, 1H).

MH+ 439.

Example 16 : 3-(Pyridin-3-yl)-*N*-methylmorphinan 2TFA salt

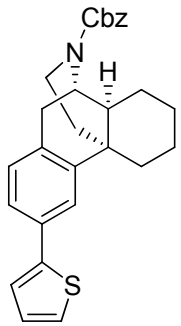


^{1}H NMR (400 MHz, $CDCl_3$) δ 11.24 (s, 1H), 10.48 (br, 1H), 9.13 (s, 1H), 8.84 (d, *J* = 5.6 Hz, 1H), 8.51 (d, *J* = 8.0 Hz, 1H), 7.97 (t, *J* = 6.8 Hz, 1H), 7.57 (s, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.40 (d, *J* = 7.6 Hz, 1H), 3.71 (s, 1H), 3.36-3.27 (m, 2H), 3.07 (d, *J* =

4.8 Hz, 1H), 2.88 (d, *J* = 4.0 Hz, 3H), 2.55-2.52 (m, 2H), 2.30 (d, *J* = 12.0 Hz, 1H), 2.33-2.14 (m, 1H), 1.73-1.41 (m, 6H), 1.26-1.20 (m, 1H), 1.12-1.05 (m, 1H).

MH+ 319.

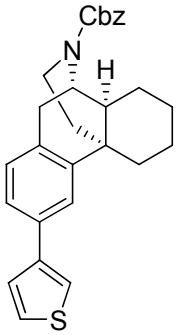
Example 17 : 3-(Thiophen-2-yl)-*N*-(benzyloxycarbonyl)morphinan



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.39-7.24 (m, 8H), 7.10-7.05 (m, 2H), 5.14 (s, 2H), 4.40 (d, J = 33.2 Hz, 1H), 3.90 (m, 1H), 3.18-3.14 (m, 1H), 2.76-2.71 (m, 2H), 2.47 (d, *J* = 12.0 Hz, 1H), 1.75-1.23 (m, 9H), 1.12-1.04 (m, 1H).

MH+ 444.

Example 18 : 3-(Thiophen-3-yl)-*N*-(benzyloxycarbonyl)morphinan



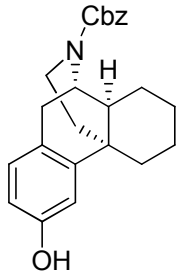
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.49 (m, 1H), 7.40-7.29 (m, 8H), 7.15-7.10 (m, 2H), 5.14 (s, 2H), 4.43 (m, 1H), 3.91 (m, 1H), 3.20-3.15 (m, 1H), 2.77-2.72 (m, 2H), 2.48 (d, *J* = 12.4 Hz, 1H), 1.75-1.23 (m, 9H), 1.14-1.05 (m, 1H).

MH+ 444.

4.3. Examples of 2-substituted (+)-3-HM derivaitves

Example 1: Preparation of (+)-2-Fluoro-3-hydroxymorphinan TFA salt

Step 1: Preparation of (+)-3-Hydroxy-*N*-(benzyloxycarbonyl)morphinan



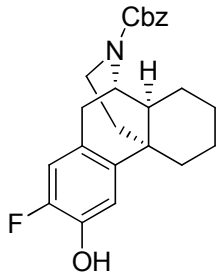
To (+)-3-hydroxymorphinan HBr (50.0 g, 154 mmol) and sodium hydroxide (12.3 g, 308 mmol) in a mixture of 1,4-dioxane (200 mL) and water (200 mL) was added

Cbz-Cl (24.2 mL, 170 mmol) dropwise at rt. The reaction mixture was stirred vigorously at rt overnight. After the reaction was completed, water (200 mL) was added thereto. The resulting mixture was extracted with diethyl ether (500 mL X 2). The combined organic phase was dried over $MgSO_4$, filtered, and evaporated under vacuum. Standing under high vacuum provided the title compound (57.7 g, 99 %) as a light yellow solid. The compound was used for the next step without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.32 (m, 5H), 6.91m, 1H), 6.76 (s, 1H), 6.62 (m, 1H), 5.17-5.12 (m, 2H), 4.35 (d, *J* = 29.25 Hz, 1H), 3.92-3.82 (m, 1H), 3.11-3.03 (m, 1H), 2.72-2.56 (m, 2H), 2.31-2.28 (m, 1H), 1.63-1.26 (m, 10H), 1.11-1.00 (m, 1H).

MH+ 378.

Step 2: Preparation of (+)-2-Fluoro-3-hydroxy-*N*-(benzyloxycarbonyl)morphinan

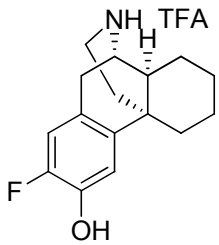


A mixture of (+)-3-hydroxy-*N*-(benzyloxycarbonyl)morphinan (1.13 g, 3 mmol)

and NFPT (0.74 g, 3 mmol) in 1,1,2-trichloroethane (8 mL) was heated at 80 ℃ for 24 hours. The reaction mixture was evaporated to remove the solvent under vacuum. The residue was poured into water (50 mL) and extracted with DCM (50 mL). The combined organic phase was dried over $MgSO_4$ and evaporated under vacuum. The residue was purified by prep. reverse-phase HPLC (Gilson, C18 column) to provide the title compound (0.29 g, 24.5 %).

MH+ 396.

Step 3: Preparation of (+)-2-Fluoro-3-hydroxymorphinan TFA salt

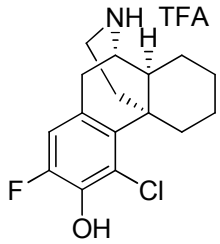


A part of the purified (+)-2-fluoro-3-hydroxy-*N*-(benzyloxycarbonyl)morphinan (224 mg, 0.566 mmol) was dissolved in EtOH (20 mL), and then 10 % Pd on charcoal (45 mg) was added to the solution. The resulting mixture was stirred under hydrogen atmosphere at room temperature for 24 hrs. The reaction mixture thus obtained was filtered to remove the catalyst and evaporated under vacuum. The residue was purified by prep. reverse-phase HPLC (0.1 % TFA added) to provide the title compound (153 mg, 72 %).

^{1}H NMR (400 MHz, CD_3OD) δ 6.92-6.82 (m, 2H), 3.65-3.62 (br, 1H), 3.29-3.20 (m, 1H), 3.15-3.07 (m, 1H), 2.95-2.85 (m, 2H), 2.78-2.70 (m, 1H), 1.90-1.64 (m, 4H), 1.56-1.41 (m, 3H), 1.40-1.09 (m, 3H).

MH+ 262.

Example 2 : Preparation of (+)-4-Chloro-2-fluoro-3-hydroxymorphinan TFA salt

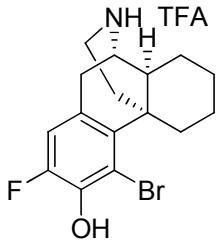


To a solution of crude (+)-2-fluoro-3-hydroxymorphinan TFA salt obtained in Example 1 (357 mg, 1.44 mmol) in glacial acetic acid (15 mL) under nitrogen atmosphere was added sulfuryl chloride (0.233 mL, 2.87 mmol) dropwise. The resulting reaction mixture was stirred overnight and evaporated under vacuum. The residue was purified by prep. reverse-phase HPLC (0.1 % TFA added) to provide the title compound (346 mg, 59 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99-6.88 (m, 1H), 3.59 (br, 1H), 3.30-3.20 (m, 1H), 3.16-3.07 (m, 2H), 2.85 (d, *J* = 13.6 Hz, 1H), 2.72 (br, 1H), 2.07-1.96 (m, 2H), 1.92-1.81 (m, 1H), 1.78-1.60 (m, 3H), 1.51-1.41 (m, 2H), 1.38-1.05 (m, 2H).

MH+ 296.

Example 3 : Preparation of (+)-4-Bromo-2-fluoro-3-hydroxymorphinan TFA salt



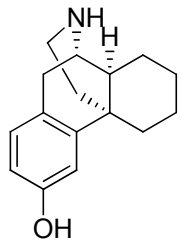
To a solution of crude (+)-2-fluoro-3-hydroxymorphinan TFA salt obtained in Example 1 (357 mg, 1.44 mmol) and TEA (0.95 mL, 7.2 mmol) in glacial acetic acid (15 mL) under nitrogen atmosphere was added dropwise bromine (0.07 mL) in acetic acid (1 mL). After stirring 0.5 hr at rt., the resulting reaction mixture was cooled to 0 ℃. Ammonium hydroxide solution (8.6 mL) was added to the reaction mixture with stirring. The precipitate thus obtained was filtered, washed with water, and purified by prep. reverse-phase HPLC (0.1 % TFA added) to provide the title compound (461 mg, 70 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14-6.92 (m, 1H), 3.62 (br, 1H), 3.35-3.04 (m, 2H), 2.85 (d, *J* = 13.6 Hz, 1H), 2.77-2.71 (m, 1H), 2.14-1.95 (m, 2H), 1.93-1.84 (m, 1H), 1.80-1.60 (m, 3H), 1.51-1.05 (m, 5H).

MH+ 340.

Example 4 : Preparation of (+)-2,4-Dichloro-3-hydroxymorphinan TFA salt

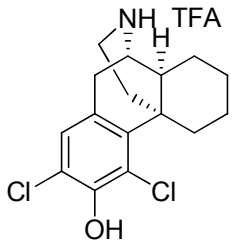
Step 1: Preparation of (+)-3-Hydroxymorphinan



To a solution of (+)-3-hydroxymorphinan HBr (32.4 g, 100 mmol) in 1,4-dioxane (200 mL) was added sodium hydroxide (8.00 g, 200 mmol) in water (200 mL) at 0 ℃. The resulting reaction mixture was stirred for 30 min at r.t. and then EtOAc (100 mL) was added thereto. The mixture thus obtained was stirred for another 30 min and filtered. The filtered cake was dried under high vacuum to provide the title compound (21.9 g, 90 %) as a yellow solid. The compound was used for the next step without further purification.

MH+ 244.

Step 2: Preparation of (+)-2,4-Dichloro-3-hydroxymorphinan TFA salt

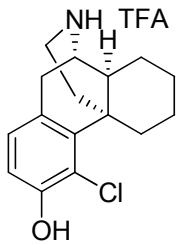


To a solution of (+)-3-hydroxymorphinan (0.973 g, 4 mmol) in glacial acetic acid (40 mL) under nitrogen atmosphere was added sulfuryl chloride (0.65 mL, 8 mmol) dropwise. The resulting reaction mixture was stirred overnight and evaporated under vacuum. The residue was purified by prep. reverse-phase HPLC (0.1 % TFA added) to provide the title compound (0.334 g, 20 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (s, 1H), 3.61-3.57 (br, 2H), 3.29-3.23 (m, 1H), 3.18-3.08 (br, 2H), 2.70 (br, 1H), 2.05 (t, *J* = 13.6 Hz, 2H), 1.85 (t, *J* = 13.6 Hz, 1H), 1.70-1.60 (m, 2H), 1.50-1.41 (m, 2H), 1.31-1.07 (m, 3H).

MH+ 312.

Example 5 : Preparation of (+)-4-Chloro-3-hydroxymorphinan TFA salt



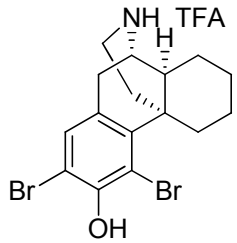
To a solution of (+)-2,4-dichloro-3-hydroxymorphinan (187 mg, 0.439 mmol) in MeOH (15 mL) was added 10 % Pd on charcoal (150 mg). The mixture was stirred

under hydrogen atmosphere at r.t. for 48 hrs. The resulting reaction mixture was filtered to remove the catalyst and evaporated under vacuum. The residue was purified by prep. reverse-phase HPLC (0.1 % TFA added) to provide the title compound (67 mg, 39 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, *J* = 8.4 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 3.61-3.59 (br, 2H), 3.29 (dd, *J* = 18.8, 6.0 Hz, 1H), 3.15-3.05 (br, 2H), 2.73 (br, 1H), 2.05-2.01 (m, 2H), 1.84 (t, *J* = 13.6 Hz, 1H), 1.70-1.60 (m, 2H), 1.50-1.41 (m, 2H), 1.31-1.10 (m, 3H).

MH+ 278.

Example 6 : Preparation of (+)-2,4-Dibromo-3-hydroxymorphinan TFA salt



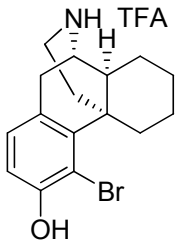
To a solution of (+)-3-hydroxymorphinan HBr (3.24 g, 10 mmol) and TEA (6.97 mL, 50 mmol) in glacial acetic acid (50 mL) under nitrogen atmosphere was added dropwise bromine (1 mL) in 5 mL acetic acid. After stirring 0.5 hr at r.t., the resulting reaction mixture was cooled to 0 ℃. Ammonium hydroxide solution (60 mL) was added to the reaction mixture with stirring. The precipitate was filtered, washed with

water, and purified by prep. reverse-phase HPLC (0.1 % TFA added) to provide the title compound (1.71 g, 33 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 1H), 3.86 (d, *J* = 14.2 Hz, 1H), 3.58 (br, 1H), 3.35-3.28 (m, 1H), 3.20-3.06 (br, 2H), 2.74 (br, 1H), 2.20-2.05 (m, 2H), 1.82 (t, *J* = 13.8 Hz, 1H), 1.72-1.58 (m, 2H), 1.54-1.42 (m, 2H), 1.29-1.04 (m, 3H).

MH+ 402.

Example 7 : Preparation of (+)-4-Bromo-3-hydroxymorphinan TFA salt



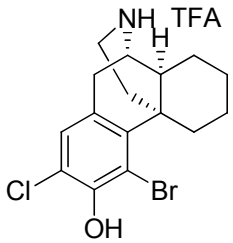
To a solution of 2,4-dibromo-3-hydroxymorphinan TFA salt obtained in Example 6 (1.39 g, 2.70 mmol) in MeOH (50 mL) was added 10 % Pd on charcoal (700 mg) and stirred under hydrogen atmosphere at r.t. for 2 hrs. The resulting reaction mixture was filtered to remove the catalyst and evaporated under vacuum. The residue was purified by prep. reverse-phase HPLC (0.1 % TFA added) to provide the title compound (0.798 g, 68 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, *J* = 8.4 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 3.84 (d, *J* = 14.0 Hz, 1H), 3.58 (br, 1H), 3.32 (dd, *J* = 18.8, 5.6 Hz, 1H), 3.16-3.09 (m,

2H), 2.74 (br, 1H), 2.09 (t, J = 12.0 Hz, 2H), 1.83 (t, J = 10.8 Hz, 1H), 1.69-1.58 (m, 2H), 1.50-1.42 (m, 2H), 1.27-1.09 (m, 3H).

MH+ 322.

Example 8 : Preparation of (+)-4-Bromo-2-chloro-3-hydroxymorphinan TFA salt



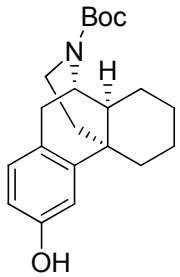
To a solution of 4-bromo-3-hydroxymorphinan TFA salt obtained in Example 7 (0.550 g, 1.26 mmol) in glacial acetic acid (13 mL) under nitrogen atmosphere was added sulfuryl chloride (0.204 mL, 2.52 mmol) dropwise. The resulting reaction mixture was stirred overnight and evaporated under vacuum. The residue was purified by prep. reverse-phase HPLC (0.1 % TFA added) to provide the title compound (0.490 g, 83 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (s, 1H), 3.87 (d, J = 13.2 Hz, 1H), 3.58 (br, 1H), 3.36-3.26 (m, 1H), 3.16-3.08 (br, 2H), 2.73 (br, 1H), 2.16-2.01 (m, 2H), 1.88-1.76 (m, 1H), 1.72-1.57 (m, 2H), 1.52-1.41 (m, 2H), 1.25-1.07 (m, 3H).

MH+ 358.

Example 9 : Preparation of (+)-3-Hydroxy-2-iodomorphinan TFA salt

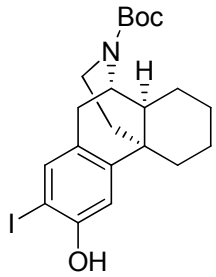
Step 1: Preparation of (+)-3-Hydroxy-*N*-(*tert*-butyloxycarbonyl)morphinan



To (+)-3-hydroxymorphinan HBr (50.0 g, 154 mmol) and sodium hydroxide (13.6 g, 339 mmol) in a mixture of 1,4-dioxane (200 mL) and water (200 mL) was added di-*tert*-butyl dicarbonate (37.0 g, 167 mmol) at r.t. The resulting reaction mixture was stirred vigorously at rt overnight. After the reaction was completed, water (200 mL) was added thereto. The mixture thus obtained was extracted with EtOAc (500 mL X 2). The combined organic phase was dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (47.8 g, 90 %) as a light yellow solid.

MH+ 344.

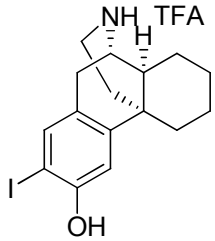
Step 2: Preparation of (+)-3-Hydroxy-2-iodo-*N*-(*tert*-butyloxycarbonyl)morphinan



To a solution of (+)-3-hydroxy-*N*-(*tert*-butyloxycarbonyl)morphinan obtained in step 1 (8.59 g, 25 mmol) in DMF (125 mL) was added dropwise NIS (8.44 g, 37.5 mmol) in DMF (75 mL). The resulting reaction mixture was stirred at room temperature for 3 hrs, and then diluted EtOAc (500 mL). The resulting mixture was washed successively with brine, dried over $MgSO_4$, and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage, silica) to provide the title compound (7.23 g, 15.4 mmol, 62 %).

MH+ 470.

Step 3: Preparation of (+)-3-Hydroxy-2-iodomorphinan TFA salt



The mixture of (+)-3-hydroxy-2-iodo-*N*-(*tert*-butyloxycarbonyl)morphinan obtained in step 2 (345 mg, 0.735 mmol) and a HCl solution (5 mL, 4M in dioxane)

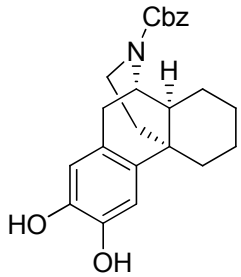
was stirred at r.t. for 18 hrs. The resulting reaction mixture was evaporated under vacuum and the residue was purified by prep. reverse-phase HPLC (0.1 % TFA added) to provide the title compound (247 mg, 70 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 1H), 6.92 (s, 1H), 3.63 (br, 1H), 3.17-3.04 (m, 3H), 2.76 (br, 1H), 2.32 (d, *J* = 13.6 Hz, 1H), 2.04 (d, J = 11.6 Hz, 1H), 1.93 (t, *J* = 12.8 Hz, 1H), 1.68 (d, *J* = 12.8 Hz, 1H), 1.58 (d, *J* = 13.2 Hz, 1H), 1.51-1.38 (m, 3H), 1.28-1.23 (m, 2H), 1.10-1.00 (m, 1H).

MH+ 370.

Example 10 : Preparation of (+)-2,3-Dihydroxymorphinan TFA salt

Step 1: Preparation of (+)-2,3-Dihydroxy-*N*-(benzyloxycarbonyl)morphinan

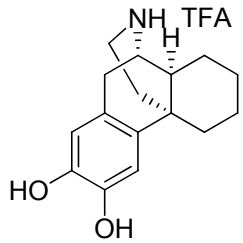


Solid 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide (IBX) (2.24 g, 8 mmol) was added to a solution of (+)-3-hydroxy-*N*-(benzyloxycarbonyl)morphinan obtained in step 1 of Example 1 (1.51 g, 4 mmol) in $CHCl_3$/MeOH (100 mL, 3/2, v/v) at -25 ℃. After stirring for 24 hrs, methanolic $NaBH_4$ (85.1 mg in 5 mL) was added to the resulting reaction mixture at -25 ℃ under vigorous stirring until the orange color disappeared

(within 20 min). The reaction mixture thus obtained was acidified by acetic acid (2 mL), and then diluted with $CHCl_3$/MeOH (150 mL, 2/1, v/v). The resulting mixture was washed three times with PBS buffer solution (100 mL, pH 7.4, containing 10 % sodium dithionite). The organic phase was dried over $MgSO_4$ and evaporated under vacuum. The residue was purified by prep. HPLC (Gilson, C18 column) to provide the title compound (0.229 g, 15 %).

MH+ 394.

Step 2: Preparation of (+)-2,3-Dihydroxymorphinan TFA salt



A part of the purified (+)-2,3-dihydroxy-*N*-(benzyloxycarbonyl)morphinan obtained in step 1 (229 mg, 0.58 mmol) was dissolved in EtOH (15 mL), and then 10 % Pd on charcoal (50 mg) was added thereto. The resulting mixture was stirred under hydrogen atmosphere at r.t. overnight, filtered to remove the catalyst, and evaporated under vacuum. The residue was purified by prep. reverse-phase HPLC (0.1 % TFA added) to provide the title compound (103 mg, 48 %).

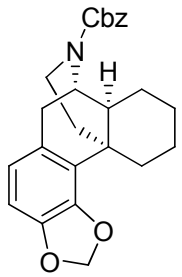
^{1}H NMR (400 MHz, CD_3OD) δ 6.77 (s, 1H), 6.59 (s, 1H), 3.62-3.60 (br, 1H), 3.18

(dd, *J* = 18.8, 6.0 Hz, 1H), 3.08 (d, *J* = 15.6 Hz, 1H), 2.83-2.74 (m, 2H), 2.35 (d, *J* = 8.8 Hz, 1H), 1.85 (d, *J* = 12.4 Hz, 1H), 1.78-1.70 (m, 2H), 1.56-1.28 (m, 6H), 1.20-1.10 (m, 1H).

MH+ 260.

Example 11 : Preparation of (+)-3,4-(Methylenedioxy)morphinan TFA salt

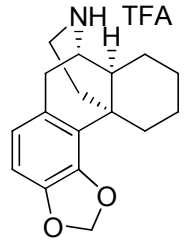
Step 1: Preparation of (+)-3,4-(Methylenedioxy)-*N*-(benzyloxycarbonyl)morphinan



The mixture of 3,4-dihydroxy-*N*-(benzyloxycarbonyl)morphinan (purified from step 2 of Example 10, 150 mg, 0.381 mmol), K_2CO_3 (263 mg, 1.91 mmol) and diiodomethane (510 mg, 1.91 mmol) in acetone/DMF (5 mL, 1/1, v/v) was heated at 150 ℃ for 0.5 hr. The resulting reaction mixture was diluted with 1 M HCl aqueous solution (30 mL), and then extracted with EtOAc (30 mL × 3). The combined EtOAc was washed with brine and evaporated under vacuum. The residue was purified by prep. HPLC (Gilson, C18 column) to provide the title compound (65 mg, 42 %).

MH+ 406.

Step 2: Preparation of (+)-3,4-(Methylenedioxy)morphinan TFA salt



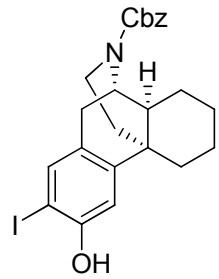
The purified (+)-3,4-(methylenedioxy)-*N*-(benzyloxycarbonyl)morphinan ontained in step 1 (65 mg, 0.16 mmol) was dissolved in MeOH (10 mL), and then 10 % Pd on charcoal (30 mg) was added thereto. The resulting mixture was stirred under hydrogen atmosphere at r.t. for 3 hours, filtered to remove the catalyst, and evaporated under vacuum. The residue was purified by prep. reverse-phase HPLC (0.1 % TFA added) to provide the title compound (34 mg, 55 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (d, *J* = 8.0 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 5.91 (s, 2H), 3.64 (br, 1H), 3.24-3.03 (m, 3H), 2.92-2.82 (m, 2H), 1.95 (d, *J* = 12.0 Hz, 1H), 1.87-1.61 (m, 4H), 1.51-1.36 (m, 2H), 1.30-1.12 (m, 3H).

MH+ 272.

Example 12 : Preparation of (+)-3-Hydroxy-2-methoxymorphinan TFA salt

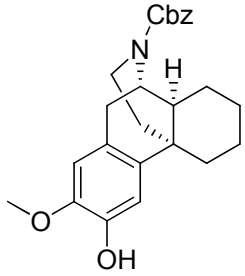
Step 1: Preparation of (+)-3-Hydroxy-2-iodo-*N*-(benzyloxycarbonyl)morphinan



To a solution of (+)-3-hydroxy-*N*-(benzyloxycarbonyl)morphinan obtained in step 1 of Example 1 (3.77 g, 10 mmol) in DMF (50 mL) was added NIS (3.38 g, 15 mmol) in DMF (30 mL). The resulting reaction mixture was stirred at r.t. for 3 hrs. and then diluted EtOAc (300 mL). The resulting mixture was washed successively with brine, dried over $MgSO_4$, and evaporated under vacuum. The residue was purified by prep. HPLC (Gilson, C18 column) to provide the title compound (3.09 g, 61 %).

MH+ 504.

Step 2: Preparation of (+)-3-Hydroxy-2-methoxy-*N*-(benzyloxycarbonyl)morphinan

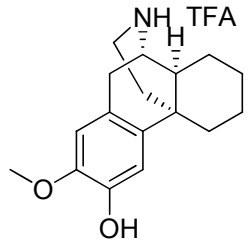


To a mixture of (+)-3-hydroxy-2-iodo-*N*-(benzyloxycarbonyl)morphinan obtained in step 1 (0.805 g, 1.6 mmol) and $CuCl_2$ (71.0 mg, 0.528 mmol) in DMF (6.4 mL) was

added NaOMe (3.6 mL, 25 % in MeOHl). The resulting reaction mixture was heated at 120 ℃ for 0.5 hr, and then filtered to remove solid particle. The resulting solution was purified by prep. reverse-phase HPLC (Gilson, C18 column) to provide the title compound (130 mg, 20 %).

MH+ 408.

Step 3: Preparation of (+)-3-Hydroxy-2-methoxymorphinan TFA salt



To a solution of (+)-3-hydroxy-2-methoxy-*N*-(benzyloxycarbonyl)morphinan obtained in step 2 (130 mg, 0.319 mmol) in MeOH (10 mL) was added 10 % Pd on charcoal (40 mg). The resulting mixture was stirred under hydrogen atmosphere at r.t. overnight. The reaction mixture thus obtained was filtered to remove the catalyst and evaporated under vacuum. The residue was purified by prep. reverse-phase HPLC (0.1 % TFA added) to provide the title compound (92 mg, 74 %).

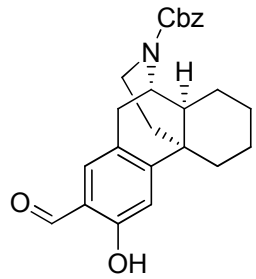
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (s. 1H), 6.62 (s, 1H), 3.88 (s, 3H), 3.64 (br, 1H), 3.16-3.02 (m, 3H), 2.81 (br, 1H), 2.31 (d, *J* = 13.6 Hz, 1H), 2.01 (d, *J* = 12.0 Hz, 1H), 1.86 (t, *J* = 10.4 Hz, 1H), 1.67 (d, *J* = 12.0 Hz, 1H), 1.57-1.26 (m, 6H), 1.16-1.05

(m, 1H).

MH+ 274.

Example 13 : Preparation of (+)-2-Formyl-3-hydroxymorphinan TFA salt

Step 1: Preparation of (+)-2-Formyl-3-hydroxy-*N*-(benzyloxycarbonyl)morphinan



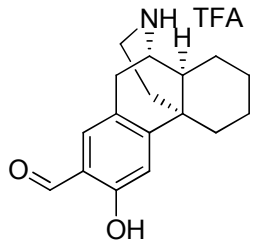
A mixture of (+)-3-hydroxy-*N*-(benzyloxycarbonyl)morphinan obtained in step 1 of Example 1 (5.00 g, 13.2 mmol), $MgCl_2$ (1.89 g, 19.8 mmol), TEA (4.6 mL, 33.0 mmol) and paraformaldehyde (3.98 g, 132 mmol) in acetonitrile (50 mL) was heated within a screw-capped vessel at 110 ℃ for 5 days. The resulting reaction mixture was filtered and washed with EtOAc (200 mL) and water (100 mL). The combined organic phase was dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (3.01 g, 56 %) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.73 (s, 1H), 9.83 (s, 1H), 7.38-7.24 (m, 6H), 6.98 (s, 1H), 5.21-5.10 (m, 2H), 4.47-4.30 (m, 1H), 3.98-3.84 (m, 1H), 3.75 (t, *J* = 6.4 Hz,

1H), 3.18-3.03 (m, 1H), 2.78-2.56 (m, 2H), 2.39-2.31 (m, 1H), 1.87-1.84 (m, 1H), 1.76-1.47 (m, 4H), 1.39-1.22 (m, 3H), 1.07-1.00 (m, 1H).

MH+ 406.

Step 2: Preparation of (+)-2-Formyl-3-hydroxymorphinan TFA salt



(+)-2-Formyl-3-hydroxy-*N*-(benzyloxycarbonyl)morphinan obtained in step 1 (250 mg, 0.617 mmol) was subjected to hydrogenation (balloon) on 10 % Pd/C (25 mg) in IPA (10 mL) at r.t. After the reaction was completed, the resulting reaction mixture was filtered through a Celite, and washed with IPA (20 mL). The combined IPA solution was evaporated under vacuum. The residue was purified by prep. reverse-phase HPLC (0.1 % TFA added) to provide the title compound (75 mg, 31 %) as a yellow solid.

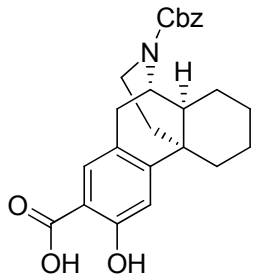
^{1}H NMR (400 MHz, CD_3OD) δ 7.18 (s, 1H), 6.79 (s, 1H), 5.55 (s, 1H), 3.65 (q, *J* = 2.8 Hz, 1H), 3.30-3.21 (m, 1H), 3.08 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.89 (d, *J* = 18.8 Hz, 1H), 2.73 (td, *J* = 13.2, 3.6 Hz, 1H), 2.40 (d, *J* = 14.0 Hz, 1H), 1.88 (d, *J* = 12.8 Hz, 1H), 1.78 (td, *J* = 14.0, 4.8 Hz, 1H), 1.70 (d, *J* = 11.2 Hz, 1H), 1.58-1.48 (m, 3H), 1.44-1.28

(m, 4H), 1.12-1.08 (m, 1H).

MH+ 272.

Example 14 : Preparation of ((+)-3-Hydroxymorphinan)-2-carboxylic acid TFA salt

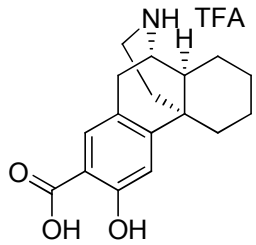
Step 1: Preparation of ((+)-3-Hydroxy-*N*-(benzyloxycarbonyl)morphinan)-2-carboyxlic acid



To a solution of (+)-2-formyl-3-hydroxy-*N*-(benzyloxycarbonyl)morphinan obtained in step 1 of Example 13 (1.20 g, 2.96 mmol) in acetone (50 mL) was added $KMnO_4$ (0.702 g, 4.44 mmol) at 0 ℃. The resulting reaction mixture was allowed to warm to room temperature and stirred overnight. Oxalic acid (2.0 g, 22.2 mmol) was added to the reaction mixture. After stirring for 0.5 hour, the resulting mixture was filtered and diluted with DCM (100 mL). The organic phase was washed with brine, dried over $MgSO_4$, and evaporated under vacuum. The residue was purified by prep. reverse-phase HPLC (Gilson, C18 column) to provide the title comlound (574 mg, 46 %).

MH+ 422.

Step 2: Preparation of ((+)-3-Hydroxymorphinan)-2-carboyxlic acid TFA salt

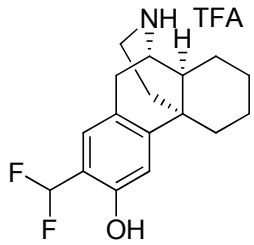


The purified ((+)-3-hydroxy-*N*-(benzyloxycarbonyl)morphinan)-2-carboyxlic acid obtained in step 1 (574 mg, 1.36 mmol) was dissolved in EtOH (30 mL), and then 10 % Pd on charcoal (200 mg) was added thereto. The resulting mixture was stirred under hydrogen atmosphere at r.t. overnight. The reaction mixture thus obtained was filtered to remove the catalyst and evaporated under vacuum. The residue was purified by prep. reverse-phase HPLC (0.1 % TFA added) to provide the title compound (415 mg, 76 %).

^{1}H NMR (400 MHz, CD_3OD) δ 7.71 (s, 1H), 6.94 (s, 1H), 3.69 (m, 1H), 3.61 (br, 1H), 3.10 (dd, *J* = 12.4, 4.4 Hz, 1H), 2.95 (d, *J* = 18.8 Hz, 1H), 2.73 (td, *J* = 13.2, 3.6 Hz, 1H), 2.45 (d, *J* = 14.0 Hz, 1 H), 1.94-1.90 (m, 1H), 1.83 (td, *J* = 14.0, 4.8 Hz, 1H), 1.76-1.68 (m, 1H), 1.64-1.51 (m, 3H), 1.49-1.36 (m, 2H), 1.34-1.22 (m, 1H), 1.14-1.02 (m, 1H).

MH+ 288.

Example 15 : Preparation of (+)-2-(Difluoromethyl)-3-hydroxymorphinan TFA salt



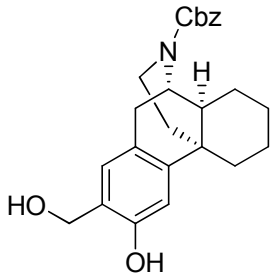
To a solution of (+)-2-formyl-3-hydroxy-*N*-(benzyloxycarbonyl)morphinan obtained in step 1 of Example 13 (339 mg, 0.836 mmol) in DCM (10 mL) was added DAST (0.331 mL, 2.51 mmol). The resulting reaction mixture was stirred at r.t. overnight and then quenched by addition of saturated $NaHCO_3$ aqueous solution (4-5 mL). The resulting mixture was washed successively with water, dried over $MgSO_4$, and evaporated under vacuum. The crude residue was dissolved in EtOH (30 mL), and then 10 % Pd on charcoal (350 mg) was added thereto. The mixture thus obtained was stirred under hydrogen atmosphere at r.t. overnight, filtered to remove the catalyst, and evaporated under vacuum. The residue was purified by prep. reverse-phase HPLC (0.1 % TFA added) to provide the title compound (133 mg, 39 %).

^{1}H NMR (400 MHz, CD_3OD) δ 7.29 (s, 1H), 7.18-6.76 (m, 2H), 3.69-3.66 (m, 1H), 3.26-3.22 (m, 1H), 3.13-3.07 (m, 1H), 2.93 (d, *J* = 18.8 Hz, 1H), 2.77-2.69 (m, 1H), 2.40 (d, *J* = 14.0 Hz, 1H), 1.96-1.67 (m, 3H), 1.62-1.26 (m, 6H), 1.15-1.07 (m, 1H).

MH+ 294.

Example 16 : Preparation of (+)-3-Hydroxy-2-(hydroxymethyl)morphinan TFA salt

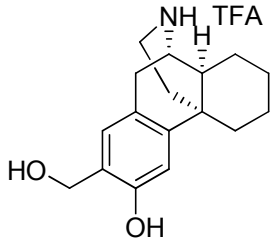
Step 1: Preparation of (+)-3-Hydroxy-2-(hydroxymethyl)-*N*-(benzyloxycarbonyl)morphinan



To a solution of (+)-2-formyl-3-hydroxy-*N*-(benzyloxycarbonyl)morphinan obtained in step 1 of Example 13 (949 mg, 2.34 mmol) in EtOH (25 mL) was added $NaBH_4$ (500 mg, 13.2 mmol). The resulting reaction mixture was stirred at r.t. overnight, and then diluted with 0.5 M HCl aqueous solution (30 mL). The resulting mixture was extracted with DCM (60 mL) and then the organic phase was evaporated under vacuum. The residue was purified by prep HPLC (Gilson, C18 column) to provide the title compound (482 mg, 51 %).

MH+ 408.

Step 2: Preparation of (+)-3-Hydroxy-2-(hydroxymethyl)morphinan TFA salt



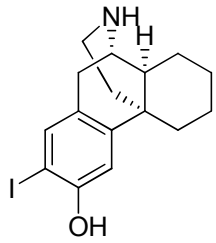
A part of the purified (+)-3-hydroxy-2-(hydroxymethyl)-*N*-(benzyloxycarbonyl)morphinan obtained in step 1 (211 mg, 0.518 mmol) was dissolved in EtOH (10 mL), and then 10 % Pd on charcoal (80 mg) was added thereto. The resulting mixture was stirred under hydrogen atmosphere at r.t. overnight. The reaction mixture thus obtained was filtered to remove the catalyst and evaporated under vacuum. The residue was purified by prep. reverse-phase HPLC (0.1 % TFA added) to provide the title compound (109 mg, 54 %).

^{1}H NMR (400 MHz, CD_3OD) δ 6.98 (s, 1H), 6.77 (s, 1H), 4.71 (d, J = 4.8 Hz, 2H), 3.61 (br, 1H), 3.22-3.16 (m, 1H), 3.09-3.05 (m, 1H), 2.93 (d, J = 18.8 Hz, 1H), 2.76 (td, J = 13.2, 3.2 Hz, 1H), 2.37 (d, J = 13.6 Hz, 1H), 1.93 (d, J = 12.8 Hz, 1H), 1.86-1.78 (m, 1H), 1.75-1.67 (m, 1H), 1.59-1.25 (m, 6H), 1.16-1.07 (m, 1H).

MH+ 274.

Example 17 : Preparation of (+)-2-(Azepan-1-yl)-3-hydroxymorphinan TFA salt

Step 1: Preparation of (+)-3-Hydroxy-2-iodomorphinan

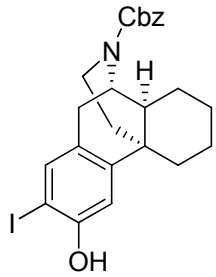


A solution of I_2 (5.08 g, 20.0 mmol) and KI (4.98 g, 30.0 mmol) in water (200 mL) was added dropwise to a stirred solution of (+)-3-hydroxymorphinan HBr (3.24 g, 10 mmol) in 2 N NaOH (65 mL) and water (135 mL). After stirring for 30 min, the resulting reaction mixture was neutralized with dry ice, and the yellowish precipitate was separated by filtration, washed with water, and dried to provide the title compound (3.48 g, 94 %) as a yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.34 (s, 1H), 6.73 (s, 1H), 2.90-2.84 (m, 2H), 2.55 (d, J = 17.2 Hz, 1H), 2.35 (t, J = 12.4 Hz, 1H), 2.09 (d, J = 13.2 Hz, 1H), 1.60-1.53 (m, 2H), 1.43-1.40 (m, 2H), 1.29-1.11 (m, 6H), 0.86-0.83 (m, 1H).

MH+ 370.

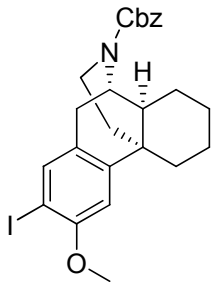
Step 2: Preparation of (+)-3-Hydroxy-2-iodo-*N*-(benzyloxycarbonyl)morphinan



To (+)-3-hydroxy-2-iodomorphinan (29) (3.26 g, 8.83 mmol) and sodium hydroxide (706 mg, 17.7 mmol) in a mixture of 1,4-dioxane (100 mL) and water (100 mL) was added Cbz-Cl (1.39 mL, 9.71 mmol) dropwise at r.t. The resulting reaction mixture was stirred vigorously at r.t. overnight. After the reaction was completed, water (100 mL) was added the reaction mixture. The mixture thus obtained was extracted with diethyl ether (100 mL X 2). The combined organic phase was dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (3.36 g, 76 %) as a white solid.

MH+ 504.

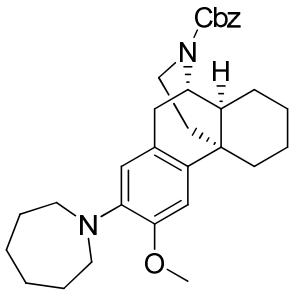
Step 3: Preparation of (+)-2-Iodo-3-methoxy-*N*-(benzyloxycarbonyl)morphinan



To (+)-3-hydroxy-2-iodo-*N*-(benzyloxycarbonyl)morphinan obtained in step 2 (8.36 g, 16.6 mmol) and K_2CO_3 (4.59 g, 33.2 mmol) in acetone (100 mL) was added iodomethane (1.55 mL, 24.9 mmol) at r.t. The resulting reaction mixture was stirred at r.t. overnight. After the reaction was completed, water (200 mL) was added thereto. The mixture thus obtained was extracted with EtOAc (200 mL X 2). The combined organic phase was dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (6.73 g, 78 %) as a white solid.

MH+ 518.

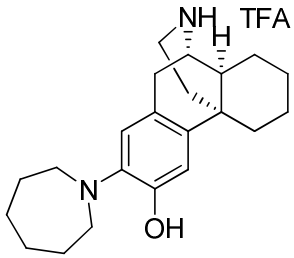
Step 4: Preparation of (+)-2-(Azepan-1-yl)-3-methoxy-*N*-(benzyloxycarbonyl)morphinan



To a solution of (+)-2-iodo-3-methoxy-*N*-(benzyloxycarbonyl)morphinan obtained in step 3 (1.00 g, 1.93 mmol) in THF (10 mL) were added hexamethyleneimine (260 μL, 2.32 mmol), NatBuO (260 mg, 2.71 mmol), $Pd_2(dba)_3$ (17.7 mg, 0.0193 mmol), BINAP (18.0 mg, 0.0289 mmol), and 15-crown-5 (540 μL, 2.71 mmol). The resulting reaction mixture was irradiated in a microwave reactor (Biotage) for 30 min at 165 ℃. After the reaction was completed, water (10 mL) was added thereto. The mixture thus obtained was extracted with EtOAc (15 mL X 2). The combined organic phase was dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (553 mg, 59 %) as a white solid.

MH+ 489.

Step 5: Preparation of (+)-2-(Azepan-1-yl)-3-hydroxymorphinan TFA salt



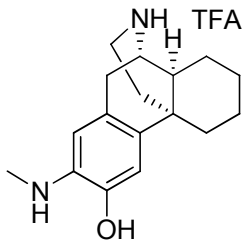
To a solution of (+)-2-(azepan-1-yl)-3-methoxy-*N*-(benzyloxycarbonyl)morphinan obtained in step 4 (553 mg, 1.13 mmol) in DCM (5 mL) was added BBr_3 solution (1M in DCM, 3.4 mL, 3.40 mmol) at 0 ℃. The reaction was quenched by MeOH (2 mL) and the resulting reaction mixture was evaporated under vacuum. The residue was purified by prep. reverse-phase HPLC (0.1 % TFA added) to provide the title compound (21 mg, 4.1 %) as a colorless gum.

^{1}H NMR (400 MHz, CD_3OD) δ 7.45 (s, 1H), 7.04 (s, 1H), 3.77-3.76 (m, 4H), 3.71 (q, *J* = 2.8 Hz, 1H), 3.32-3.25 (m, 1H), 3.12 (dd, *J* = 13.2, 3.2 Hz, 1H), 3.00 (d, *J* = 19.2 Hz, 1H), 2.71 (td, *J* = 13.6, 3.6 Hz, 1H), 2.38 (d, *J* = 14.0 Hz, 1H), 2.68-2.22 (m, 4H), 1.95 (dt, *J* = 12.4, 2.8 Hz, 1H), 1.88-1.80 (m, 5H), 1.69 (d, *J* = 12.4 Hz, 1H), 1.61-1.42 (m, 5H), 1.24-1.21 (m, 1H), 1.05-1.01 (m, 1H).

MH+ 341.

The following compounds of Examples 18 to 24 were obtained by repeating the procedure of Example 17.

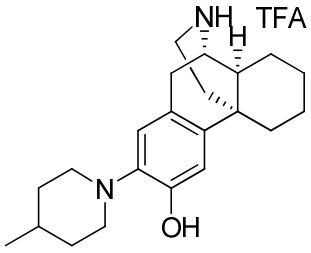
Example 18 : Preparation of (+)-3-Hydroxy-2-(methylamino)morphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.22 (s, 1H), 7.00 (s, 1H), 3.71 (dd, *J* = 5.6, 3.2 Hz, 1H), 3.37-3.28 (m, 1H), 3.12 (dd, *J* = 12.8, 3.6 Hz, 1H), 3.02-2.97 (m, 4H), 2.72 (td, *J* = 13.6, 3.6 Hz, 1H), 2.39 (d, *J* = 14.8 Hz, 1H), 1.97-1.94 (m, 1H), 1.84 (td, *J*= 13.6, 4.8 Hz, 1H), 1.70 (d, *J* = 12.4 Hz, 1H), 1.60-1.43 (m, 5H), 1.29-1.23 (m, 1H), 1.11-1.03 (m, 1H).

MH+ 273.

Example 19 : Preparation of (+)-3-Hydroxy-2-(4-methylpiperidin-1-yl)morphinan TFA salt

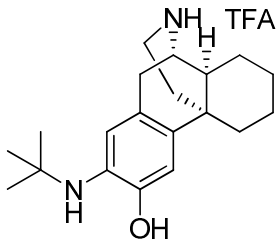


^{1}H NMR (400 MHz, CD_3OD) δ 7.52 (s, 1H), 7.03 (s, 1H), 3.78-3.66 (m, 5H),

3.34-3.28 (m, 2H), 3.13 (dd, *J* = 13.2, 3.2 Hz, 1H), 3.05 (d, *J* = 19.2 Hz, 1H), 2.72 (td, *J* = 13.6, 3.6 Hz, 1H), 2.39 (d, *J* = 14.4 Hz, 1H), 2.04-1.96 (m, 2H), 1.86 (td, *J* = 13.6, 4.8 Hz, 2H), 1.78-1.68 (m, 3H), 1.60-1.40 (m, 5H), 1.27-1.21 (m, 1H), 1.07 (d, *J* = 6.4 Hz, 3H), 1.04-0.99 (m, 1H).

MH+ 341.

Example 20 : Preparation of (+)-2-(*tert*-Butylamino)-3-hydroxymorphinan TFA salt

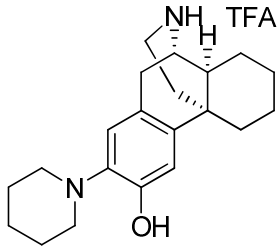


^{1}H NMR (400 MHz, CD_3OD) δ 7.14 (s, 1H), 7.04 (s, 1H), 3.73 (dd, *J* = 6.0, 3.2 Hz, 1H), 3.45-3.28 (m, 1H), 3.14 (dd, *J* = 13.6, 3.6 Hz, 1H), 3.02 (d, *J* = 19.6 Hz, 1H), 2.73 (td, *J* = 13.6, 3.6 Hz, 1H), 2.41 (d, *J* = 14.0 Hz, 1H), 1.98-1.95 (m, 1H), 1.86 (td, *J*= 14.0, 4.4 Hz, 1H), 1.72 (d, *J* = 12.8 Hz, 1H), 1.63-1.37 (m, 14H), 1.30-1.21 (m, 1H), 1.12-1.02 (m, 1H).

MH+ 315.

Example 21 Preparation of (+)-3-Hydroxy-2-(piperidin-1-yl)morphinan TFA

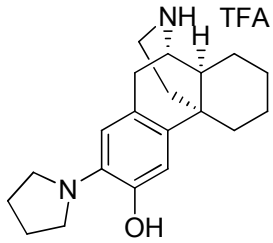
salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.43 (s, 1H), 7.03 (s, 1H), 3.72-3.70 (m, 1H), 3.67-3.64 (m, 4H), 3.12 (dd, *J* = 13.2, 3.2 Hz, 1H), 3.00 (d, *J* = 19.6 Hz, 1H), 2.71 (td, *J* = 13.6, 4.0 Hz, 1H), 2.39 (d, *J* = 14.0 Hz, 1H), 2.06-2.01 (m, 4H), 1.95 (dt, *J* = 12.4, 2.8 Hz, 1H), 1.88-1.68 (m, 4H), 1.61-1.39 (m, 6H), 1.27-1.17 (m, 1H), 1.08-0.98 (m, 1H).

MH+ 327.

Example 22 : Preparation of (+)-3-Hydroxy-2-(pyrrolidin-1-yl)morphinan TFA salt

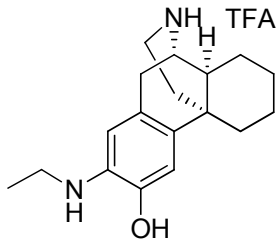


^{1}H NMR (400 MHz, CD_3OD) δ 7.39 (s, 1H), 7.05 (s, 1H), 3.81-3.80 (m, 4H), 3.74-3.71 (m, 1H), 3.14 (dd, *J* = 13.6, 3.2 Hz, 1H), 3.01 (d, *J* = 19.2 Hz, 1H), 2.73 (td, *J* = 13.6, 3.6 Hz, 1H), 2.41 (d, *J* = 14.8 Hz, 1H), 2.30-2.25 (m, 5H), 1.97 (dt, *J* = 12.4, 2.8

Hz, 1H), 1.86 (td, *J* = 13.6, 4.8 Hz, 1H)1.72 (d, *J* = 12.8 Hz, 1H), 1.63-1.41 (m, 5H), 1.31-1.23 (m, 1H), 1.11-1.04 (m, 1H).

MH+ 312.

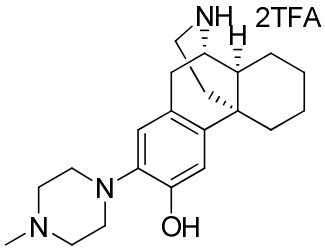
Example 23 : Preparation of (+)-2-Ethylamino-3-hydroxymorphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.24 (s, 1H), 7.01 (s, 1H), 3.72 (dd, *J* = 6.0, 3.2 Hz, 1H), 3.43 (q, *J* = 3.2 Hz, 2H), 3.32-3.26 (m, 1H), 3.13 (dd, *J* = 13.6, 3.6 Hz, 1H), 3.01 (d, *J* = 19.2 Hz, 1H), 2.72 (td, *J* = 13.6, 3.6 Hz, 1H), 2.40 (d, *J* = 14.0 Hz, 1H), 1.96 (dt, *J* = 12.4, 2.8 Hz, 1H), 1.85 (td, *J*= 14.0, 3.2 Hz, 1H), 1.71 (d, *J* = 13.2 Hz, 1H), 1.61-1.38 (m, 5H), 1.35 (t, *J* = 7.6 Hz, 3H), 1.30-1.22 (m, 1H), 1.10-1.00 (m, 1H).

MH+ 287.

Example 24 : Preparation of (+)-3-Hydroxy-2-(4-methylpiperazin-1-yl)morphinan 2TFA salt

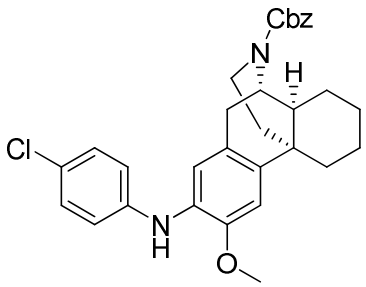


^{1}H NMR (400 MHz, CD_3OD) δ 6.89 (s, 1H), 6.80 (s, 1H), 4.19-4.13 (m, 2H), 3.66-3.64 (m, 1H), 3.55 (d, *J* = 12.8 Hz, 2H), 3.48-3.42 (m, 2H), 3.35-3.21 (m, 5H), 3.08 (dd, *J* = 13.2, 3.6 Hz, 1H), 2.89 (d, *J* = 19.2 Hz, 1H), 2.74 (td, *J* = 13.6, 3.6 Hz, 1H), 2.38 (d, *J* = 13.6 Hz, 1H), 1.89-1.85 (m, 1H), 1.77 (td, *J* = 13.6, 4.8 Hz, 1H), 1.71-1.68 (m, 1H), 1.56-1.48 (m, 3H), 1.43-1.27 (m, 4H), 1.13-1.08 (m, 1H).

MH+ 342.

Example 25 : Preparation of (+)-2-(4-Chlorophenylamino)-3-hydroxymorphinan TFA salt

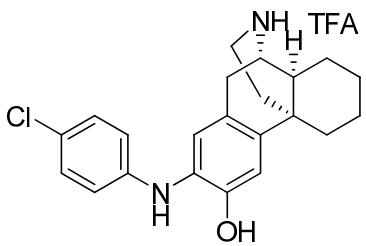
Step 1: Preparation of (+)-2-(4-Chlorophenylamino)-3-methoxy-*N*-(benzyloxycarbonyl)morphinan



To a solution of (+)-2-iodo-3-methoxy-*N*-(benzyloxycarbonyl)morphinan obtained in step 3 of Example 17 (1.00 g, 1.93 mmol) in THF (10 mL) were added 4-chloroaniline (246 mg, 1.93 mmol), NatBuO (186 mg, 1.93 mmol), (dppf)$PdCl_2.CH_2Cl_2$ (63.0 mg, 0.0772 mmol), and dppf (128 mg, 0.232 mmol). The resulting reaction mixture was irradiated in a microwave reactor (Biotage) for 30 min at 155 ℃. After the reaction was completed, water (10 mL) was added thereto. The resulting mixture was extracted with EtOAc (15 mL X 2). The combined organic phase was dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (572 mg, 57 %) as a white solid.

MH+ 517.

Step 2: Preparation of (+)-2-(4-Chlorophenylamino)-3-hydroxymorphinan TFA salt



To a solution of (+)-2-(4-chlorophenylamino)-3-methoxy-*N*-

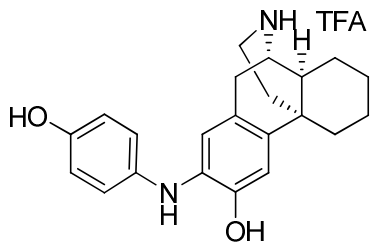
(benzyloxycarbonyl)morphinan obtained in step 1 (572 mg, 1.11 mmol) in DCM (10 mL) was added BBr_3 solution (1M in DCM, 6.7 mL, 6.70 mmol) at 0 ℃. The reaction was quenched by MeOH (2 mL) and the resulting reaction mixture was evaporated under vacuum. The residue was purified by prep. reverse-phase HPLC (0.1 % TFA added) to provide the title compound (335 mg, 75 %) as a brown solid.

^{1}H NMR (400 MHz, CD_3OD) δ 7.15 (d, *J* = 8.8 Hz, 2H), 6.99-6.97 (m, 3H), 6.81 (s, 1H), 3.64-3.61 (m, 1H), 3.21 (dd, *J* = 19.2, 6.0 Hz, 1H), 3.12-3.06 (m, 1H), 2.84-2.72 (m, 2H), 2.45-2.37 (m, 1H), 1.94-1.73 (m, 3H), 1.58-1.33 (m, 6H), 1.23-1.06 (m, 1H).

MH+ 369.

The following compounds of Examples 26 to 71 were obtained by repeating the procedure of Example 25.

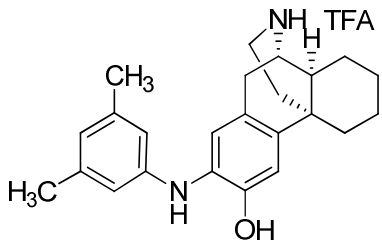
Example 26 : Preparation of (+)-3-Hydroxy-2-(4-hydroxyphenylamino)morphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.00-6.98 (m, 2H), 6.74-6.72 (m, 4H), 3.59-3.56 (m, 1H), 3.14 (dd, *J* = 18.8, 6.0 Hz, 1H), 3.05 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.83-2.72 (m, 2H), 2.35 (d, *J* = 8.4 Hz, 1H), 1.84 (dt, *J* = 12.0, 2.8 Hz, 1H), 1.78-1.70 (m, 2H), 1.56-1.34 (m, 6H), 1.20-1.11 (m, 1H).

MH+ 351.

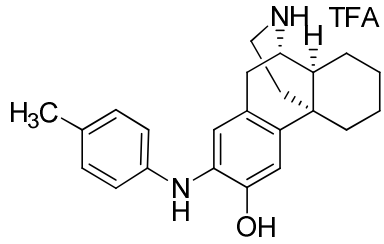
Example 27 : Preparation of(+)-2-(3,5-Dimethylphenylamino)-3-hydroxymorphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 6.97 (s, 1H), 6.78 (s, 2H), 6.67 (s, 1H), 6.51 (s, 1H), 3.62-3.60 (m, 1H), 3.20 (dd, *J* = 19.2, 6.4 Hz, 1H), 3.07 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.85-2.78 (m, 2H), 2.37 (d, *J* = 10.4 Hz, 1H), 2.22 (s, 6H), 1.86 (dt, *J* = 12.0, 2.8 Hz, 1H), 1.80-1.70 (m, 2H), 1.56-1.36 (m, 6H), 1.23-1.16 (m, 1H).

MH+ 363.

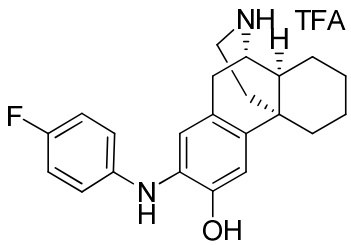
Example 28 : Preparation of (+)-3-Hydroxy-2-(4-methylphenylamino)morphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.04 (d, *J* = 8.4 Hz, 2H), 6.97 (d, *J* = 8.4 Hz, 2H), 6.92 (s, 1H), 6.76 (s, 1H), 3.61-3.58 (m, 1H), 3.17 (dd, *J* = 19.2, 6.4 Hz, 1H), 3.07 (dd, *J* = 12.4, 4.8 Hz, 1H), 2.84-2.76 (m, 2H), 2.36 (d, *J* = 10.8 Hz, 1H), 2.25 (s, 3H), 1.85 (dt, *J* = 12.4, 3.2 Hz, 1H), 1.79-1.69 (m, 2H), 1.55-1.34 (m, 6H), 1.21-1.14 (m, 1H).

MH+ 349.

Example 29 : Preparation of (+)-2-(4-Fluorophenylamino)-3-hydroxymorphinan TFA salt

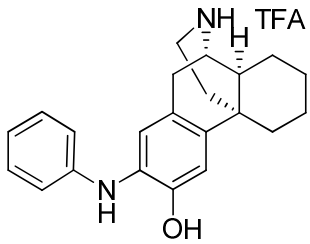


^{1}H NMR (400 MHz, CD_3OD) δ 7.22-7.18 (m, 2H), 7.08-7.03 (m, 2H), 6.99 (s, 1H), 6.85 (s, 1H), 3.66-3.62 (m, 1H), 3.21 (dd, *J* = 19.2, 6.4 Hz, 1H), 3.09 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.86 (d, *J* = 18.8 Hz, 1H), 2.78 (td, *J* = 13.2, 3.6 Hz, 1H), 2.38 (d, *J* = 13.6 Hz, 1H), 1.90 (dt, *J* = 12.0, 3.2 Hz, 1H), 1.79 (td, *J* = 13.6, 4.8 Hz, 1H), 1.71 (d, *J* = 13.2 Hz,

1H), 1.59-1.27 (m, 6H), 1.19-1.09 (m, 1H).

MH+ 353.

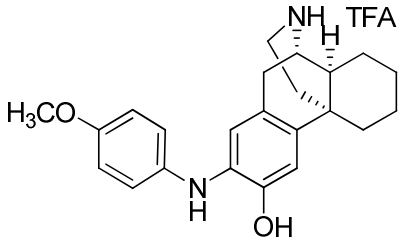
Example 30 : Preparation of (+)-3-Hydroxy-2-(phenylamino)morphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.20 (t, *J* = 8.0 Hz, 2H), 7.04 (dd, *J* = 8.8, 0.8 Hz, 2H), 7.01 (s, 1H), 6.83 (t, *J* = 7.2 Hz, 1H), 6.79 (s, 1H), 3.61-3.59 (m, 1H), 3.20 (dd, *J* = 19.2, 6.4 Hz, 1H), 3.08 (dd, *J* = 12.0, 4.8 Hz, 1H), 2.86-2.77 (m, 2H), 2.38 (d, *J* = 10.8 Hz, 1H), 1.86 (dt, *J* = 12.0, 3.2 Hz, 1H), 1.80-1.70 (m, 2H), 1.57-1.37 (m, 6H), 1.24-1.14 (m, 1H).

MH+ 335.

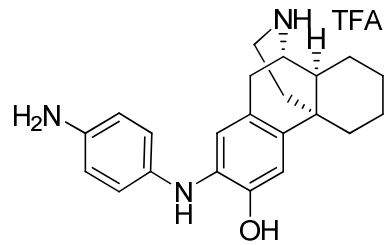
Example 31 : Preparation of(+)-3-Hydroxy-2-(4-methoxyphenylamino)morphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.05 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.76 (s, 1H), 6.74 (s, 1H), 3.75 (s, 3H), 3.58 (dd, *J* = 5.6, 3.2 Hz, 1H), 3.15 (dd, *J* = 19.2, 6.4 Hz, 1H), 3.06 (dd, *J* = 12.4, 3.2 Hz, 1H), 2.85-2.72 (m, 2H), 2.37 (d, *J* = 10.8 Hz, 1H), 1.84 (dt, *J* = 12.0, 3.2 Hz, 1H), 1.75-1.70 (m, 2H), 1.55-1.35 (m, 6H), 1.22-1.14 (m, 1H).

MH+ 365.

Example 32 : Preparation of (+)-2-(4-Aminophenyamino)-3-hydroxymorphinan TFA salt

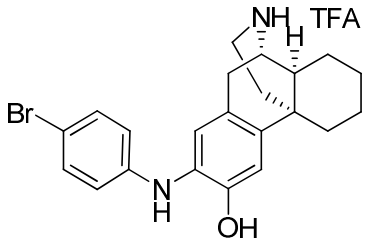


^{1}H NMR (400 MHz, CD_3OD) δ 7.17 (d, *J* = 8.8 Hz, 2H), 7.06 (d, *J* = 8.8 Hz, 2H), 7.03 (s, 1H), 6.84 (s, 1H), 6.79 (s, 1H), 3.65-3.63 (m, 1H), 3.22 (dd, *J* = 18.4, 6.0 Hz, 1H), 3.09 (dd, *J* = 12.8, 3.2 Hz, 1H), 2.87-2.78 (m, 2H), 2.39 (d, *J* = 13.2 Hz, 1H), 1.88

(d, *J* = 12.4 Hz, 1H), 1.82-1.71 (m, 2H), 1.58-1.27 (m, 6H), 1.19-1.15 (m, 1H).

MH+ 350.

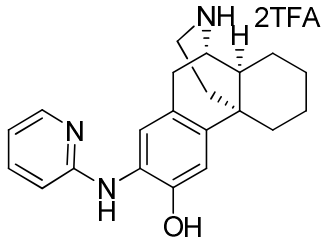
Example 33 : Preparation of (+)-2-(4-Bromophenylamino)-3-hydroxymorphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.28 (d, *J* = 8.8 Hz, 2H), 7.00 (s, 1H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.81 (s, 1H), 3.62 (q, *J* = 2.8 Hz, 1H), 3.22 (dd, *J* = 19.2, 6.4 Hz, 1H), 3.09 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.84-2.74 (m, 2H), 2.39 (d, *J* = 12.8 Hz, 1H), 1.86 (d, *J* = 12.4 Hz, 1H), 1.80-1.72 (m, 2H), 1.58-1.33 (m, 6H), 1.23-1.14 (m, 1H).

MH+ 413.

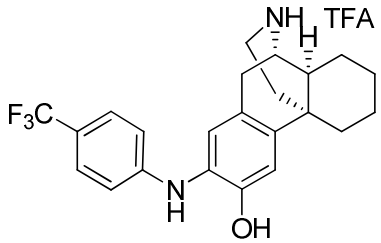
Example 34 : Preparation of (+)-3-Hydroxy-2-(pyridin-2-ylamino)morphinan 2TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.98-7.94 (m, 1H), 7.85-7.83 (m, 1H), 7.14-7.12 (m, 2H), 7.02-6.94 (m, 2H), 3.70-3.69 (m, 1H), 3.26-3.19 (m, 1H), 3.17-3.11 (m, 1H), 2.84-2.74 (m, 2H), 2.46-2.38 (m, 1H), 1.93-1.71 (m, 3H), 1.62-1.35 (m, 6H), 1.16-1.12 (m, 1H).

MH+ 336.

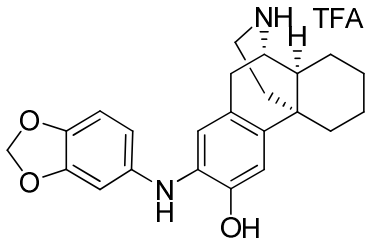
Example 35 : Preparation of (+)-3-Hydroxy-2-(4-(trifluoromethyl)phenylamino)morphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.41 (d, *J* = 8.4 Hz, 2H), 7.09 (s, 1H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.86 (s, 1H), 3.64 (q, *J* = 2.8 Hz, 1H), 3.25 (dd, *J* = 19.2, 6.8 Hz, 1H), 3.10 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.88-2.78 (m, 2H), 2.40 (d, *J* = 12.8 Hz, 1H), 1.88 (d, *J* = 12.8 Hz, 1H), 1.82-1.72 (m, 2H), 1.60-1.34 (m, 6H), 1.27-1.14 (m, 1H).

MH+ 403.

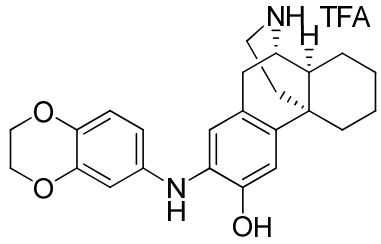
Example 36 : Preparation of (+)-3-Hydroxy-2-((3,4-methylendioxy)phenylamino)morphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 6.81 (s, 1H), 6.75 (s, 1H), 6.71-6.69 (m, 1H), 6.66 (d, *J* = 2.0 Hz, 1H), 6.54 (dd, *J* = 8.0, 2.0 Hz, 1H), 5.87 (s, 2H), 3.59 (q, *J* = 2.8 Hz, 1H), 3.16 (dd, *J* = 19.2, 6.4 Hz, 1H), 3.06 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.84-2.74 (m, 2H), 2.36 (d, *J* = 9.2 Hz, 1H), 1.85 (d, *J* = 12.4 Hz, 1H), 1.79-1.70 (m, 2H), 1.55-1.35 (m, 6H), 1.21-1.13 (m, 1H).

MH+ 379.

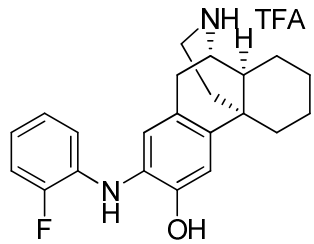
Example 37 : Preparation of (+)-2-((3,4-Ethylenedioxy)phenylamino)-3-hydroxymorphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 6.83 (s, 1H), 6.74 (s, 1H), 6.72 (d, *J* = 7.6 Hz, 1H), 6.58 (td, *J* = 8.4, 2.8 Hz, 2H), 4.19 (dd, *J* = 8.8, 6.0 Hz, 4H), 3.59 (q, *J* = 2.8 Hz, 1H), 3.17 (dd, *J* = 19.2, 6.4 Hz, 1H), 3.06 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.84-2.74 (m, 2H), 2.37 (d, *J* = 7.2 Hz, 1H), 1.84 (d, *J* = 12.0 Hz, 1H), 1.74-1.71 (m, 2H), 1.56-1.35 (m, 6H), 1.24-1.14 (m, 1H).

MH+ 393.

Example 38 : Preparation of (+)-2-(2-Fluorophenylamino)-3-hydroxymorphinan TFA salt

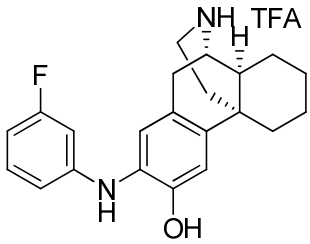


^{1}H NMR (400 MHz, CD_3OD) δ 7.23 (td, *J* = 8.0, 1.2 Hz, 1H), 7.10-7.01 (m, 2H), 6.93 (s, 1H), 6.87-6.82 (m, 2H), 3.62 (q, *J* = 2.8 Hz, 1H), 3.21 (dd, *J* = 19.2, 6.4 Hz, 1H), 3.08 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.85-2.77 (m, 2H), 2.38 (d, *J* = 12.4 Hz, 1H), 1.87

(d, *J* = 12.4 Hz, 1H), 1.81-1.71 (m, 2H), 1.57-1.33 (m, 6H), 1.22-1.16 (m, 1H).

MH+ 353.

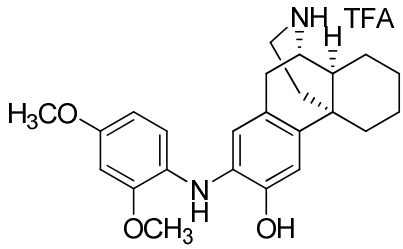
Example 39 : Preparation of (+)-2-(3-Fluorophenylamino)-3-hydroxymorphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.17-12 (m, 1H), 7.04 (s, 1H), 6.83 (s, 1H), 6.79-6.77 (m, 1H), 6.69 (dt, *J* = 11.6, 2.4 Hz, 1H), 6.50-6.45 (m, 1H), 3.63 (q, *J* = 2.8 Hz, 1H), 3.23 (dd, *J* = 19.2, 6.4 Hz, 1H), 3.09 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.87-2.78 (m, 2H), 2.41-2.38 (m, 1H), 1.87 (d, *J* = 12.4 Hz, 1H), 1.81-1.72 (m, 2H), 1.58-1.31 (m, 6H), 1.24-1.14 (m, 1H).

MH+ 353.

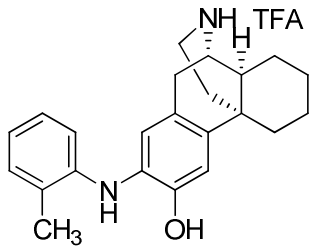
Example 40 : Preparation of (+)-2-(2,4-Dimethoxyphenylamino)-3-hydroxymorphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.16 (br s, 1H), 6.75 (br s, 2H), 6.60 (s, 1H), 6.48 (br s, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.59 (q, *J* = 2.8 Hz, 1H), 3.15 (dd, *J* = 28.8, 7.2 Hz, 1H), 3.06 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.79 (td, *J* = 13.2, 3.6 Hz, 2H), 2.36 (d, *J* = 10.4 Hz, 1H), 1.85 (d, *J* = 12.4 Hz, 1H), 1.78-1.69 (m, 2H), 1.55-1.27 (m, 6H), 1.20-1.11 (m, 1H).

MH+ 395.

Example 41 : Preparation of (+)-3-Hydroxy-2-(2-methylphenylamino)morphinan TFA salt

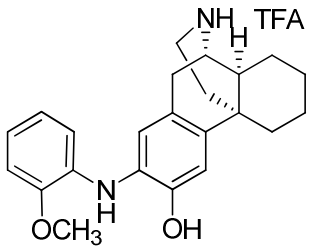


^{1}H NMR (400 MHz, CD_3OD) δ 7.16 (t, *J* = 7.2 Hz, 2H), 7.09 (t, *J* = 7.6 Hz, 1H), 6.88 (td, *J* = 7.2, 1.2 Hz, 1H), 6.78 (s, 1H), 6.67 (s, 1H), 3.59 (q, *J* = 2.8 Hz, 1H), 3.15 (dd, *J* = 19.2, 6.4 Hz, 1H), 3.07 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.84-2.72 (m, 2H), 2.38-2.36

(m, 1H), 2.23 (s, 3H), 1.86-1.83 (m, 3H), 1.56-1.35 (m, 6H), 1.21-1.12 (m, 1H).

MH+ 349.

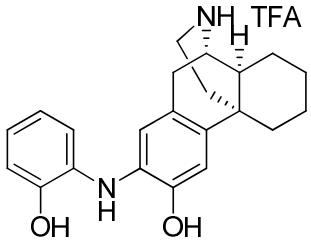
Example 42 : Preparation of (+)-3-Hydroxy-2-(2-methoxyphenylamino)morphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.26-7.22 (m, 1H), 7.06 (s, 1H), 6.96-6.94 (m, 1H), 6.87-6.82 (m, 2H), 6.79 (s, 1H), 3.88 (s, 3H), 3.62 (q, *J* = 3.2 Hz, 1H), 3.22 (dd, *J* = 18.8, 5.6 Hz, 1H), 3.07 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.85-2.78 (m, 2H), 2.38 (d, *J* = 11.2 Hz, 1H), 1.88-1.72 (m, 3H), 1.57-1.36 (m, 6H), 1.27-1.14 (m, 1H).

MH+ 365.

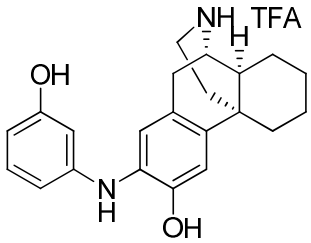
Example 43 : Preparation of (+)-3-Hydroxy-2-(2-hydroxyphenylamino)morphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.22-7.20 (m, 1H), 6.95 (s, 1H), 6.82-6.80 (m, 1H), 6.77-6.73 (m, 3H), 3.60 (q, *J* = 2.8 Hz, 1H), 3.19 (dd, *J* = 19.2, 6.4 Hz, 1H), 3.06 (dd, *J* = 12.0, 3.6 Hz, 1H), 2.84-2.78 (m, 2H), 2.36 (d, *J* = 8.4 Hz, 1H), 1.87-1.69 (m, 3H), 1.55-1.31 (m, 6H), 1.19-1.15 (m, 1H).

MH+ 351.

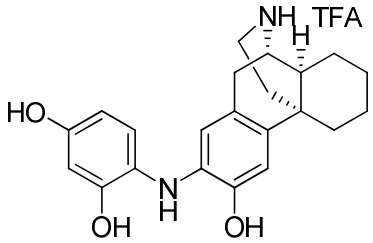
Example 44 : Preparation of(+)-3-Hydroxy-2-(3-hydroxyphenylamino)morphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.03 (s, 2H), 7.00 (s, 1H), 6.79 (s, 2H), 6.51 (s, 1H), 3.61 (q, *J* = 2.8 Hz, 1H), 3.19 (dd, *J* = 19.2, 6.4 Hz, 1H), 3.06 (dd, *J* = 12.0, 3.6 Hz, 1H), 2.80-2.76 (m, 2H), 2.36 (d, *J* = 8.4 Hz, 1H), 1.87-1.69 (m, 3H), 1.55-1.31 (m, 6H), 1.19-1.15 (m, 1H).

MH+ 351.

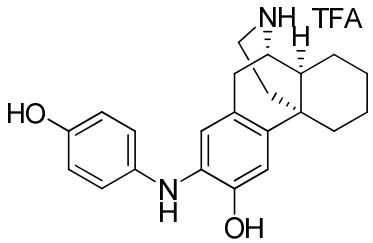
Example 45 : Preparation of (+)-2-(2,4-Dihydroxyphenylamino)-3-hydroxymorphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 6.99 (d, *J* = 8.4 Hz, 1H), 6.74 (s, 1H), 6.55 (s, 1H), 6.39 (s, 1H), 6.28 (d, *J* = 8.0 Hz, 1H), 3.57 (q, *J* = 2.8 Hz, 1H), 3.13 (dd, *J* = 19.2, 6.0 Hz, 1H), 3.04 (dd, *J* = 12.8, 3.2 Hz, 1H), 2.82-2.70 (m, 2H), 2.35 (d, *J* = 8.8 Hz, 1H), 1.85-1.69 (m, 3H), 1.55-1.35 (m, 6H), 1.17-1.13 (m, 1H).

MH+ 367.

Example 46 : Preparation of (+)-2-(4-Hydroxyphenylamino)-3-hydroxymorphinan TFA salt

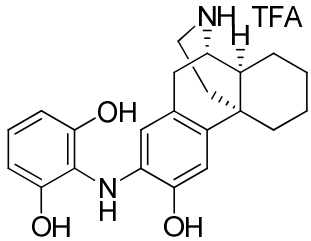


^{1}H NMR (400 MHz, CD_3OD) δ 6.88-6.83 (m, 2H), 6.76-6.66, (m, 3H), 6.54 (s, 1H), 3.59 (q, *J* = 2.8 Hz, 1H), 3.12-3.06 (m, 2H), 2.76-2.72 (m, 2H), 2.40 (d, *J* = 12.4

Hz, 1H), 1.88-1.71 (m, 3H), 1.59-1.31 (m, 6H), 1.16-1.11 (m, 1H).

MH+ 352.

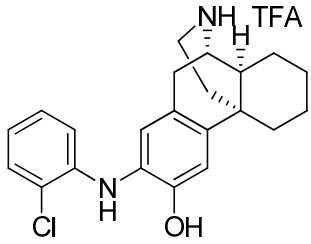
Example 47 : Preparation of (+)-2-(2,6-Dihydroxyphenylamino)-3-hydroxymorphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 6.87 (d, *J* = 8.0 Hz, 1H), 6.72 (s, 1H), 6.41 (d, *J* = 8.0 Hz, 2H), 6.12 (s, 1H), 3.54 (q, *J* = 2.8 Hz, 1H), 3.11-3.00 (m, 2H), 2.79 (td, *J* = 13.2, 3.6 Hz, 1H), 2.67 (d, *J* = 18.8 Hz, 1H), 2.36 (d, *J* = 9.6 Hz, 1H), 1.82-1.68 (m, 3H), 1.53-1.36 (m, 6H), 1.19-1.09 (m, 1H).

MH+ 367.

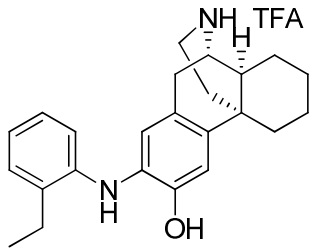
Example 48 : Preparation of (+)-2-(2-Chlorophenylamino)-3-hydroxymorphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.35 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.24 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.15 (td, *J* = 8.0, 1.6 Hz, 1H), 7.03 (s, 1H), 6.84 (s, 1H), 6.81 (td, *J* = 8.0, 1.2 Hz, 1H), 3.63 (q, *J* = 2.8 Hz, 1H), 3.24 (dd, *J* = 19.2, 6.4 Hz, 1H), 3.09 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.86-2.78 (m, 2H), 2.40 (d, *J* = 12.8 Hz, 1H), 1.88 (d, *J* = 12.4 Hz, 1H), 1.81-1.72 (m, 2H), 1.59-1.31 (m, 6H), 1.24-1.15 (m, 1H).

MH+ 369.

Example 49 : Preparation of (+)-2-(2-Ethylphenylamino)-3-hydroxymorphinan TFA salt

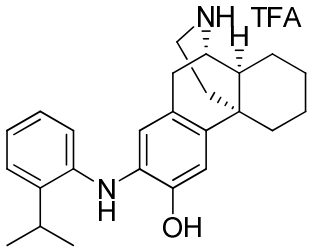


^{1}H NMR (400 MHz, CD_3OD) δ 7.21-7.18 (m, 2H), 7.11 (td, *J* = 7.6, 1.2 Hz, 1H), 6.95 (td, *J* = 7.6, 1.2 Hz, 1H), 6.77 (s, 1H), 6.54 (s, 1H), 3.58 (q, *J* = 2.8 Hz, 1H), 3.14 (dd, *J* = 19.2, 6.4 Hz, 1H), 3.06 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.80-2.71 (m, 2H), 2.62 (q, *J*

= 7.6 Hz, 2H), 2.39-2.37 (m, 1H), 1.84 (d, *J* = 12.4 Hz, 1H), 1.75-1.71 (m, 2H), 1.56-1.35 (m, 7H), 1.19 (t, *J* = 7.6 Hz, 3H).

MH+ 363.

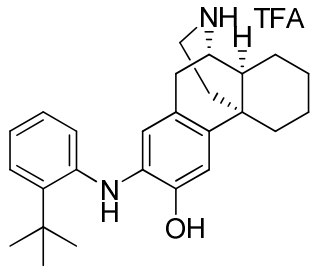
Example 50 : Preparation of(+)-3-Hydroxy-2-(2-isopropylphenylamino)morphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.30 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.19 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.11 (td, *J* = 8.0, 1.6 Hz, 1H), 7.03 (t, *J* = 7.2 Hz, 1H), 6.76 (s, 1H), 6.54 (s, 1H), 3.57 (q, *J* = 2.8 Hz, 1H), 3.20-3.04 (m, 3H), 2.79 (td, *J* = 13.2, 3.6 Hz, 1H), 2.71 (d, *J* = 18.8 Hz, 1H), 2.37 (d, *J* = 10.4 Hz, 1H), 1.84 (d, *J* = 12.0 Hz, 1H), 1.78-1.70 (m, 2H), 1.56-1.38 (m, 7H), 1.21 (d, *J* = 6.8 Hz, 6H).

MH+ 377.

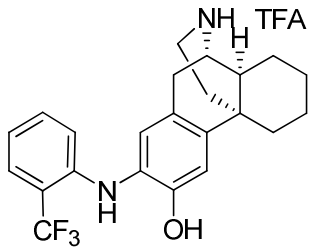
Example 51 : Preparation of (+)-2-(2-*t*-Butylphenylamino)-3-hydroxymorphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.41 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.27 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.14 (td, *J* = 7.6, 1.6 Hz, 1H), 7.01 (td, *J* = 7.6, 1.6 Hz, 1H), 6.76 (s, 1H), 6.55 (s, 1H), 3.56 (q, *J* = 2.8 Hz, 1H), 3.15-3.04 (m, 2H), 2.80-2.68 (m, 2H), 2.38 (d, *J* = 10.4 Hz, 1H), 1.83 (d, *J* = 12.4 Hz, 1H), 1.74-1.70 (m, 2H), 1.56-1.35 (m, 15H), 1.24-1.17 (m, 1H).

MH+ 391.

Example 52 : Preparation of (+)-3-Hydroxy-2-(2-(trifluoromethyl)phenylamino)morphinan TFA salt

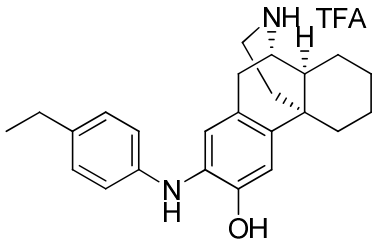


^{1}H NMR (400 MHz, CD_3OD) δ 7.56 (d, *J* = 7.6 Hz, 1H), 7.45-7.38 (m, 2H), 7.01 (s, 1H), 6.97 (t, *J* = 7.6 Hz, 1H), 6.84 (s, 1H), 3.63 (q, *J* = 2.8 Hz, 1H), 3.22 (dd, *J* = 19.2, 6.4 Hz, 1H), 3.09 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.86-2.78 (m, 2H), 2.39 (d, *J* = 12.8

Hz, 1H), 1.88 (d, *J* = 12.8 Hz, 1H), 1.82-1.72 (m, 2H), 1.59-1.31 (m, 6H), 1.24-1.15 (m, 1H).

MH+ 403.

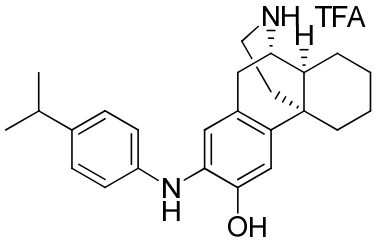
Example 53 : (+)-2-(4-Ethylphenylamino)-3-hydroxymorphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.07 (d, *J* = 8.4 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 6.94 (s, 1H), 6.77 (s, 1H), 3.60 (q, *J* = 2.8 Hz, 1H), 3.18 (dd, *J* = 19.2, 6.4 Hz, 1H), 3.07 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.84-2.76 (m, 2H), 2.56 (q, *J* = 7.6 Hz, 2H), 2.37 (d, *J* = 8.8 Hz, 1H), 1.85 (d, *J* = 12.4 Hz, 1H), 1.78-1.71 (m, 2H), 1.56-1.35 (m, 7H), 1.19 (t, *J* = 7.6 Hz, 3H).

MH+ 363.

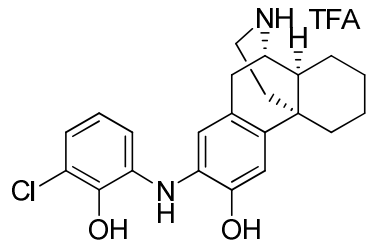
Example 54 : (+)-3-Hydroxy-2-(4-isopropylphenylamino)morphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.10 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 8.4 Hz, 2H), 6.95 (s, 1H), 6.77 (s, 1H), 3.60 (q, *J* = 2.8 Hz, 1H), 3.18 (dd, *J* = 19.2, 6.0 Hz, 1H), 3.07 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.86-2.76 (m, 3H), 2.37 (d, *J* = 9.2 Hz, 1H), 1.85 (d, *J* = 12.0 Hz, 1H), 1.79-1.71 (m, 2H), 1.56-1.36 (m, 7H), 1.21 (d, *J* = 6.8 Hz, 6H).

MH+ 377.

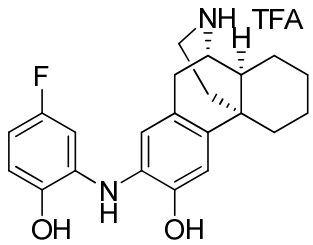
Example 55 : Preparation of (+)-2-(3-Chloro-2-hydroxyphenylamino)-3-hydroxymorphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.12 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.97 (s, 1H), 6.82 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.80 (s, 1H), 6.74 (t, *J* = 8.0 Hz, 1H), 3.61 (q, *J* = 2.8 Hz, 1H), 3.21 (dd, *J* = 19.2, 6.4 Hz, 1H), 3.08 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.85-2.77 (m, 2H), 2.38 (d, *J* = 12.0 Hz, 1H), 1.87 (d, *J* = 12.4 Hz, 1H), 1.84-1.70 (m, 2H), 1.56-1.33 (m, 6H), 1.22-1.15 (m, 1H).

MH+ 385.

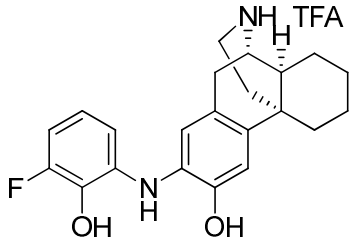
Example 56 : Preparation of(+)-2-(5-Fluoro-2-hydroxyphenylamino)-3-hydroxymorphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.05 (s, 1H), 6.90 (dd, *J* = 10.8, 3.2 Hz, 1H), 6.81 (s, 1H), 6.72 (dd, *J* = 8.4, 5.6 Hz, 1H), 6.36 (td, *J* = 8.4, 2.8 Hz, 1H), 3.63 (q, *J* = 2.8 Hz, 1H), 3.24 (dd, *J* = 18.8, 6.0 Hz, 1H), 3.08 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.89-2.78 (m, 2H), 2.38 (d, *J* = 12.4 Hz, 1H), 1.88 (d, *J* = 12.4 Hz, 1H), 1.85-1.70 (m, 2H), 1.57-1.33 (m, 6H), 1.22-1.16 (m, 1H).

MH+ 369.

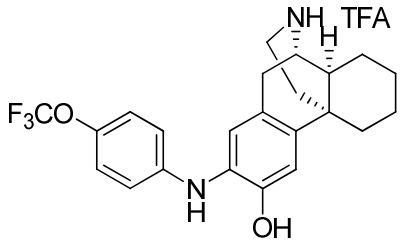
Example 57 : Preparation of (+)-2-(3-Fluoro-2-hydroxyphenylamino)-3-hydroxymorphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 6.85-6.79 (m, 3H), 6.76-6.72 (m, 2H), 3.59 (q, *J* = 2.8 Hz, 1H), 3.17 (dd, *J* = 19.2, 6.0 Hz, 1H), 3.07 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.83-2.76 (m, 2H), 2.36 (d, *J* = 10.8 Hz, 1H), 1.85 (d, *J* = 12.4 Hz, 1H), 1.76-1.69 (m, 2H), 1.55-1.35 (m, 6H), 1.18-1.14 (m, 1H).

MH+ 369.

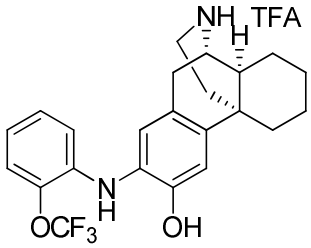
Example 58 : Preparation of (+)-3-Hydroxy-2-(4-(trifluoromethoxy)phenylamino)morphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.10-7.01 (m, 5H), 6.82 (s, 1H), 3.62 (q, *J* = 2.8 Hz, 1H), 3.21 (dd, *J* = 19.2, 6.4 Hz, 1H), 3.09 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.85-2.77 (m, 2H), 2.38 (d, *J* = 12.0 Hz, 1H), 1.87 (d, *J* = 12.4 Hz, 1H), 1.81-1.71 (m, 2H), 1.57-1.33 (m, 6H), 1.22-1.16 (m, 1H).

MH+ 419.

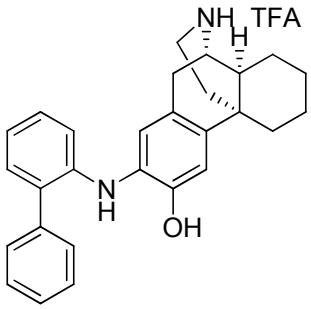
Example 59 : Preparation of (+)-3-Hydroxy-2-(2-(trifluoromethoxy)phenylamino)morphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.31 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.24 (dt, *J* = 8.0, 1.6 Hz, 1H), 7.19 (td, *J* = 8.0, 1.6 Hz, 1H), 7.03 (s, 1H), 6.87 (td, *J* = 8.0, 1.6 Hz, 1H), 6.84 (s, 1H), 3.63 (q, *J* = 2.8 Hz, 1H), 3.23 (dd, *J* = 19.2, 6.4 Hz, 1H), 3.09 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.85-2.78 (m, 2H), 2.39 (d, *J* = 12.8 Hz, 1H), 1.88 (d, *J* = 12.4 Hz, 1H), 1.82-1.71 (m, 2H), 1.58-1.34 (m, 6H), 1.23-1.16 (m, 1H).

MH+ 419.

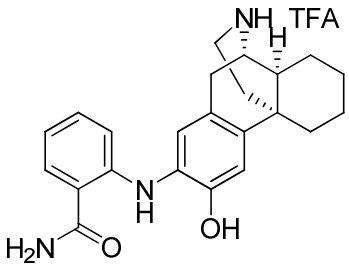
Example 60 : Preparation of (+)-2-(Biphenyl-2-ylamino)-3-hydroxymorphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.40-7.31 (m, 5H), 7.28-7.21 (m, 3H), 6.99 (t, *J* = 7.6 Hz, 1H), 6.83 (s, 1H), 6.68 (s, 1H), 3.58 (q, *J* = 2.8 Hz, 1H), 3.13 (dd, *J* = 19.2, 6.0 Hz, 1H), 3.04 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.78-2.71 (m, 2H), 2.32 (d, *J* = 11.2 Hz, 1H), 1.83 (d, *J* = 12.0 Hz, 1H), 1.80-1.68 (m, 2H), 1.54-1.29 (m, 6H), 1.17-1.09 (m, 1H).

MH+ 411.

Example 61 : Preparation of (+)-2-(2-Carbamoylphenylamino)-3-hydroxymorphinan TFA salt

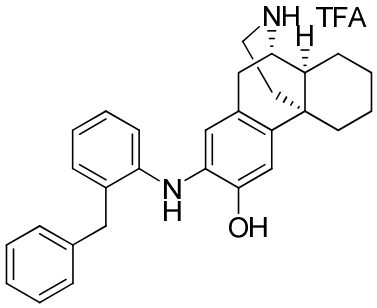


^{1}H NMR (400 MHz, CD_3OD) δ 7.62 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.28 (td, *J* = 8.4, 1.6 Hz, 1H), 7.22 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.10 (s, 1H), 6.84 (s, 1H), 6.86 (td, *J* = 8.0, 1.2 Hz, 1H), 3.63 (q, *J* = 2.8 Hz, 1H), 3.23 (dd, *J* = 18.8, 6.4 Hz, 1H), 3.09 (dd, *J* = 13.2, 3.6 Hz, 1H), 2.86-2.78 (m, 2H), 2.39 (d, *J* = 12.0 Hz, 1H), 1.87 (d, *J* = 12.0 Hz, 1H), 1.81-1.72 (m, 2H), 1.59-1.30 (m, 6H), 1.23-1.15 (m, 1H).

MH+ 378.

Example 62 : Preparation of (+)-2-(2-Benzylphenylamino)-3-

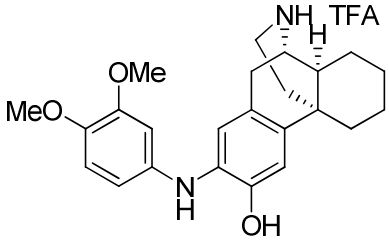
hydroxymorphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.25-7.09 (m, 8H), 6.98 (td, *J* = 7.6, 1.6 Hz, 1H), 6.71 (s, 1H), 6.59 (s, 1H), 3.56 (q, *J* = 2.8 Hz, 1H), 3.13-3.03 (m, 2H), 2.77 (td, *J* = 13.2, 3.6 Hz, 1H), 2.69 (d, *J* = 18.8 Hz, 1H), 2.34 (d, *J* = 7.2 Hz, 1H), 1.82 (d, *J* = 12.4 Hz, 1H), 1.77-1.69 (m, 2H), 1.54-1.33 (m, 6H), 1.19-1.13 (m, 1H).

MH+ 425.

Example 63 : Preparation of (+)-2-(3,4-Dimethoxyphenylamino)-3-hydroxymorphinan TFA salt

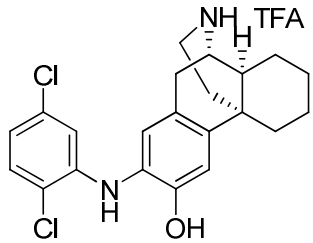


^{1}H NMR (400 MHz, CD_3OD) δ 7.27 (d, *J* = 8.4 Hz, 1H), 7.09 (d, *J* = 2.4 Hz, 1H), 7.12 (s, 1H), 6.97 (dd, *J* = 10.8, 2.4 Hz, 1H), 6.87 (s, 1H), 3.82 (s, 3H), 3.79 (s, 3H),

3.66-3.63 (m, 1H), 3.25 (d, *J* = 6.0 Hz 1H), 3.11 (dd, *J* = 12.0, 3.4 Hz, 1H), 2.77-2.74 (m, 2H), 2.39 (s, 1H), 1.89 (d, *J* = 12.4 Hz, 1H), 1.74 (dd, *J* = 13.6, 4.4 Hz, 1H), 1.70 (s, 1H), 1.59-1.49 (m, 3H), 1.46-1.39 (m, 3H), 1.17 (dd, *J* = 12.8, 4.0 Hz, 1H).

MH+ 395.

Example 64 : Preparation of (+)-2-(2,5-Dichlorophenylamino)-3-hydroxymorphinan TFA salt

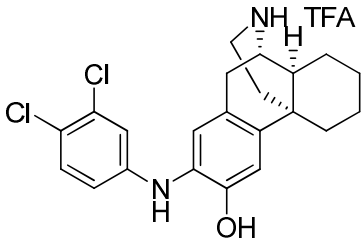


^{1}H NMR (400 MHz, CD_3OD) δ 7.29 (d, *J* = 8.8 Hz, 1H), 7.04 (s, 1H), 6.98 (d, *J* = 2.4 Hz, 1H), 6.89 (s, 1H), 6.75 (dd, *J* = 8.4, 2.4 Hz, 1H), 3.96 (s, 1H), 3.65 (dd, *J* = 3.2, 5.6 Hz, 1H), 3.24 (d, *J* = 6.4 Hz, 1H), 3.11 (dd, *J* = 13.2, 4.4 Hz, 1H), 2.91 (s, 1H), 2.86 (s, 1H), 2.83 (d, *J* = 3.6 Hz, 1H), 2.39 (s, 1H), 1.89 (td, *J* = 12.0, 2.8 Hz, 1H), 1.77 (dd, *J* = 13.6, 4.8 Hz, 1H), 1.73 (s, 1H), 1.61-1.57 (m, 2H), 1.53-1.50 (m, 2H), 1.46-1.37 (m, 3H), 1.18 (dd, *J* = 12.4, 3.6 Hz, 2H).

MH+ 403.

Example 65 : Preparation of (+)-2-(3,4-Dichlorophenylamino)-3-

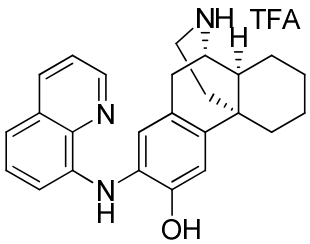
hydroxymorphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.25 (d, *J* = 8.8 Hz, 1H), 7.04 (d, *J* = 2.8 Hz, 1H), 7.00 (s, 1H), 6.87 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.84 (s, 1H), 3.65-3.63 (m, 1H), 3.24 (d, *J* = 6.4 Hz 1H), 3.10 (dd, *J* = 12.4, 3.2 Hz, 1H), 2.87-2.77 (m, 2H), 2.39 (s, 1H), 1.88 (d, *J* = 12.4 Hz, 1H), 1.76 (dd, *J* = 13.6, 4.4 Hz, 1H), 1.72 (s, 1H), 1.59-1.49 (m, 3H), 1.44-1.38 (m, 3H), 1.18 (dd, *J* = 12.8, 4.0 Hz, 1H).

MH+ 403.

Example 66 : Preparation of (+)-3-Hydroxy-2-(quinolin-8-ylamino)morphinan TFA salt

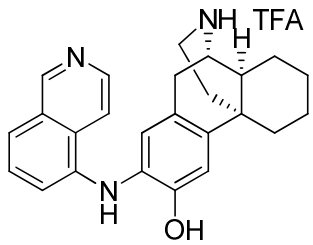


^{1}H NMR (400 MHz, CD_3OD) δ 8.82 (d, *J* = 3.2 Hz, 1H), 8.33 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.56 (dd, *J* = 8.4, 4.4 Hz, 1H) , 7.51 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.47 (t, *J* = 7.6 Hz,

1H), 7.34 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.31 (s, 1H), 6.89 (s, 1H), 3.66-3.65 (m, 1H), 3.33 (d, *J* = 2.4 Hz, 1H), 3.10 (dd, *J* = 12.4, 3.2 Hz, 1H), 2.92-2.87 (m, 2H), 2.42 (s, 1H), 1.90 (d, *J* = 12.4 Hz, 1H), 1.76 (dd, *J* = 13.6, 4.4 Hz, 1H), 1.72 (s, 1H), 1.61-1.50 (m, 3H), 1.42-1.39 (m, 2H), 1.27 (d, *J* = 3.2 Hz, 1H).

MH+ 386.

Example 67 : Preparation of (+)-3-Hydroxy-2-(isoquinolin-5-ylamino)morphinan TFA salt

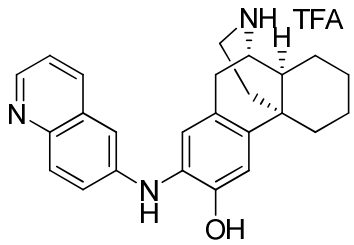


^{1}H NMR (400 MHz, CD_3OD) δ 9.61 (s, 1H), 8.67 (s, 1H), 8.48 (d, *J* = 6.8 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.80 (t, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.02 (s, 1H), 6.95 (s, 1H), 3.65-3.63 (m, 1H), 3.23 (d, *J* = 6.4 Hz, 1H), 3.12 (d, *J* = 12.4 Hz, 1H), 2.89-2.85 (m, 2H), 2.43 (s, 1H), 1.92 (d, *J* = 12.4 Hz, 1H), 1.81 (d, *J* = 13.6 Hz, 1H), 1.72 (s, 1H), 1.64-1.61 (m, 3H), 1.45-1.41 (m, 3H), 1.27 (s, 2H).

MH+ 386.

Example 68 : Preparation of (+)-3-Hydroxy-2-(quinolin-6-ylamino)morphinan

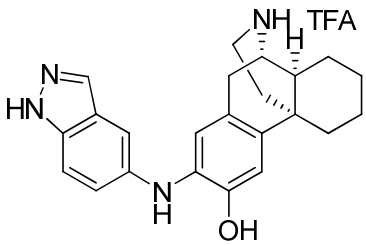
TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 8.77-8.72 (m, 2H), 8.02-7.98 (m, 2H), 7.83-7.81 (m, 2H), 7.35 (d, *J* = 3.2 Hz, 1H), 7.21 (d, *J* = 4.8 Hz, 1H), 6.95 (d, *J* = 4.8 Hz, 1H), 3.69 (s, 1H), 3.14 (d, *J* = 12.0 Hz, 2H), 2.90-2.83 (m, 4H), 2.42 (s, 1H), 2.13 (s, 1H), 1.95-1.91 (m, 1H), 1.83-1.75 (m, 3H), 1.64-1.53 (m, 3H), 1.43 (d, *J* = 10.8 Hz, 1H).

MH+ 386.

Example 69 : Preparation of (+)-3-Hydroxy-2-((1*H*-indazol-5-yl)amino)morphinan TFA salt

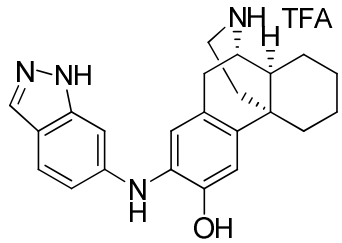


^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (s, 2H), 7.90 (s, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.37 (s, 1H), 7.21 (dd, *J* = 8.8, 1.6 Hz, 1H), 6.85 (s, 1H), 6.75 (s, 1H), 3.97 (s, 1H), 3.58 (s, 1H), 3.06-3.00 (m, 2H), 2.73 (d, *J* = 18.8 Hz, 1H), 2.59-2.56 (m, 1H), 2.26-2.23

(m, 1H), 1.80 (d, *J* = 12.0 Hz, 1H), 1.72-1.62 (m, 2H), 1.51 (d, *J* = 10.4 Hz, 1H), 1.42 (d, *J* = 12.8 Hz, 1H), 1.34-1.26 (m, 3H), 1.00 (q, *J* = 12.8 Hz, 1H).

MH+ 375.

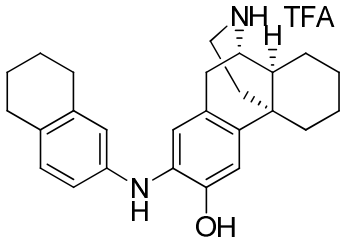
Example 70 : Preparation of (+)-3-Hydroxy-2-((1*H*-indazol-5-yl)amino)morphinan TFA salt



^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63 (s, 2H), 7.85 (s, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.05 (s, 1H), 6.95 (s, 1H), 6.91 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.81 (s, 1H), 3.96 (s, 1H), 3.62 (s, 1H), 3.07 (dd, *J* = 18.8, 6.0 Hz, 2H), 2.80 (d, *J* = 19.2 Hz, 1H), 2.59-2.56 (m, 1H), 2.33-2.24 (m, 1H), 1.82 (d, *J* = 12.4 Hz, 1H), 1.72-1.66 (m, 2H), 1.53 (d, *J* = 11.2 Hz, 1H), 1.45 (d, *J* = 14.0 Hz, 2H), 1.35-1.21 (m, 3H), 1.05-0.99 (m, 1H).

MH+ 375.

Example 71 : Preparation of (+)-3-Hydroxy-2-((5,6,7,8-tetrahydronaphthalen-2-yl)amino)morphinan TFA salt

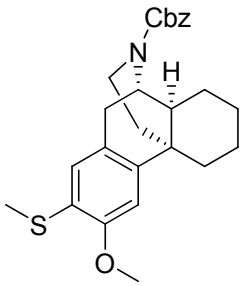


^{1}H NMR (400 MHz, DMSO-d_6) δ 9.303 (s, 1H), 8.56 (s, 2H), 6.89 (d, *J* = 9.2 Hz, 1H), 6.82 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.75 (d, *J* = 17.2 Hz, 2H), 3.59 (s, 1H), 3.42 (s, 1H), 3.04 (dd, *J* = 19.2, 6.4 Hz, 2H), 2.75 (d, *J* = 18.8 Hz, 1H), 2.64-2.57 (m, 1H), 2.23 (d, *J* = 11.2 Hz, 1H), 1.79 (d, *J* = 12.4 Hz, 1H), 1.66-1.62 (m, 2H), 1.51 (d, *J* = 11.6 Hz, 1H), 1.41 (d, *J* = 12.4 Hz, 2H), 1.33-1.20 (m, 3H), 1.04-0.96 (m, 1H).

MH+ 389.

Example 72 : Preparation of (+)-3-Hydroxy-2-methylthiomorphinan TFA salt

Step 1: Preparation of (+)-3-Methoxy-2-methylthio-*N*-(benzyloxycarbonyl)morphinan

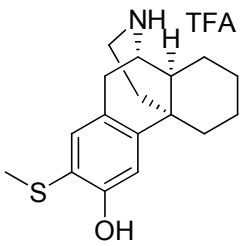


To a solution of (+)-2-iodo-3-methoxy-*N*-(benzyloxycarbonyl)morphinan obtained

in step 3 of Example 17 (533 mg, 1.03 mmol) in EtOH (10 mL) were added NaSMe (86.9 mg, 1.24 mmol), NatBuO (148 mg, 1.55 mmol), and $Pd(PPh_3)_4$ (119 mg, 0.103 mmol). The resulting reaction mixture was irradiated in a microwave reactor (Biotage) for 30 min at 160 ℃. After the reaction was completed, water (10 mL) was added thereto. The resulting mixture was extracted with EtOAc (15 mL X 2). The combined organic phase was dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (385 mg, 85 %) as a white solid.

MH+ 438.

Step 2: Preparation of (+)-3-Hydroxy-2-methylthiomorphinan TFA salt



To a solution of (+)-3-methoxy-2-methylthio-*N*-(benzyloxycarbonyl)morphinan obtained in step 1 (385 mg, 0.880 mmol) in DCM (10 mL) was added BBr_3 solution (1M in DCM, 2.6 mL, 2.60 mmol) at 0 ℃. The reaction was quenched by MeOH (2 mL) and the resulting reaction mixture was evaporated under vacuum. The residue

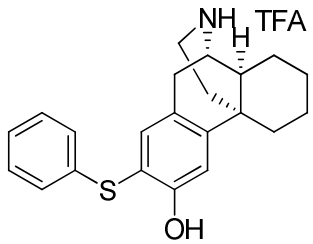
was purified by prep. reverse-phase HPLC (0.1 % TFA added) to provide the title compound (233 mg, 66 %) as a white solid.

^{1}H NMR (400 MHz, CD_3OD) δ 7.03 (s, 1H), 6.77 (s, 1H), 3.65 (dd, *J* = 6.0, 3.2 Hz, 1H), 3.24 (dd, *J* = 19.2, 6.4 Hz, 1H), 3.08 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.90 (d, *J* = 19.2 Hz, 1H), 2.75 (td, *J* = 13.6, 3.6 Hz, 1H), 2.39-2.37 (m, 4H), 1.88 (dt, *J* = 12.8, 3.2 Hz, 1H), 1.78 (td, *J* = 6.0, 4.8 Hz, 1H), 1.70 (d, *J* = 10.8 Hz, 1H), 1.57-1.27 (m, 6H), 1.13-1.09 (m, 1H).

MH+ 290.

The following compound of Example 73 was obtained by repeating the procedure of Example 72.

Example 73 : Preparation of (+)-3-Hydroxy-2-phenylthiomorphinan TFA salt



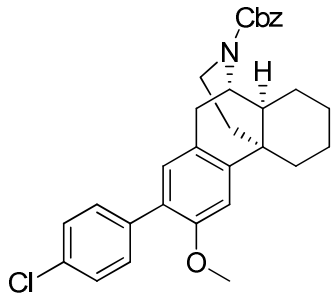
^{1}H NMR (400 MHz, CD_3OD) δ 7.28-7.16 (m, 5H), 7.05 (s, 1H), 6.90 (s, 1H), 3.63 (dd, *J* = 6.0, 3.2 Hz, 1H), 3.18 (dd, *J* = 19.2, 6.4 Hz, 1H), 3.09 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.84-2.71 (m, 2H), 2.44-2.39 (m, 1H), 1.89 (dt, *J* = 12.4, 3.2 Hz, 1H), 1.80 (td, *J* =

13.6, 4.8 Hz, 1H), 1.73 (d, *J* = 13.2 Hz, 1H), 1.61-1.27 (m, 6H), 1.16-1.06 (m, 1H).

MH+ 352.

Example 74 : Preparation of (+)-2-(4-Chlorophenyl)-3-hydroxymorphinan TFA salt

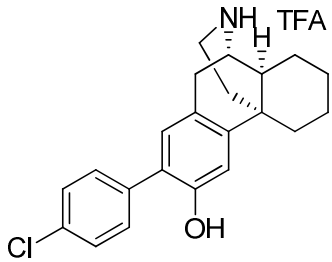
Step 1: (+)-2-(4-Chlorophenyl)-3-methoxy-*N*-(benzyloxycarbonyl)morphinan



To a solution of (+)-2-iodo-3-methoxy-*N*-(benzyloxycarbonyl)morphinan obtained in step 3 of Example 17 (533 mg, 1.03 mmol) in 1,4-dioxane (5 mL) were added 4-chlorophenylboronic acid (324 mg, 2.07 mmol), K_2CO_3 (572 mg, 4.14 mmol), and $Pd(PPh_3)_4$ (119 mg, 0.103 mmol). The resulting reaction mixture was irradiated in a microwave reactor (Biotage) for 30 min at 160 ℃. After the reaction was completed, water (10 mL) was added thereto. The resulting mixture was extracted with EtOAc (15 mL X 2). The combined organic phase was dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (378 mg, 73 %) as a yellow solid.

MH+ 503.

Step 2: Preparation of (+)-2-(4-Chlrophenyl)-3-hydroxymorphinan TFA salt



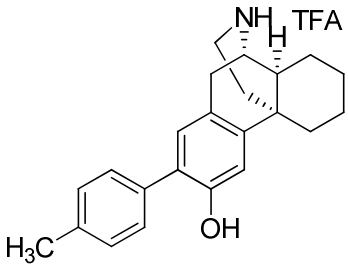
To a solution of (+)-2-(4-chlorophenyl)-3-methoxy-*N*-(benzyloxycarbonyl)morphinan obtained in step 1 (214 mg, 0.427 mmol) in DCM (10 mL) was added BBr_3 solution (1M in DCM, 120 μL, 1.30 mmol) at 0 ℃. The reaction was quenched by MeOH (2 mL) and the resulting reaction mixture was evaporated under vacuum. The residue was purified by prep. reverse-phase HPLC (0.1 % TFA added) to provide the title compound (152 mg, 76 %) as a white solid.

^{1}H NMR (400 MHz, CD_3OD) δ 7.54 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.10 (s, 1H), 6.89 (s, 1H), 3.68 (dd, *J* = 5.6, 3.2 Hz, 1H), 3.27 (dd, *J* = 19.2, 6.0 Hz, 1H), 3.11 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.96 (d, *J* = 18.8 Hz, 1H), 2.81 (td, *J* = 13.6, 3.2 Hz, 1H), 2.42 (d, *J* = 13.2 Hz, 1H), 2.00-1.93 (m, 1H), 1.84 (td, *J* = 14.0, 4.4 Hz, 1H), 1.72 (d, *J* = 12.8 Hz, 1H), 1.66-1.13 (m, 6H), 0.94-0.86 (m, 1H).

MH+ 354.

The following compounds of Examples 75 to 80 were obtained by repeating the procedure of Example 74.

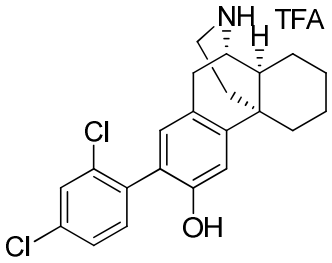
Example 75 : Preparation of (+)-3-Hydroxy-2-(4-methylphenyl)morphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.42 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.08 (s, 1H), 6.87 (s, 1H), 3.67-3.66 (m, 1H), 3.28-3.25 (m, 1H), 3.11 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.94 (d, *J* = 18.8 Hz, 1H), 2.82 (td, *J* = 13.2, 3.2 Hz, 1H), 2.43 (d, *J* = 15.6 Hz, 1H), 2.34 (s, 3H), 2.00-1.91 (m, 1H), 1.82 (td, *J* = 13.6, 4.8 Hz, 1H), 1.73 (d, *J* = 11.2 Hz, 1H), 1.61-1.14 (m, 6H), 0.94-0.88 (m, 1H).

MH+ 334.

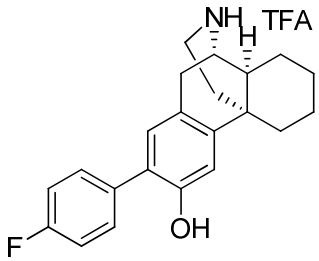
Example 76 : Preparation of (+)-2-(2,4-Dichlorophenyl)-3-hydroxymorphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.50 (d, *J* = 1.6 Hz, 1H), 7.35-7.27 (m, 2H), 6.95 (s, 1H), 6.89 (s, 1H), 3.69-3.66 (m, 1H), 3.33-3.24 (m, 1H), 3.13 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.92 (d, *J* = 18.8 Hz, 1H), 2.82 (td, *J* = 13.2, 3.2 Hz, 1H), 2.44 (d, *J* = 13.2 Hz, 1H), 1.93 (d, *J* = 12.4 Hz, 1H), 1.83 (td, *J* = 13.6, 4.4 Hz, 1H), 1.75 (d, *J* = 12.8 Hz, 1H), 1.64-1.14 (m, 6H), 0.95-0.87 (m, 1H).

MH+ 388.

Example 77 : Preparation of (+)-2-(4-Fluorophenyl)-3-hydroxymorphinan TFA salt

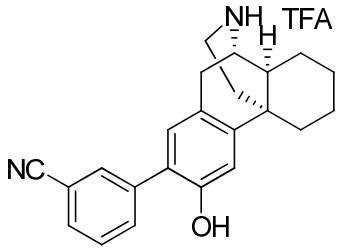


^{1}H NMR (400 MHz, CD_3OD) δ 7.57-7.54 (m, 2H), 7.11-7.07 (m, 3H), 6.88 (s, 1H), 3.67-3.66 (m, 1H), 3.33-3.26 (m, 1H), 3.09 (dd, *J* = 12.4, 4.0 Hz, 1H), 2.93 (d, *J* = 18.8 Hz, 1H), 2.82 (td, *J* = 13.2, 3.6 Hz, 1H), 2.43 (d, *J* = 12.0 Hz, 1H), 1.91 (d, *J* = 12.0 Hz,

1H), 1.82 (td, *J* = 14.0, 4.8 Hz, 1H), 1.74 (d, *J* = 13.6 Hz, 1H), 1.66-1.16 (m, 6H), 0.95-0.88 (m, 1H).

MH+ 338.

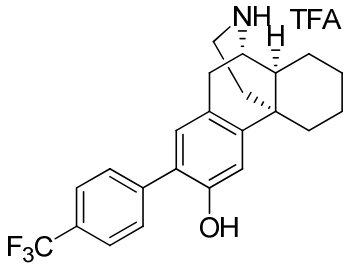
Example 78 : Preparation of (+)-2-(3-Cyanophenyl)-3-hydroxymorphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.96 (s, 1H) 7.91 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.19 (s, 1H), 6.94 (s, 1H), 3.68-3.64 (m, 1H), 3.36-3.31 (m, 1H), 3.14 (dd, *J* = 13.2, 4.0 Hz, 1H), 2.98 (d, *J* = 19.2 Hz, 1H), 2.84 (td, *J* = 13.6, 3.2 Hz, 1H), 2.46 (d, *J* = 13.6 Hz, 1H), 1.95 (d, *J* = 12.4 Hz, 1H), 1.85 (td, *J* = 13.6, 4.4 Hz, 1H), 1.76 (d, *J* = 12.4 Hz, 1H), 1.65-1.29 (m, 6H), 1.23-1.17 (m, 1H).

MH+ 345.

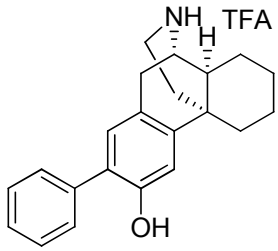
Example 79 : Preparation of (+)-3-Hydroxy-2-(4-trifluorophenyl)morphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 8.04 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.19, (s, 1H), 6.93 (s, 1H), 3.74-3.70 (m, 1H), 3.36-3.30 (m, 1H), 3.14 (dd, *J* = 13.2, 3.6 Hz, 1H), 2.98 (d, *J* = 18.8 Hz, 1H), 2.84 (td, *J* = 13.2, 3.2 Hz, 1H), 2.46 (d, *J* = 12.8 Hz, 1H), 1.95 (d, *J* = 12.4 Hz, 1H), 1.85 (td, *J* = 14.0, 4.4 Hz, 1H), 1.75 (d, *J* = 13.2 Hz, 1H), 1.65-1.40 (m, 6H), 1.20-1.17 (m, 1H).

MH+ 388.

Example 80 : (+)-3-Hydroxy-2-phenylmorphinan TFA salt



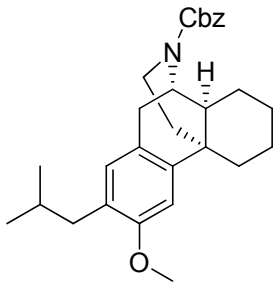
^{1}H NMR (400 MHz, CD_3OD) δ 7.54 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.26 (td, *J* = 8.4, 1.2 Hz, 1H), 7.10, (s, 1H), 6.88 (s, 1H), 3.68-3.67 (m, 1H), 3.33-3.23 (m, 1H), 3.11 (dd, *J* = 12.8, 3.2 Hz, 1H), 2.96 (d, *J* = 19.2 Hz, 1H), 2.83 (td, *J* = 13.6, 3.2 Hz, 1H), 2.44 (d, *J* = 13.2 Hz, 1H), 1.94 (d, *J* = 12.4 Hz, 1H), 1.84 (td, *J* =

13.6, 4.8 Hz, 1H), 1.74 (d, *J* = 12.0 Hz, 1H), 1.62-1.14 (m, 6H), 0.88-0.86 (m, 1H).

MH+ 320.

Example 81 : Preparation of (+)-3-Hydroxy-2-isobutylmorphinan TFA salt

Step 1: Preparation of (+)-2-Isobutyl-3-methoxy-*N*-(benzyloxycarbonyl)morphinan

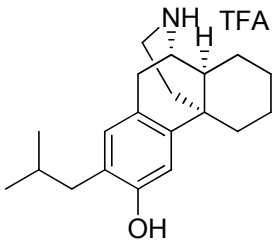


To a solution of (+)-2-iodo-3-methoxy-*N*-(benzyloxycarbonyl)morphinan obtained in step 3 of Example 17 (1.07 g, 2.07 mmol) in 1,4-dioxane (10 mL) were added isobutylboronic acid (211 mg, 2.07 mmol), Cs_2CO_3 (2.70 g, 8.28 mmol), and (dppf)$PdCl_2CH_2Cl_2$ (169 mg, 0.207 mmol). The resulting reaction mixture was irradiated in a microwave reactor (Biotage) for 30 min at 160 ℃. After the reaction was completed, water (10 mL) was added thereto. The resulting mixture was extracted with EtOAc (15 mL X 2). The combined organic phase was dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (207 mg, 22 %)

as a white solid.

MH+ 448.

Step 2: Preparation of (+)-3-Hydroxy-2-isobutylmorphinan TFA salt



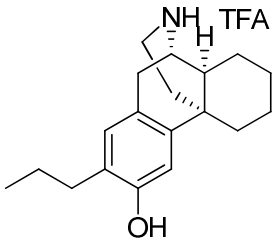
To a solution of (+)-2-Isobutyl-3-methoxy-*N*-(benzyloxycarbonyl)morphinan (40) (346 mg, 0.774 mmol) in DCM (10 mL) was added BBr_3 solution (1M in DCM, 2.3 mL, 2.30 mmol) at 0 ℃. The reaction was quenched by MeOH (2 mL) and the resulting reaction mixture was evaporated under vacuum. The residue was purified by prep. reverse-phase HPLC (0.1 % TFA added) to provide the title compound (91.0 mg, 28 %) as a white solid.

^{1}H NMR (400 MHz, CD_3OD) δ 6.84 (s, 1H), 6.72 (s, 1H), 3.65-3.63 (m, 1H), 3.21 (d, *J* = 18.8 Hz, 1H), 3.07 (d, *J* = 10.8 Hz, 1H), 2.88 (d, *J* = 18.8 Hz, 1H), 2.76-2.72 (m, 1H), 2.42-2.37 (m, 3H), 1.94-1.88 (m, 2H), 1.78 (t, *J* = 12.8 Hz, 1H), 1.70 (d, *J* = 12.0 Hz, 1H), 1.55-1.11 (m, 6H), 0.94-0.91 (m, 1H), 0.88 (d, *J* = 6.4 Hz, 6H).

MH+ 300.

The following compounds of Examples 82 to 85 were obtained by repeating the procedure of Example 81.

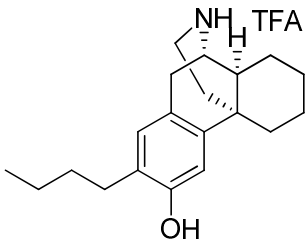
Example 82 : Preparation of (+)-3-Hydroxy-2-propylmorphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 6.87 (s, 1H), 6.72 (s, 1H), 3.65-3.63 (m, 1H), 3.20 (d, *J* = 18.8 Hz, 1H), 3.07 (d, *J* = 11.2 Hz, 1H), 2.87 (d, *J* = 18.4 Hz, 1H), 2.75 (t, *J* = 11.6 Hz, 1H), 2.51 (t, *J* = 7.2 Hz, 2H), 2.38 (d, *J* = 11.6 Hz, 1H), 1.88 (d, *J* = 12.0 Hz, 1H), 1.77-1.68 (m, 2H), 1.61-1.27 (m, 7H), 1.20-1.08 (m, 1H), 0.95-0.90 (m, 4H).

MH+ 286.

Example 83 : Preparation of (+)-2-Butyl-3-hydroxymorphinan TFA salt

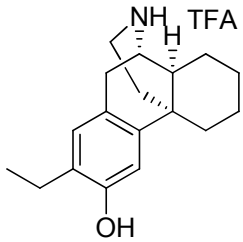


^{1}H NMR (400 MHz, CD_3OD) δ 6.87 (s, 1H), 6.71 (s, 1H), 3.65-3.63 (m, 1H), 3.20

(d, *J* = 18.0 Hz, 1H), 3.06 (d, *J* = 11.2 Hz, 1H), 2.87 (d, *J* = 18.8 Hz, 1H), 2.74 (t, *J* = 11.6 Hz, 1H), 2.53 (t, *J* = 7.6 Hz, 2H), 2.37 (d, *J* = 12.0 Hz, 1H), 1.89 (d, *J* = 11.6 Hz, 1H), 1.81-1.74 (m, 1H), 1.69 (d, *J* = 11.2 Hz, 1H), 1.56-1.13 (m, 10H), 0.92 (t, *J* = 7.6 Hz, 3H), 0.89-0.87 (m, 1H).

MH+ 300.

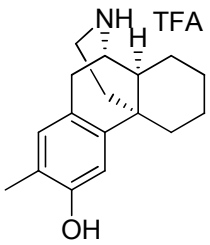
Example 84 : Preparation of (+)-2-Ethyl-3-hydroxymorphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 6.83 (s, 1H), 6.68 (s, 1H), 3.56-3.52 (m, 1H), 3.03-2.83 (m, 3H), 2.19 (d, *J* = 13.2 Hz, 1H), 1.83 (d, *J* = 12.4 Hz, 1H), 1.67 (t, *J* = 11.4 Hz, 1H), 1.57 (d, *J* = 11.6 Hz, 1H), 1.45 (d, *J* = 11.6 Hz, 1H), 1.39-1.14 (m, 7H), 1.09 (t, *J* = 7.6 Hz, 3H), 0.94-0.82 (m, 2H).

MH+ 272.

Example 85 : Preparation of (+)-3-Hydroxy-2-methylmorphinan TFA salt

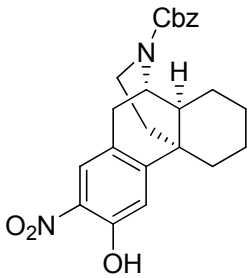


^{1}H NMR (400 MHz, CD_3OD) δ 6.90 (s, 1H), 6.72 (s, 1H), 3.65-3.61 (m, 1H), 3.24-3.18 (m, 1H), 3.07 (d, *J* = 12.8 Hz, 1H), 2.85 (d, *J* = 18.8 Hz, 1H), 2.78-2.74 (m, 1H), 2.39 (d, *J* = 12.0 Hz, 1H), 2.15 (s, 3H), 1.87 (d, *J* = 12.0 Hz, 1H), 1.77-1.70 (m, 2H), 1.55-1.15 (m, 7H).

MH+ 258.

Example 86 : Preparation of (+)-3-Hydroxy-2-morpholinomorphinan TFA salt

Step 1: Preparation of (+)-3-Hydroxy-2-nitro-*N*-(benzyloxycarbonyl)morphinan



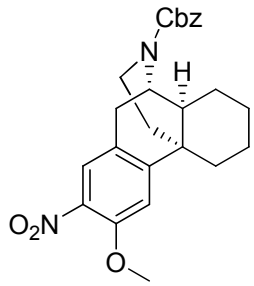
To a solution of (+)-3-hydroxymorphinan (20.7 g, 85.1 mmol) in formic acid (200 mL) was added HNO_3 (70 %, 5.5 mL, 85.1 mmol) at 0 ℃. The resulting reaction mixture was stirred vigorously at r.t. overnight and evaporated under vacuum. The

residue was neutralized by saturated $NaHCO_3$ solution and extracted by EtOAc (200 mL X 2). The combined organic phase was dried over $MgSO_4$, filtered, and evaporated under vacuum. To the residue was added 1,4-dioxane (170 mL) 1N NaOH (170 mL). To the resulting solution was added Cbz-Cl (12.2 mL, 85.1 mmol) at 0 ℃ and then the reaction mixture was stirred at r.t. overnight. After the reaction was completed, water (200 mL) was added thereto. The mixture thus obtained was extracted with diethyl ether (500 mL X 2). The combined organic phase was dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (21.0 g, 58 %) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.36 (s, 1H), 7.85 (s, 1H), 7.38-7.26 (m, 5H), 7.10 (s, 1H), 5.21-5.10 (m, 2H), 4.42 (d, *J* = 46.8 Hz, 1H), 4.00-3.88 (m, 1H), 3.12 (td, *J* = 13.2, 5.2 Hz, 1H), 2.79-2.71 (m, 1H), 2.67-2.54 (m, 1H), 2.36 (d, *J* = 13.6 Hz, 1H), 1.77-1.50 (m, 5H), 1.45-1.17 (m, 4H), 1.02-0.93 (m, 1H).

MH+ 423.

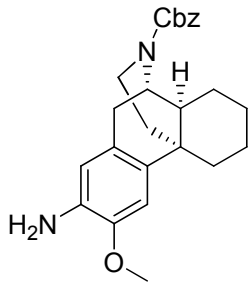
Step 2: Preparation of (+)-3-Methoxy-2-nitro-*N*-(benzyloxycarbonyl)morphinan



To (+)-3-hydroxy-2-nitro-*N*-(benzyloxycarbonyl)morphinan obtained in step 1 (21.0 g, 49.7 mmol) and K_2CO_3 (13.7 g, 99.4 mmol) in acetone (250 mL) was added iodomethane (4.65 mL, 74.6 mmol) at r.t. The reaction mixture was stirred at r.t. overnight. After the reaction was completed, water (300 mL) was added thereto. The resulting mixture was extracted with EtOAc (300 mL X 2). The combined organic phase was dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (21.2 g, 98 %) as a yellow solid.

MH+ 437.

Step 3: Preparation of (+)-2-Amino-3-methoxy-*N*-(benzyloxycarbonyl)morphinan

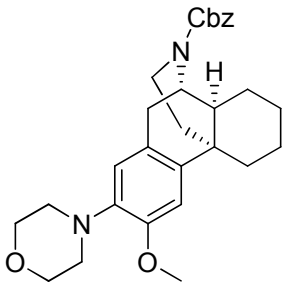


To a solution of (+)-3-methoxy-2-nitro-*N*-(benzyloxycarbonyl)morphinan obtained in step 2 (21.2 g, 48.6 mmol) and hydrazine hydrate (11.8 mL, 243 mmol) in MeOH (100 mL) was added Raney Ni (slurry in water, 1 mL) at r.t. The resulting reaction mixture was stirred at r.t. for 2 hr. After the reaction was completed, the Raney Ni was separated by filtration over celite and the solvent evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (16.6 g, 81 %) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.26 (m, 5H), 6.64 (s, 1H), 6.44 (d, *J* = 10.8 Hz, 1H), 5.20-5.12 (m, 2H), 4.32 (d, *J* = 40.0 Hz, 1H), 3.94-3.82 (m, 4H), 3.01 (td, *J* = 17.6, 5.6 Hz, 1H), 2.76-2.64 (m, 1H), 2.60-2.52 (m, 1H), 2.30 (d, *J* = 9.6 Hz, 1H), 1.64-1.24 (m, 9H), 1.12-1.09 (m, 1H).

MH+ 407.

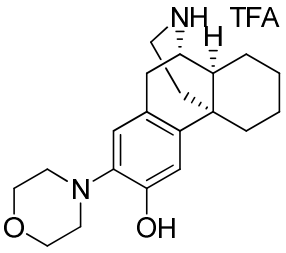
Step 4: **Preparation of (+)-3-Methoxy-2-morpholino-*N*-(benzyloxycarbonyl)morphinan**



To a solution of (+)-2-amino-3-methoxy-*N*-(benzyloxycarbonyl)morphinan obtained in step 3 (1.00 g, 2.46 mmol) and $NaHCO_3$ (454 mg, 5.41 mmol) in DMF (20 mL) was added 2-chloroethyl ether (320 μL, 2.71 mmol) at r.t. The resulting reaction mixture was stirred at 100 ℃ overnight. After the reaction was completed, water (40 mL) was added thereto. The mixture thus obtained was extracted with EtOAc (50 mL X 2). The combined organic phase was dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (1.06 g, 90 %) as a white solid.

MH+ 477.

Step 5: Preparation of (+)-3-Hydroxy-2-morpholinomorphinan TFA salt



To a solution of (+)-3-methoxy-2-morpholino-*N*-(benzyloxycarbonyl)morphinan

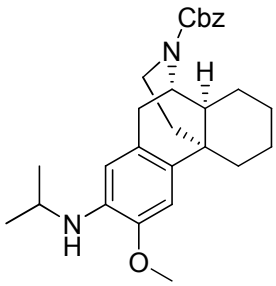
obtained in step 4 (1.06 g, 2.22 mmol) in DCM (10 mL) was added BBr_3 solution (1M in DCM, 6.7 mL, 6.70 mmol) at 0 ℃. The reaction was quenched by MeOH (2 mL) and the resulting reaction mixture was evaporated under vacuum. The residue was purified by prep. reverse-phase HPLC (0.1 % TFA added) to provide the title compound (197 mg, 20 %) as a brown solid.

^{1}H NMR (400 MHz, CD_3OD) δ 7.27 (s, 1H), 6.97 (s, 1H), 4.10-3.94 (m, 4H), 3.71-3.69 (m, 1H), 3.52 (t, *J* = 4.8 Hz, 4H), 3.34-3.24 (m, 1H), 3.11 (dd, *J* = 13.2, 3.6 Hz, 1H), 2.98 (d, *J* = 19.2 Hz, 1H), 2.73 (td, *J* = 13.6, 3.6 Hz, 1H), 2.39 (d, *J* = 14.0 Hz, 1H), 1.95-1.91 (m, 1H), 1.83 (td, *J* = 13.6, 4.8 Hz, 1H), 1.70 (d, *J* = 12.4 Hz, 1H), 1.60-1.38 (m, 5H), 1.29-1.20 (m, 1H), 1.11-1.01 (m, 1H).

MH+ 329.

Example 87 : Preparation of (+)-3-Hydroxy-2-isopropylaminomorphinan TFA salt

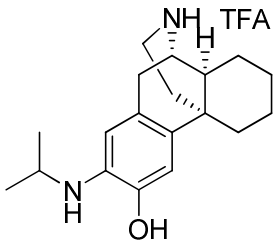
Step 1: Preparation of (+)-2-Isopropylamino-3-methoxy-*N*-(benzyloxycarbonyl)morphinan



To a solution of (+)-2-amino-3-methoxy-*N*-(benzyloxycarbonyl)morphinan obtained in step 3 of Example 86 (1.00 g, 2.46 mmol) in 1,2-dichloroethane (20 mL) was added acetone (540 μL, 7.38 mmol) at r.t. After stirring for 10 min at r.t., $NaBH(OAc)_3$ (1.56 g, 7.38 mmol) was added thereto. The resulting mixture was stirred overnight and washed with saturated $NaHCO_3$. The combined water layer was extracted EtOAc (50 mL X 2). The combined organic phase was dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (843 mg, 76 %) as a white solid.

MH+ 449.

Step 2: Preparation of (+)-3-Hydroxy-2-isopropylaminomorphinan TFA salt



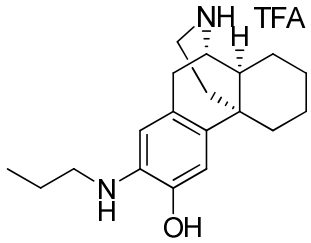
To a solution of (+)-2-isopropylamino-3-methoxy-*N*-(benzyloxycarbonyl)morphinan obtained in step 1 (843 mg, 1.88 mmol) in DCM (10 mL) was added BBr_3 solution (1M in DCM, 5.64 mL, 5.64 mmol) at 0 ℃. The reaction was quenched by MeOH (2 mL) and the resulting reaction mixture was evaporated under vacuum. The residue was purified by prep. reverse-phase HPLC (0.1 % TFA added) to provide the title compound (508 mg, 65 %) as a colorless gum.

^{1}H NMR (400 MHz, CD_3OD) δ 7.24 (s, 1H), 7.04 (s, 1H), 3.84-3.81 (m, 1H), 3.75-3.73 (m, 1H), 3.33-3.32 (m, 1H), 3.14 (dd, *J* = 13.6, 3.6 Hz, 1H), 3.06 (d, *J* = 19.2 Hz, 1H), 2.73 (td, *J* = 13.6, 3.6 Hz, 1H), 2.41 (d, *J* = 13.6 Hz, 1H), 2.00 (dt, *J* = 12.8, 3.2 Hz, 1H), 1.88 (td, *J* = 14.0, 4.8 Hz, 1H), 1.71 (d, *J* = 12.4 Hz, 1H), 1.62-1.40 (m, 5H), 1.37 (d, *J* = 6.8 Hz, 6H), 1.31-1.23 (m, 1H), 1.08-1.03 (m, 1H).

MH+ 301.

The following compounds of Examples 88 to 101 were obtained by repeating the procedure of Example 87.

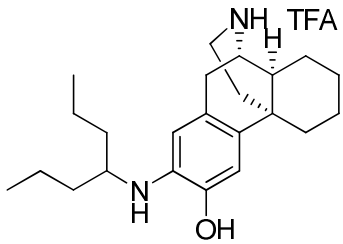
Example 88 : Preparation of (+)-3-Hydroxy-2-propylaminomorphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.16 (s, 1H), 7.00 (s, 1H), 3.71-3.68 (m, 1H), 3.32-3.25 (m, 3H), 3.12 (dd, *J* = 13.6, 3.6 Hz, 1H), 2.96 (d, *J* = 19.2 Hz, 1H), 2.72 (td, *J* = 13.6, 3.6 Hz, 1H), 2.39 (d, *J* = 13.6 Hz, 1H), 1.94 (dt, *J* = 12.8, 3.2 Hz, 1H), 1.87-1.69 (m, 4H), 1.60-1.39 (m, 5H), 1.29-1.23 (m, 1H), 1.11-1.07 (m, 1H), 1.03 (t, *J* = 7.2 Hz, 3H).

MH+ 301.

Example 89 : Preparation of (+)-2-(Heptan-4-ylamino)-3-hydroxymorphinan TFA salt

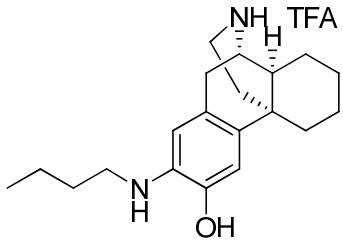


^{1}H NMR (400 MHz, CD_3OD) δ 7.17 (s, 1H), 7.03 (s, 1H), 3.71 (dd, *J* = 6.0, 3.2 Hz, 1H), 3.60-3.57 (m, 1H), 3.32-3.25 (m, 1H), 3.13 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.98 (d, *J* = 19.6 Hz, 1H), 2.70 (td, *J* = 13.6, 3.6 Hz, 1H), 2.40 (d, *J* = 14.0 Hz, 1H), 1.96 (dt, *J* = 12.4, 2.8 Hz, 1H), 1.84 (td, *J* = 13.6, 4.8 Hz, 1H), 1.72-1.35 (m, 14H), 1.25-1.22 (m,

1H), 1.09-1.03 (m, 1H), 0.92 (t, *J* = 7.2 Hz, 6H).

MH+ 357.

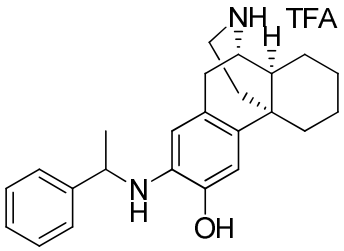
Example 90 : Preparation of (+)-2-Butylamino-3-hydroxymorphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.20 (s, 1H), 7.01 (s, 1H), 3.70 (dd, *J* = 6.0, 3.2 Hz, 1H), 3.36-3.24 (m, 3H), 3.12 (dd, *J* = 13.6, 3.6 Hz, 1H), 2.97 (d, *J* = 19.2 Hz, 1H), 2.71 (td, *J* = 13.6, 3.6 Hz, 1H), 2.39 (d, *J* = 14.0 Hz, 1H), 1.95 (dt, *J* = 12.4, 3.2 Hz, 1H), 1.84 (td, *J* = 14.0, 4.8 Hz, 1H), 1.76-1.68 (m, 3H), 1.61-1.39 (m, 7H), 1.29-1.22 (m, 1H), 1.10-1.00 (m, 1H), 0.97 (t, *J* = 7.2 Hz, 3H).

MH+ 315.

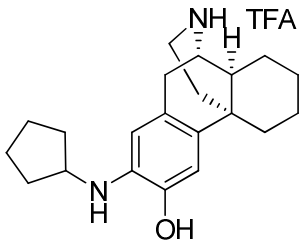
Example 91 : Preparation of (+)-3-Hydroxy-2-(1-phenylethylamino)morphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.36-7.32 (m, 5H) 6.94 (s, 1H), 6.65 (d, *J* = 14.8 Hz, 1H), 4.81-4.80 (m, 1H), 3.62 (dd, *J* = 5.6, 3.2 Hz, 1H), 3.11-2.96 (m, 2H), 2.80 (d, *J* = 19.2 Hz, 1H), 2.68-2.63 (m, 1H), 2.35 (d, *J* = 14.0 Hz, 1H), 1.89 (d, *J* = 12.0 Hz, 1H), 1.83-1.67 (m, 5H), 1.59-1.37 (m, 5H), 1.22-1.16 (m, 1H), 1.04-0.84 (m, 1H).

MH+ 363.

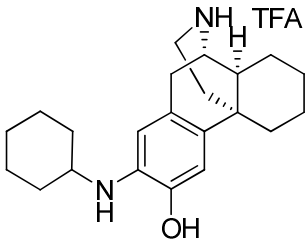
Example 92 : (+)-2-Cyclopentylamino-3-hydroxymorphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.17 (s, 1H), 7.01 (s, 1H), 4.05-3.99 (m, 1H), 3.70 (dd, *J* = 6.0, 3.2 Hz, 1H), 3.33-3.25 (m, 1H), 3.12 (dd, *J* = 13.2, 3.6 Hz, 1H), 2.97 (d, *J* = 19.2 Hz, 1H), 2.71 (td, *J* = 13.6, 3.6 Hz, 1H), 2.39 (d, *J* = 14.0 Hz, 1H), 2.00-1.38 (m, 16H), 1.29-1.09 (m, 1H), 1.07-1.00 (m, 1H).

MH+ 327.

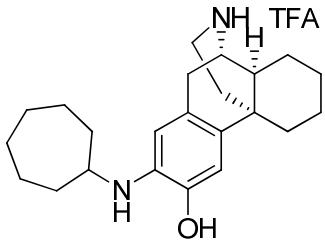
Example 93 : Preparation of (+)-2-Cyclohexylamino-3-hydroxymorphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.13 (s, 1H), 7.02 (s, 1H), 3.70 (dd, *J* = 5.6, 3.2 Hz, 1H), 3.49-3.41 (m, 1H), 3.34-3.23 (m, 1H), 3.12 (dd, *J* = 13.2, 3.6 Hz, 1H), 2.96 (d, *J* = 19.2 Hz, 1H), 2.72 (td, *J* = 13.6, 3.6 Hz, 1H), 2.40 (d, *J* = 14.4 Hz, 1H), 2.04-1.20 (m, 19H), 1.08-1.04 (m, 1H).

MH+ 341.

Example 94 : Preparation of (+)-2-Cycloheptylamino-3-hydroxymorphinan TFA salt

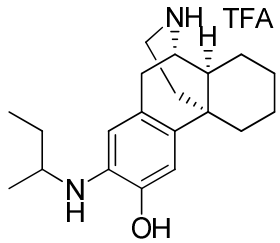


^{1}H NMR (400 MHz, CD_3OD) δ 7.16 (s, 1H), 7.02 (s, 1H), 3.71-3.62 (m, 2H), 3.33-3.25 (m, 1H), 3.12 (dd, *J* = 13.6, 3.6 Hz, 1H), 2.97 (d, *J* = 19.6 Hz, 1H), 2.71 (td, *J* = 13.2, 3.6 Hz, 1H), 2.39 (d, *J* = 14.0 Hz, 1H), 2.08-2.03 (m, 2H), 1.96-1.93 (m, 1H),

1.88-1.39 (m, 17H), 1.29-1.20 (m, 1H), 1.11-1.00 (m, 1H).

MH+ 355.

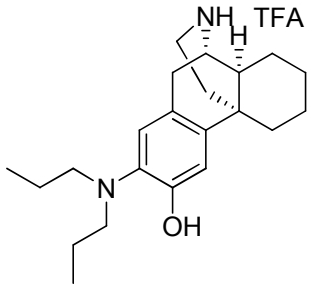
Example 95 : Preparation of (+)-2-(*sec*-Butylamino)-3-hydroxymorphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.16 (s, 1H), 7.03 (s, 1H), 3.70 (dd, *J* = 6.0, 3.2 Hz, 1H), 3.63-3.55 (m, 1H), 3.33-3.25 (m, 1H), 3.16 (dd, *J* = 13.2, 3.6 Hz, 1H), 2.97 (d, *J* = 19.2 Hz, 1H), 2.71 (td, *J* = 13.6, 3.6 Hz, 1H), 2.40 (d, *J* = 14.0 Hz, 1H), 1.95 (d, *J* = 14.0 Hz, 1H), 1.89-1.80 (m, 2H), 1.71 (d, *J* = 12.8 Hz, 1H), 1.66-1.39 (m, 6H), 1.31 (d, *J* = 6.8 Hz, 3H), 1.26-1.23 (m, 1H), 1.11-1.07 (m, 1H), 1.01 (td, *J* = 7.6, 1.2 Hz, 3H).

MH+ 315.

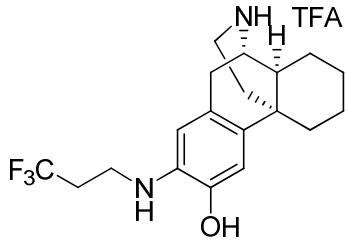
Example 96 : Preparation of (+)-2-(Dipropylamino)-3-hydroxymorphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.40 (s, 1H), 7.04 (s, 1H), 3.72 (dd, *J* = 6.0, 3.2 Hz, 1H), 3.57-3.46 (m, 4H), 3.35-3.28 (m, 1H), 3.14 (dd, *J* = 13.6, 3.2 Hz, 1H), 3.01 (d, *J* = 19.2 Hz, 1H), 2.71 (td, *J* = 13.6, 3.6 Hz, 1H), 2.40 (d, *J* = 14.0 Hz, 1H), 1.96 (dt, *J* = 12.4, 2.8 Hz, 1H), 1.85 (td, *J* = 14.0, 4.8 Hz, 1H), 1.72 (d, *J* = 12.8 Hz, 1H), 1.62-1.40 (m, 9H), 1.29-1.22 (m, 1H), 1.10-1.01 (m, 1H), 0.91 (t, *J* = 7.2 Hz, 6H).

MH+ 343.

Example 97 : Preparation of (+)-3-Hydroxy-2-(3-trifluoropropylamino)morphinan TFA salt

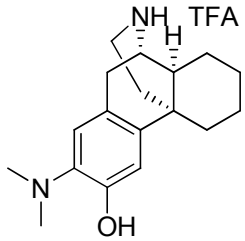


^{1}H NMR (400 MHz, CD_3OD) δ 6.79 (s, 1H), 6.70 (s, 1H), 3.64 (dd, *J* = 6.0, 3.2 Hz, 1H), 3.51-3.47 (m, 2H), 3.24 (dd, *J* = 19.2, 6.0 Hz, 1H), 3.08 (dd, *J* = 13.2, 3.6 Hz, 1H), 2.88 (d, *J* = 19.2 Hz, 1H), 2.77 (td, *J* = 13.6, 4.0 Hz, 1H), 2.61-2.53 (m, 2H), 2.35 (d, *J*

= 13.2 Hz, 1H), 1.88 (dt, *J* = 12.4, 2.8 Hz, 1H), 1.81-1.69 (m, 2H), 1.57-1.24 (m, 6H), 1.18-1.08 (m, 1H).

MH+ 355.

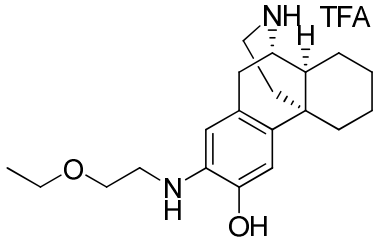
Example 98 : Preparation of (+)-2-(Dimethylamino)-3-hydroxymorphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.54 (s, 1H), 7.03 (s, 1H), 3.74 (dd, *J* = 6.0, 3.2 Hz, 1H), 3.35-3.27 (m, 7H), 3.13 (dd, *J* = 13.6, 3.6 Hz, 1H), 3.06 (d, *J* = 19.2 Hz, 1H), 2.73 (td, *J* = 13.6, 3.6 Hz, 1H), 2.40 (d, *J* = 14.4 Hz, 1H), 1.98 (dt, *J* = 12.4, 3.2 Hz, 1H), 1.87 (td, *J* = 14.0, 4.8 Hz, 1H), 1.70 (d, *J* = 12.8 Hz, 1H), 1.61-1.39 (m, 5H), 1.26-1.21 (m, 1H), 1.09-0.99 (m, 1H).

MH+ 287.

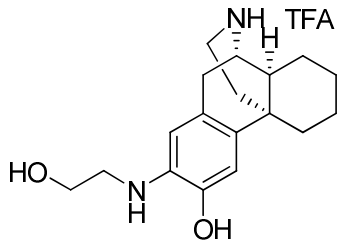
Example 99 : Preparation of (+)-2-(2-Ethoxyethylamino)-3-hydroxymorphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.56 (s, 1H), 6.80 (s, 1H), 3.18 (q, *J* = 7.2 Hz, 2H), 3.64 (dd, *J* = 6.0, 3.6 Hz, 1H), 3.31-3.28 (m, 4H), 3.23 (dd, *J* = 19.2, 6.0 Hz, 1H), 3.07 (dd, *J* = 13.6, 3.6 Hz, 1H), 2.88 (d, *J* = 18.8 Hz, 1H), 2.77 (td, *J* = 13.6, 4.0 Hz, 1H), 2.36 (d, *J* = 13.2 Hz, 1H), 1.88 (dt, *J* = 12.4, 2.8 Hz, 1H), 1.77 (td, *J* = 13.6, 4.8 Hz, 1H), 1.70 (d, *J* = 11.2 Hz, 1H), 1.57-1.35 (m, 6H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.15-1.11 (m, 1H).

MH+ 331.

Example 100 : Preparation of (+)-3-Hydroxy-2-(2-hydroxyethylamino)morphinan TFA salt

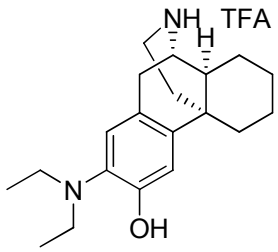


^{1}H NMR (400 MHz, CD_3OD) δ 7.07 (s, 1H), 6.94 (s, 1H), 3.78-3.75 (m, 2H), 3.68 (dd, *J* = 6.0, 3.2 Hz, 1H), 3.42-3.40 (m, 2H), 3.32 (dd, *J* = 12.4, 1.6 Hz, 1H), 3.11 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.93 (d, *J* = 18.8 Hz, 1H), 2.73 (td, *J* = 13.2, 3.6 Hz, 1H), 2.38 (d, *J*

= 13.6 Hz, 1H), 1.92 (dt, *J* = 12.4, 2.8 Hz, 1H), 1.81 (td, *J* = 13.6, 4.8 Hz, 1H), 1.71 (d, *J* = 13.2 Hz, 1H), 1.58-1.39 (m, 5H), 1.31-1.21 (m, 1H), 1.13-1.03 (m, 1H).

MH+ 303.

Example 101 : Preparation of (+)-2-(Diethylamino)-3-hydroxymorphinan TFA salt



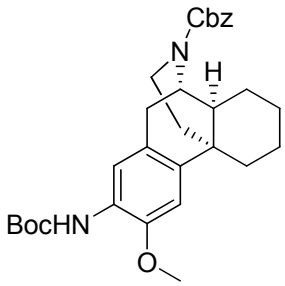
^{1}H NMR (400 MHz, CD_3OD) δ 7.48 (s, 1H), 7.05 (s, 1H), 3.75 (dd, *J* = 6.0, 3.2 Hz, 1H), 3.71-3.65 (m, 2H), 3.61-3.56 (m, 2H), 3.36-3.29 (m, 1H), 3.15 (dd, *J* = 13.6, 3.6 Hz, 1H), 3.01 (d, *J* = 19.2 Hz, 1H), 2.73 (td, *J* = 13.6, 3.6 Hz, 1H), 2.41 (d, *J* = 14.4 Hz, 1H), 2.00 (dt, *J* = 12.4, 2.8 Hz, 1H), 1.88 (td, *J* = 14.0, 4.8 Hz, 1H), 1.72 (d, *J* = 12.4 Hz, 1H), 1.63-1.41 (m, 5H), 1.27-1.22 (m, 1H), 1.13 (t, *J* = 7.2 Hz, 6H), 1.08-1.01 (m, 1H).

MH+ 315.

Example 102 : Preparation of (+)-3-Hydroxy-2-(methylpropylamino)morphinan TFA salt

Step 1: Preparation of (+)-2-(*tert*-Butyloxycarbonylamino)-3-methoxy-*N*-

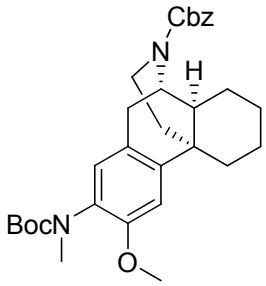
(benzyloxycarbonyl)morphinan



To a solution of (+)-2-amino-3-methoxy-*N*-(benzyloxycarbonyl)morphinan obtained in step 3 of Example 86 (2.88 g, 6.60 mmol) in THF (40 mL) was added di-*tert*-butyl dicarbonate (2.16 g, 9.90 mmol) at r.t. The resulting reaction mixture was stirred overnight and then saturated $NaHCO_3$ (50 mL) was added. The mixture thus obtained was extracted with EtOAc (50 mL X 2). The combined organic phase was dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (2.04 g, 61 %) as a white solid.

MH+ 507.

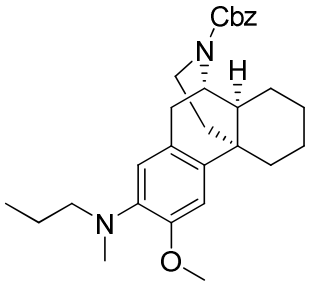
Step 2: Preparation of (+)-2-(*tert*-Buyloxycarbonyl(methyl)amino)-3-methoxy-*N*-(benzyloxycarbonyl)morphinan



To a solution of (+)-2-(*tert*-buyloxycarbonylamino)-3-methoxy-*N*-(benzyloxycarbonyl)morphinan obtained in step 1 (1.00 g, 1.97 mmol) and iodomethane (180 μL, 2.96 mmol) in THF (20 mL) was added NaH (118 mg, 2.96 mmol) at 0 ℃. The resulting reaction mixture was stirred at r.t. overnight. After the reaction was completed, water (30 mL) was added thereto. The resulting mixture was extracted with EtOAc (30 mL X 2). The combined organic phase was dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (847 mg, 83 %) as a white solid.

MNa+ 543.

Step 3: Preparation of (+)-3-Methoxy-2-(methylpropylamino)-*N*-(benzyloxycarbonyl)morphinan

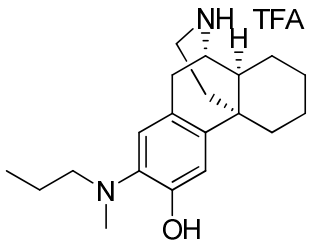


To a solution of (+)-2-(*tert*-buyloxycarbonyl(methyl)amino)-3-methoxy-*N*-(benzyloxycarbonyl)morphinan obtained in step 2 (500 mg, 1.19 mmol) in DCM (10 mL) was added TFA (280 μL, 3.57 mmol) at r.t. The resulting reaction mixture was stirred at r.t. for 2 hr. After the reaction was completed, the resulting mixture was evaporated under vacuum. To the residue were added 1,2-dichloroethane (15 mL) and propionaldehyde (170 μL, 2.38 mmol). After stirring for 10 min at r.t., $NaBH(OAc)_3$ (504 mg, 2.38 mmol) was added to the resulting reaction mixture. The mixture thus obtained was stirred overnight and washed with saturated $NaHCO_3$. The combined water layer was extracted EtOAc (20 mL X 2). The combined organics were dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (540 mg, 98 %) as a yellow solid.

MH+ 463.

Step 4: Preparation of (+)-3-Hydroxy-2-(methylpropylamino)morphinan TFA

salt



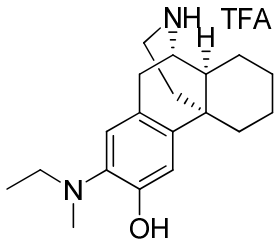
To a solution of (+)-3-Methoxy-2-(methylpropylamino)-*N*-(benzyloxycarbonyl)morphinan obtained in step 3 (540 mg, 1.17 mmol) in DCM (10 mL) was added BBr_3 solution (1M in DCM, 3.51 mL, 3.51 mmol) at 0 ℃. The reaction was quenched by MeOH (2 mL) and the resulting reaction mixture was evaporated under vacuum. The residue was purified by prep. reverse-phase HPLC (0.1 % TFA added) to provide the title compound (177 mg, 35 %) as a yellow solid.

^{1}H NMR (400 MHz, CD_3OD) δ 7.43 (s, 1H), 7.04 (s, 1H), 3.73-3.70 (m, 1H), 3.54-3.50 (m, 2H), 3.35-3.29 (m, 1H), 3.23 (s, 3H), 3.14 (dd, *J* = 13.6, 3.6 Hz, 1H), 3.01 (d, *J* = 19.2 Hz, 1H), 2.71 (td, *J* = 13.6, 3.6 Hz, 1H), 2.40 (d, *J* = 13.6 Hz, 1H), 1.95 (dt, *J* = 12.8, 3.2 Hz, 1H), 1.84 (td, *J* = 14.0, 4.8 Hz, 1H), 1.72 (d, *J* = 13.2 Hz, 1H), 1.61-1.40 (m, 7H), 1.29-1.21 (m, 1H), 1.10-1.00 (m, 1H), 0.94 (t, *J* = 7.2 Hz, 3H).

MH+ 315.

The following compound of Example 103 was obtained by repeating the procedure of Example 102.

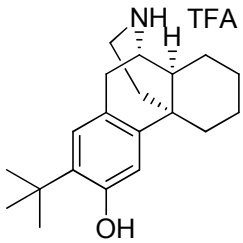
Example 103 : Preparation of (+)-2-(Ethylmethylamino)-3-hydroxymorphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.42 (s, 1H), 7.04 (s, 1H), 3.72 (dd, *J* = 6.0, 3.2 Hz, 1H), 3.63-3.61 (m, 2H), 3.32 (dd, *J* = 6.4, 1.6 Hz, 1H), 3.23 (s, 3H), 3.13 (dd, *J* = 14.4, 3.6 Hz, 1H), 3.00 (d, *J* = 19.2 Hz, 1H), 2.72 (td, *J* = 13.6, 4.0 Hz, 1H), 2.40 (d, *J* = 13.6 Hz, 1H), 1.95 (dt, *J* = 12.8, 3.2 Hz, 1H), 1.85 (td, *J* = 14.0, 4.8 Hz, 1H), 1.71 (d, *J* = 12.4 Hz, 1H), 1.61-1.40 (m, 5H), 1.29-1.21 (m, 1H), 1.18 (t, *J* = 7.2 Hz, 3H), 1.10-0.99 (m, 1H).

MH+ 301.

Example 104 : Preparation of (+)-2-*tert*-Butyl-3-hydroxymorphinan TFA salt



To a solution of (+)-3-hydroxymorphinan (HM) HBr (200 mg, 0.617 mmol) in

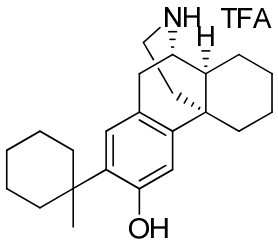
tert-BuOH (4 mL) was added conc. H_2SO_4 (1 mL, 18.8 mmol) at r.t. The resulting reaction mixture was stirred at 45 ℃ overnight. After the reaction was completed, water (10 mL) was added thereto. The mixture thus obtained was extracted with EtOAc (10 mL X 2). The combined organic phase was dried over $MgSO_4$, filtered and evaporated under vacuum. The residue was purified by prep. reverse-phase HPLC (0.1 % TFA added) to provide the title compound (53 mg, 21 %) as a white solid.

^{1}H NMR (400 MHz, CD_3OD) δ 6.99 (s, 1H), 6.69 (s, 1H), 3.63 (dd, *J* = 6.0, 3.2 Hz, 1H), 3.22 (dd, *J* = 19.2, 6.4 Hz, 1H), 3.05 (dd, *J* = 13.2, 3.6 Hz, 1H), 2.85 (d, *J* = 19.2 Hz, 1H), 2.75 (td, *J* = 13.2, 3.6 Hz, 1H), 2.38 (d, *J* = 12.4 Hz, 1H), 1.85 (dt, *J* = 12.4, 3.2 Hz, 1H), 1.79-1.69 (m, 2H), 1.56-1.31 (m, 15H), 1.20-1.09 (m, 1H).

MH+ 300.

The following compound of Example 105 was obtained by repeating the procedure of Example 104.

Example 105 : Preparation of (+)-3-Hydroxy-2-(1-methylcyclohexyl)morphinan TFA salt

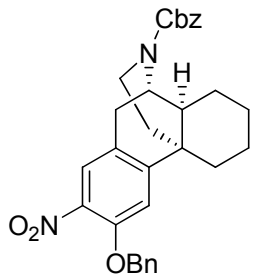


^{1}H NMR (400 MHz, CD_3OD) δ 7.03 (s, 1H), 6.71 (s, 1H), 3.65 (dd, *J* = 5.6, 3.2 Hz, 1H), 3.24 (dd, *J* = 18.8, 6.4 Hz, 1H), 3.08 (dd, *J* = 13.2, 3.6 Hz, 1H), 2.88 (d, *J* = 19.2 Hz, 1H), 2.77 (td, *J* = 13.2, 3.6 Hz, 1H), 2.39 (d, *J* = 9.2 Hz, 1H), 2.20-2.17 (m, 2H), 1.90-1.83 (m, 2H), 1.82-1.66 (m, 3H), 1.58-1.30 (m, 15H), 1.21-1.11 (m, 1H).

MH+ 340.

Example 106 : Preparation of (+)-3-Hydroxy-2-morpholinomorphinan TFA salt

Step 1: **Preparation of (+)-3-Benzyloxy-2-nitro-*N*-(benzyloxycarbonyl)morphinan**



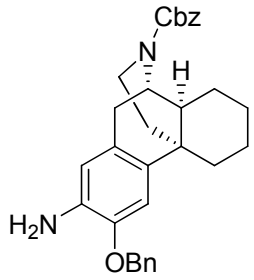
To a solution of (+)-3-hydroxy-2-nitro-*N*-(benzyloxycarbonyl)morphinan (42) (11.3 g, 26.7 mmol) and K_2CO_3 (7.38 g, 53.4 mmol) in DMF (100 mL) was added

benzyl bromide (3.94 mL, 40.1 mmol). The resulting reaction mixture was heated at 70 ℃ overnight and evaporated to remove the solvent under vacuum. The residue was poured into water (300 mL) and extracted with EtOAc (150 mL X 2). The combined organic phase was dried over $MgSO_4$ and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (13.6 g, 99 %) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.45-1.29 (m, 10H), 6.96 (s, 1H), 5.26-5.12 (m, 4H), 4.39 (d, *J* = 46.0 Hz, 1H), 3.97-3.85 (m, 1H), 3.08 (td, *J* = 18.0, 5.6 Hz, 1H), 2.74-2.54 (m, 2H), 2.20 (d, *J* = 14.0 Hz, 1H), 1.73-1.57 (m, 3H), 1.53-1.44 (m, 2H), 1.38-1.24 (m, 3H), 1.02-0.93 (m, 2H).

MH+ 513.

Step 2: **Preparation of (+)-2-Amino-3-benzyloxy-*N*-(benzyloxycarbonyl)morphinan**



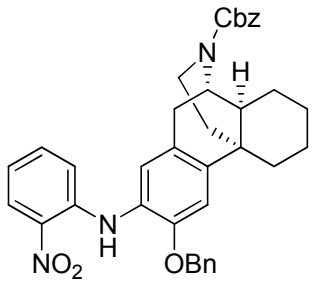
To a solution of (+)-3-benzyloxy-2-nitro-*N*-(benzyloxycarbonyl)morphinan obtained in step 1 (13.6 g, 26.5 mmol) and hydrazine hydrate (12.9 mL, 265 mmol) in

MeOH (200 mL) was added Raney Ni (water solution, 1 mL) dropwise. The resulting reaction mixture was stirred at r.t. for 2 hr and filtered to remove the catalyst. The filtrate was evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (12.5 g, 98 %) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.30 (m, 10H), 6.69 (s, 1H), 6.45 (d, *J* = 10.8 Hz, 1H), 5.17-5.01 (m, 4H), 4.32 (d, *J* = 40.8 Hz, 1H), 3.96-3.82 (m, 1H), 3.72 (br s, 2H), 3.01 (td, *J* = 17.6, 5.6 Hz, 1H), 2.73-2.52 (m, 2H), 2.20 (d, *J* = 11.6 Hz, 1H), 1.66-1.06 (m, 10H).

MH+ 483.

Step 3: **Preparation of (+)-3-Benzyloxy-2-(2-nitrophenylamino)-*N*-(benzyloxycarbonyl)morphinan**

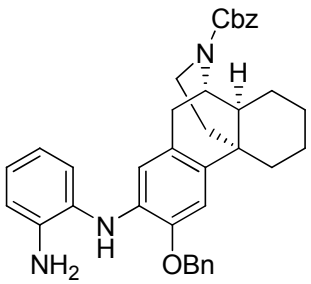


A mixture of (+)-2-amino-3-benzyloxy-*N*-(benzyloxycarbonyl)morphinan obtained in step 2 (2.5 g, 5.18 mmol), 1-chloro-2-nitrobenzene (1.63 g, 10.4 mmol), $Pd(OAc)_2$

(350 mg, 0.518 mmol), BINAP (650 mg, 1.04 mmol), and sodium *t*-butoxide (1.00 g, 10.4 mmol) in toluene (15 mL) was heated at 110 ℃ overnight and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (2.4 g, 77 %) as a yellow solid.

MH+ 604.

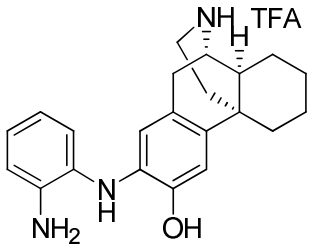
Step 4: **Preparation of (+)-2-(2-Aminophenylamino)-3-benzyloxy-*N*-(benzyloxycarbonyl)morphinan**



To a solution of (+)-3-benzyloxy-2-(2-nitrophenylamino)-*N*-(benzyloxycarbonyl)morphinan obtained in step 3 (910 mg, 1.51 mmol) and hydrazine hydrate (0.73 mL, 15.1 mmol) in MeOH (200 mL) was added Raney Ni (water solution, 1 mL) dropwise. The resulting reaction mixture was stirred at r.t. for 2 hr. and filtered to remove the catalyst. The filtrate was evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (860 mg, 99 %) as a white solid.

MH+ 574.

Step 5: Preparation of (+)-2-(2-Aminophenylamino)-3-hydroxymorphinan TFA salt



To a solution of (+)-2-(2-aminophenylamino)-3-benzyloxy-*N*-(benzyloxycarbonyl)morphinan obtained in step 4 (200 mg, 0.349 mmol) in DCM (10 mL) was added BBr_3 solution (1M in DCM, 1.05 mL, 1.05 mmol) at 0 ℃. The reaction was quenched by MeOH (2 mL) and the resulting reaction mixture was evaporated under vacuum. The residue was purified by prep. reverse-phase HPLC (0.1 % TFA added) to provide the title compound (45 mg, 28 %) as a yellow solid.

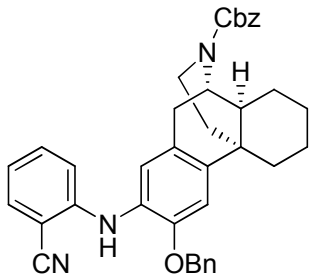
^{1}H NMR (400 MHz, CD_3OD) δ 7.34-7.29 (m, 3H), 7.14-7.09 (m, 1H), 6.82 (s, 1H), 6.63 (s, 1H), 3.60 (q, *J* = 2.8 Hz, 1H), 3.18-3.07 (m, 2H), 2.84-2.72 (m, 2H), 2.38 (d, *J* = 12.0 Hz, 1H), 1.92-1.69 (m, 3H), 1.58-1.32 (m, 6H), 1.19-1.12 (m, 1H).

MH+ 350.

Example 107 : Preparation of (+)-2-(2-Cyanophenylamino)-3-

hydroxymorphinan TFA salt

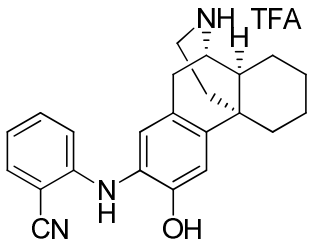
Step 1: **Preparation of (+)-3-Benzyloxy-2-(2-cyanophenylamino)-*N*-(benzyloxycarbonyl)morphinan**



A mixture of (+)-2-amino-3-benzyloxy-*N*-(benzyloxycarbonyl)morphinan obtained in step 2 of Example 106 (500 mg, 1.23 mmol), 1-chloro-2-cyanobenzene (338 mg, 2.46 mmol), $Pd(OAc)_2$ (83 mg, 0.123 mmol), BINAP (153 mg, 0.246 mmol), and sodium *t*-butoxide (236 mg, 2.46 mmol) in toluene (10 mL) was heated at 110 ℃ overnight and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (330 mg, 53 %) as a brown solid.

MH+ 508.

Step 2: Preparation of (+)-2-(2-Cyanophenylamino)-3-hydroxymorphinan TFA salt



To a solution of (+)-3-benzyloxy-2-(2-cyanophenylamino)-*N*-(benzyloxycarbonyl)morphinan obtained in step 1 (340 mg, 0.670 mmol) in DCM (10 mL) was added BBr_3 solution (1M in DCM, 2.0 mL, 2.01 mmol) at 0 ℃. The reaction was quenched by MeOH (2 mL) and the resulting reaction mixture was evaporated under vacuum. The residue was purified by prep. reverse-phase HPLC (0.1 % TFA added) to provide the title compound (210 mg, 65 %) as a yellow solid.

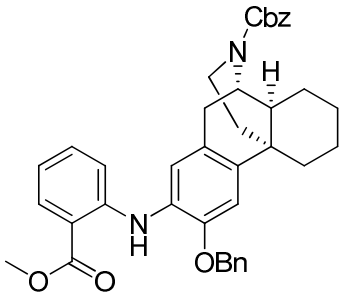
^{1}H NMR (400 MHz, CD_3OD) δ 7.51 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.41 (td, *J* = 7.2, 1.6 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 7.04 (s, 1H), 6.88 (s, 1H), 6.86 (t, *J* = 8.0 Hz, 1H), 3.65 (q, *J* = 2.8 Hz, 1H), 3.25 (dd, *J* = 18.8, 6.4 Hz, 1H), 3.10 (dd, *J* = 13.2, 3.6 Hz, 1H), 2.89-2.79 (m, 2H), 2.40 (d, *J* = 12.4 Hz, 1H), 1.89 (d, *J* = 12.8 Hz, 1H), 1.83-1.72 (m, 2H), 1.60-1.33 (m, 6H), 1.22-1.14 (m, 1H).

MH+ 360.

Example 108 : Preparation of (+)-3-Hydroxy-2-(2-(methoxycarbonyl)phenylamino)morphinan TFA salt

Step 1: Preparation of (+)-3-Benzyloxy-2-(2-(methoxycarbonyl)phenylamino)-

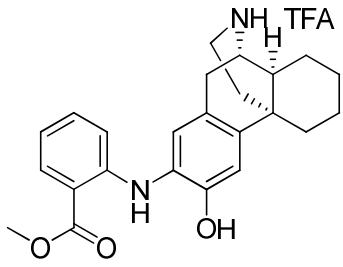
***N*-(benzyloxycarbonyl)morphinan**



A mixture of (+)-2-amino-3-benzyloxy-*N*-(benzyloxycarbonyl)morphinan obtained in step 2 of Example 106 (1.50 g, 3.11 mmol), methyl 2-chlorobenzoate (0.89 mL, 6.22 mmol), $Pd(OAc)_2$ (209 mg, 0.311 mmol), BINAP (387 mg, 0.622 mmol), and sodium *t*-butoxide (299 mg, 3.11 mmol) in toluene (15 mL) was heated at 110 ℃ overnight and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (530 mg, 28 %) as a yellow solid.

MH+ 617.

Step 2: Preparation of (+)-3-Hydroxy-2-(2-(methoxycarbonyl)phenylamino)morphinan TFA salt



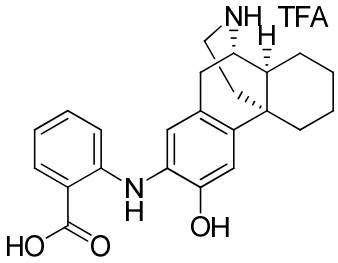
To a solution of (+)-3-benzyloxy-2-(2-(methoxycarbonyl)phenylamino)-*N*-(benzyloxycarbonyl)morphinan obtained in step 1 (250 mg, 0.405 mmol) in DCM (10 mL) was added BBr_3 solution (1M in DCM, 1.2 mL, 1.20 mmol) at 0 ℃. The reaction was quenched by MeOH (2 mL) and the resulting reaction mixture was evaporated under vacuum. The residue was purified by prep. reverse-phase HPLC (0.1 % TFA added) to provide the title compound (15 mg, 8 %) as a yellow solid.

^{1}H NMR (400 MHz, CD_3OD) δ 7.97 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.37-7.29 (m, 2H), 7.24 (s, 1H), 6.93 (s, 1H), 6.75 (td, *J* = 8.0, 1.2 Hz, 1H), 3.66 (q, *J* = 2.8 Hz, 1H), 3.33-3.25 (m, 1H), 3.10 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.88 (d, *J* = 19.2 Hz, 1H), 2.80 (td, *J* = 13.2, 3.6 Hz, 1H), 2.51 (d, *J* = 13.2 Hz, 1H), 1.91 (d, *J* = 12.4 Hz, 1H), 1.84-1.72 (m, 2H), 1.66-1.33 (m, 6H), 1.24-1.15 (m, 1H).

MH+ 393.

The following compound of Example 109 was obtained by repeating the procedure of Example 108.

Example 109 : Preparation of (+)-2-(2-Carboxyphenylamino)-3-hydroxymorphinan TFA salt

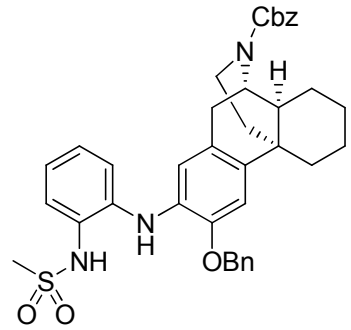


^{1}H NMR (400 MHz, CD_3OD) δ 7.96 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.34-7.30 (m, 1H), 7.17 (s, 1H), 7.16 (s, 1H), 6.87 (s, 1H), 6.71 (t, *J* = 8.0 Hz, 1H), 3.64 (q, *J* = 2.8 Hz, 1H), 3.25 (dd, *J* = 19.2, 6.4 Hz, 1H), 3.10 (dd, *J* = 13.2, 3.6 Hz, 1H), 2.89-2.79 (m, 2H), 2.41 (d, *J* = 12.0 Hz, 1H), 1.89 (d, *J* = 12.4 Hz, 1H), 1.84-1.72 (m, 2H), 1.59-1.34 (m, 6H), 1.23-1.17 (m, 1H).

MH+ 379.

Example 110 : Preparation of (+)-3-Hydroxy-2-(2-(methanesulfonamido)phenylamino)morphinan TFA salt

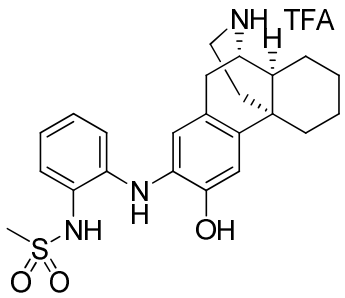
Step 1: Preparation of (+)-3-Benzyloxy-2-(2-(methanesulfonamido)phenylamino)-*N*-(benzyloxycarbonyl)morphinan



To a solution of (+)-2-(2-aminophenylamino)-3-benzyloxy-*N*-(benzyloxycarbonyl)morphinan obtained in step 4 of Example 106 (295 mg, 0.514 mmol) in DCM (10 mL) were added methanesulfonyl chloride (40 μL, 0.514 mmol) and TEA (0.14 mL, 1.03 mmol) at 0 ℃ stepwisely. The resulting reaction mixture was stirred at r.t. overnight and water (20 mL) was added thereto. The mixture thus obtained was extracted with DCM (20 mL X 2). The combined organic phase was dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (170 mg, 51 %) as a yellow solid.

MH+ 652.

Step 2: **Preparation of (+)-3-Hydroxy-2-(2-(methanesulfonamido)phenylamino)morphinan TFA salt**



To a solution of (+)-3-benzyloxy-2-(2-(methanesulfonamido)phenylamino)-*N*-(benzyloxycarbonyl)morphinan obtained in step 1 (171 mg, 0.262 mmol) in DCM (10

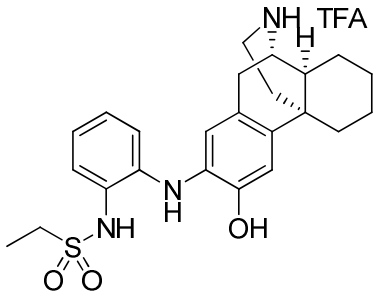
mL) was added BBr_3 solution (1M in DCM, 0.79 mL, 0.79 mmol) at 0 ℃. The reaction was quenched by MeOH (2 mL) and the resulting reaction mixture was evaporated under vacuum. The residue was purified by prep. reverse-phase HPLC (0.1 % TFA added) to provide the title compound (17 mg, 12 %) as a brown solid.

^{1}H NMR (400 MHz, CD_3OD) δ 7.31 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.24 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.20 (td, *J* = 7.2, 1.2 Hz, 1H), 6.93 (td, *J* = 7.2, 1.2 Hz, 1H), 6.85 (s, 1H), 6.81 (s, 1H), 3.60 (q, *J* = 2.8 Hz, 1H), 3.17 (dd, *J* = 19.2, 6.4 Hz, 1H), 3.07 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.97 (s, 3H), 2.84-2.77 (m, 2H), 2.37 (d, *J* = 10.4 Hz, 1H), 1.91-1.69 (m, 3H), 1.56-1.27 (m, 6H), 1.17-1.14 (m, 1H).

MH+ 428.

The following compounds of Examples 111 to 123 were obtained by repeating the procedure of Example 110.

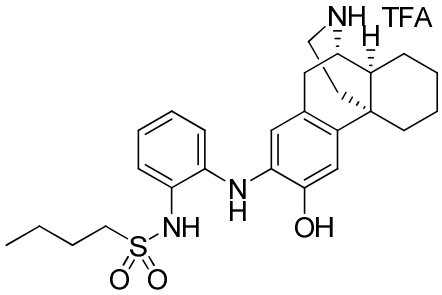
Example 111 : Preparation of (+)-2-(2-(Ethanesulfonamido)phenylamino)-3-hydroxymorphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.31 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.25 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.17 (td, *J* = 8.0, 1.2 Hz, 1H), 6.93 (td, *J* = 8.0, 1.2 Hz, 1H), 6.81 (s, 1H), 6.80 (s, 1H), 3.60 (q, *J* = 2.8 Hz, 1H), 3.20-3.06 (m, 4H), 2.84-2.76 (m, 2H), 2.38 (d, *J* = 11.6 Hz, 1H), 1.88-1.85 (m, 1H), 1.80-1.72 (m, 2H), 1.57-1.31 (m, 9H), 1.20-1.12 (m, 1H).

MH+ 442.

Example 112 : Preparation of (+)-2-(2-(Butanesulfonamido)phenylamino)-3-hydroxymorphinan TFA salt

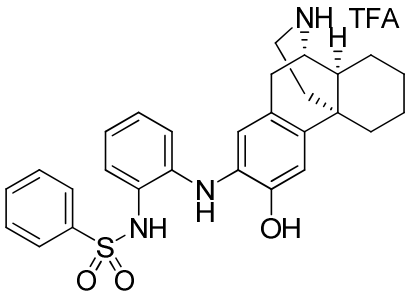


^{1}H NMR (400 MHz, CD_3OD) δ 7.33 (d, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.19 (t, *J* = 8.0 Hz, 1H), 6.95 (t, *J* = 7.6 Hz, 1H), 6.82 (s, 1H), 6.80 (s, 1H), 3.60 (q, *J* =

2.8 Hz, 1H), 3.16 (dd, *J* = 19.2, 6.4 Hz, 1H), 3.08 (dd, *J* = 12.8, 3.6 Hz, 1H), 3.02 (t, *J* = 8.0 Hz, 2H), 2.84-2.75 (m, 2H), 2.38 (d, *J* = 11.2 Hz, 1H), 1.86 (d, *J* = 12.4 Hz, 1H), 1.80-1.70 (m, 4H), 1.56-1.12 (m, 8H), 0.83 (t, *J* = 7.6 Hz, 3H).

MH+ 470.

Example 113 : Preparation of (+)-2-(2-(Benzenesulfonamido)phenylamino)-3-hydroxymorphinan TFA salt

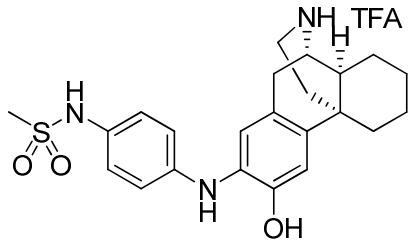


^{1}H NMR (400 MHz, CD_3OD) δ 7.70 (d, *J* = 7.2 Hz, 2H), 7.54 (td, *J* = 5.6, 1.6 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 2H), 7.19 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.10 (td, *J* = 7.2, 1.6 Hz, 1H), 6.82 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.77 (s, 1H), 6.73 (td, *J* = 7.6, 1.2 Hz, 1H), 6.66 (s, 1H), 3.60 (q, *J* = 2.8 Hz, 1H), 3.17-3.07 (m, 2H), 2.82-2.71 (m, 2H), 2.38 (d, *J* = 7.6 Hz, 1H), 1.87-1.72 (m, 3H), 1.58-1.37 (m, 6H), 1.20-1.17 (m, 1H).

MH+ 490.

Example 114 : Preparation of (+)-3-Hydroxy-2-(4-

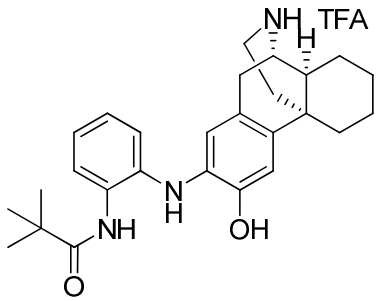
(methanesulfonamido)phenylamino)morphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.13 (dt, *J* = 9.2, 2.4 Hz, 1H), 7.03 (dt, *J* = 8.8, 2.4 Hz, 1H), 6.99 (s, 1H), 6.79 (s, 1H), 3.61 (q, *J* = 2.8 Hz, 1H), 3.20 (dd, *J* = 19.2, 6.4 Hz, 1H), 3.08 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.88 (s, 3H), 2.85-2.77 (m, 2H), 2.38 (d, *J* = 11.6 Hz, 1H), 1.88-1.71 (m, 3H), 1.57-1.34 (m, 6H), 1.23-1.14 (m, 1H).

MH+ 428.

Example 115 : Preparation of (+)-3-Hydroxy-2-(2-(pivalamido)phenylamino)morphinan TFA salt

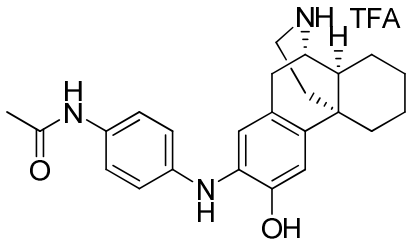


^{1}H NMR (400 MHz, CD_3OD) δ 7.54 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.28 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.18 (td, *J* = 7.6, 1.6 Hz, 1H), 7.08 (td, *J* = 7.6, 1.6 Hz, 1H), 6.76 (s, 1H), 6.41 (s, 1H), 3.56 (q, *J* = 2.8 Hz, 1H), 3.11-3.03 (m, 2H), 2.75-2.66 (m, 2H), 2.36 (d, *J*

= 10.4 Hz, 1H), 1.84-1.68 (m, 3H), 1.56-1.34 (m, 7H), 1.15 (s, 9H).

MH+ 434.

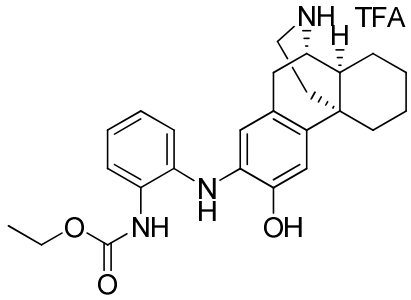
Example 116 : Preparation of (+)-2-(2-(Acetamido)phenylamino)-3-hydroxymorphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.37 (dt, *J* = 8.8, 3.2 Hz, 2H), 7.03 (dt, *J* = 8.8, 3.2 Hz, 2H), 6.96 (s, 1H), 6.78 (s, 1H), 3.61 (q, *J* = 2.8 Hz, 1H), 3.19 (dd, *J* = 19.2, 6.4 Hz, 1H), 3.07 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.84-2.77 (m, 2H), 2.37 (d, *J* = 10.8 Hz, 1H), 2.08 (s, 3H), 1.87-1.71 (m, 3H), 1.56-1.36 (m, 6H), 1.22-1.14 (m, 1H).

MH+ 392.

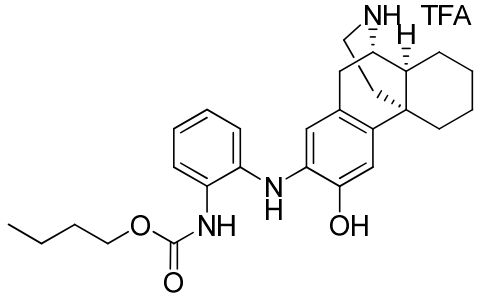
Example 117 : Preparation of (+)-2-(2-(Ethoxycarbonylamino)phenylamino)-3-hydroxymorphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.45 (d, *J* = 7.6 Hz, 1H), 7.21 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.10 (td, *J* = 7.6, 1.2 Hz, 1H), 7.00 (td, *J* = 7.6, 1.2 Hz, 1H), 6.77 (s, 1H), 6.57 (s, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.58 (q, *J* = 2.8 Hz, 1H), 3.16-3.04 (m, 2H), 2.82-2.70 (m, 2H), 2.36 (d, *J* = 10.4 Hz, 1H), 1.84 (d, *J* = 12.4 Hz, 1H), 1.75-1.69 (m, 2H), 1.56-1.36 (m, 6H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.17-1.04 (m, 1H).

MH+ 422.

Example 118 : Preparation of (+)-2-(2-(Butoxycarbonylamino)phenylamino)-3-hydroxymorphinan TFA salt

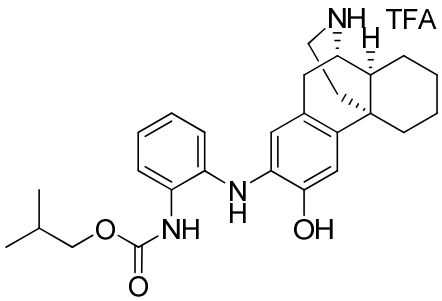


^{1}H NMR (400 MHz, CD_3OD) δ 7.45 (d, *J* = 7.6 Hz, 1H), 7.21 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.10 (td, *J* = 8.0, 1.2 Hz, 1H), 7.00 (td, *J* = 8.0, 1.2 Hz, 1H), 6.78 (s, 1H), 6.58 (s,

1H), 4.10 (td, *J* = 6.4, 1.6 Hz, 2H), 3.58 (q, *J* = 2.8 Hz, 1H), 3.15-3.04 (m, 2H), 2.82-2.70 (m, 2H), 2.37 (d, *J* = 10.8 Hz, 1H), 1.84 (d, *J* = 12.4 Hz, 1H), 1.79-1.69 (m, 2H), 1.54-1.36 (m, 10H), 1.17-1.13 (m, 1H), 0.92 (t, *J* = 7.6 Hz, 3H).

MH+ 450.

Example 119 : Preparation of (+)-3-Hydroxy-2-(2-(isobutyloxycarbonylamino)phenylamino)morphinan TFA salt

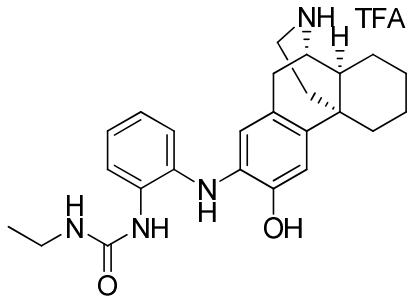


^{1}H NMR (400 MHz, CD_3OD) δ 7.44 (d, *J* = 7.2 Hz, 1H), 7.22 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.10 (td, *J* = 7.6, 1.6 Hz, 1H), 7.00 (td, *J* = 7.6, 1.2 Hz, 1H), 6.77 (s, 1H), 6.58 (s, 1H), 3.92-3.84 (m, 2H), 3.58 (q, *J* = 2.8 Hz, 1H), 3.15-3.04 (m, 2H), 2.81-2.70 (m, 2H), 2.37 (d, *J* = 10.4 Hz, 1H), 1.95-1.69 (m, 4H), 1.55-1.35 (m, 6H), 1.19-1.07 (m, 1H), 0.92 (d, *J* = 6.8 Hz, 6H).

MH+ 450.

Example 120 : Preparation of (+)-2-(2-(Ethylureido)phenylamino)-3-

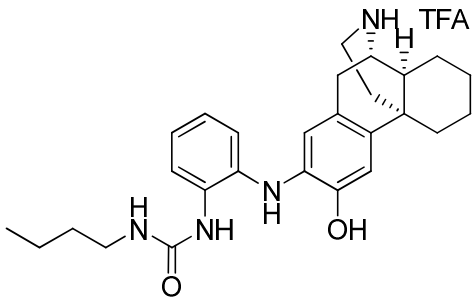
hydroxymorphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.59-7.57 (m, 1H), 7.16-7.14 (m, 1H), 7.04-7.01 (m, 2H), 6.75 (s, 1H), 6.44 (s, 1H), 3.92-3.84 (m, 2H), 3.57 (q, *J* = 2.8 Hz, 1H), 3.16-3.07 (m, 4H), 2.81-2.68 (m, 2H), 2.37 (d, *J* = 10.4 Hz, 1H), 1.86-1.69 (m, 4H), 1.54-1.32 (m, 6H), 1.19-1.11 (m, 1H), 1.07 (t, *J* = 7.2 Hz, 3H).

MH+ 421.

Example 121 : Preparation of (+)-2-(2-(Butylureido)phenylamino)-3-hydroxymorphinan TFA salt

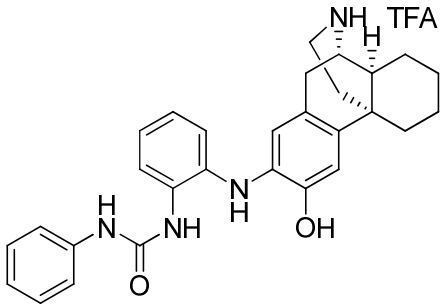


^{1}H NMR (400 MHz, CD_3OD) δ 7.60-7.58 (m, 1H), 7.16-7.14 (m, 1H), 7.03-7.01 (m, 2H), 6.76 (s, 1H), 6.44 (s, 1H), 3.92-3.84 (m, 2H), 3.56 (q, *J* = 2.8 Hz, 1H), 3.15-

3.06 (m, 4H), 2.80-2.68 (m, 2H), 2.36 (d, *J* = 10.4 Hz, 1H), 1.86-1.68 (m, 3H), 1.54-1.29 (m, 10H), 1.18-1.12 (m, 1H), 0.90 (t, *J* = 7.2 Hz, 3H).

MH+ 449.

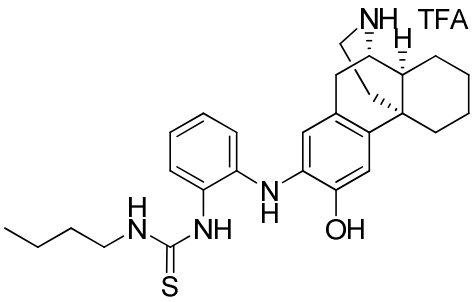
Example 122 : Preparation of (+)-3-Hydroxy-2-(2-(phenylureido)phenylamino)morphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.71 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.34 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.24-7.07 (m, 5H), 6.95 (t, *J* = 7.6 Hz, 1H), 6.74 (s, 1H), 6.29 (s, 1H), 3.45 (q, *J* = 2.8 Hz, 1H), 3.01 (d, *J* = 19.2, 6.4 Hz, 1H), 2.94 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.69-2.61 (m, 2H), 2.33 (d, *J* = 11.6 Hz, 1H), 1.76-1.66 (m, 2H), 1.56-1.45 (m, 3H), 1.32-1.19 (m, 4H), 0.96-0.88 (m, 1H).

MH+ 469.

Example 123 : Preparation of(+)-2-(2-(Butylthioureido)phenylamino)-3-hydroxymorphinan TFA salt

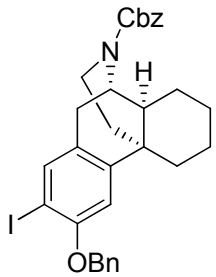


^{1}H NMR (400 MHz, CD_3OD) δ 7.27 (d, *J* = 3.2 Hz, 1H), 7.20-7.14 (m, 2H), 6.93 (t, *J* = 6.8 Hz, 1H), 6.85 (s, 1H), 6.79 (s, 1H), 3.60 (q, *J* = 2.8 Hz, 1H), 3.49 (br s, 2H), 3.19 (dd, *J* = 18.8, 6.0 Hz, 1H), 3.07 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.84-2.78 (m, 2H), 2.37 (d, *J* = 12.4 Hz, 1H), 1.86 (d, *J* = 12.4 Hz, 1H), 1.79-1.69 (m, 2H), 1.56-1.10 (m, 11H), 0.84 (t, *J* = 7.6 Hz, 3H).

MH+ 465.

Example 124 : Preparation of (+)-2-(4-Fluorophenyl(methyl)amino)-3-hydroxymorphinan TFA salt

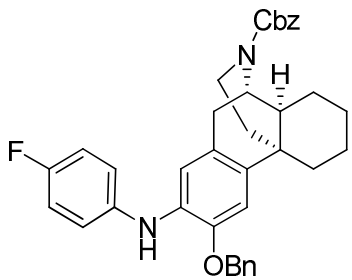
Step 1: **Preparation of (+)-3-Benzyloxy-2-iodo-*N*-(benzyloxycarbonyl)morphinan**



To a solution of (+)-3-hydroxy-2-iodo-*N*-(benzyloxycarbonyl)morphinan obtained in step 1 of Example 12 (13.5 g, 26.8 mmol) and K_2CO_3 (7.41 g, 53.6 mmol) in DMF (100 mL) was added benzyl bromide (4.8 mL, 40.2 mmol). The resulting reaction mixture was heated at 70 ℃ overnight and evaporated to remove the solvent under vacuum. The residue was poured into water (300 mL) and extracted with EtOAc (150 mL X 2). The organic phase was dried over $MgSO_4$ and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (13.6 g, 99 %) as a yellow solid.

MH+ 594.

Step 2: Preparation of (+)-3-Benzyloxy-2-(4-fluorophenylamino)-*N*-(benzyloxycarbonyl)morphinan

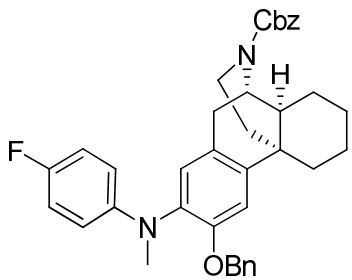


To a solution of (+)-3-benzyloxy-2-iodo-*N*-(benzyloxycarbonyl)morphinan obtained in step 1 (1.00 g, 1.68 mmol) in toluene (10 mL) were added 4-fluoroaniline (373 mg, 3.36 mmol), NatBuO (323 mg, 3.36 mmol), (dppf)$PdCl_2.CH_2Cl_2$ (54.9 mg, 0.0672 mmol), and dppf (102 mg, 0.202 mmol). The resulting reaction mixture was

heated at 100 °C overnight. After the reaction was completed, water (10 mL) was added thereto. The mixture was extracted with EtOAc (15 mL X 2). The combined organic phase was dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (540 mg, 56 %) as a yellow solid.

MH+ 577.

Step 3: Preparation of (+)-3-Benzyloxy-2-(4-fluorophenyl(methyl)amino)-*N*-(benzyloxycarbonyl)morphinan

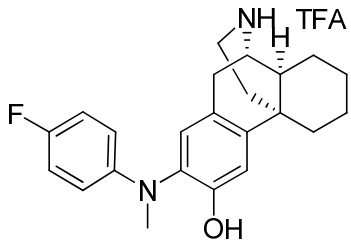


To a solution of (+)-3-benzyloxy-2-(4-fluorophenylamino)-*N*-(benzyloxycarbonyl)morphinan obtained in step 2 (410 mg, 0.711 mmol) in THF (10 mL) was added NaHMDS (1.4 mL, 1.42 mmol) at -78 ℃ slowly. After stirring of resulting reaction mixture for 30 min., methyl iodide (90 μL, 1.42 mmol) was added thereto at the same temperature. The mixture thus obtained was stirred at r.t. for 2 hrs and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (295 mg, 70 %) as a

yellow solid.

MH+ 591.

Step 4: Preparation of (+)-2-(4-Fluorophenyl(methyl)amino)-3-hydroxymorphinan TFA salt

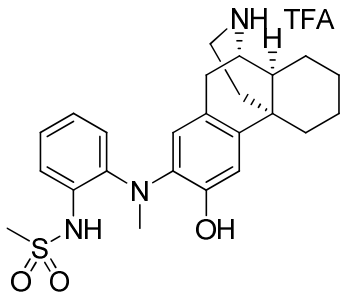


To a solution of (+)-3-benzyloxy-2-(4-fluorophenyl(methyl)amino)-*N*-(benzyloxycarbonyl)morphinan obtained in step 3 (295 mg, 0.499 mmol) in DCM (10 mL) was added BBr_3 solution (1M in DCM, 1.5 mL, 1.50 mmol) at 0 ^oC. The reaction was quenched by MeOH (2 mL) and the resulting reaction mixture was evaporated under vacuum. The residue was further purified by prep. reverse-phase HPLC (0.1 % TFA added) to provide the title compound (96 mg, 40 %) as a white solid.

^1H NMR (400 MHz, CD_3OD) δ 6.91-6.82 (m, 4H), 6.64-6.59 (m, 2H), 3.64 (q, *J* = 2.8 Hz, 1H), 3.26 (dd, *J* = 19.2, 6.4 Hz, 1H), 3.14-3.09 (m, 4H), 2.86-2.76 (m, 2H), 2.43 (d, *J* = 12.8 Hz, 1H), 1.90 (d, *J* = 12.4 Hz, 1H), 1.84-1.73 (m, 2H), 1.62-1.34 (m, 6H), 1.21-1.11 (m, 1H).

MH+ 367.

Example 125 : Preparation of (+)-3-Hydroxy-2-(2-(methanesulfonamido)phenyl(methyl)amino)morphinan TFA salt



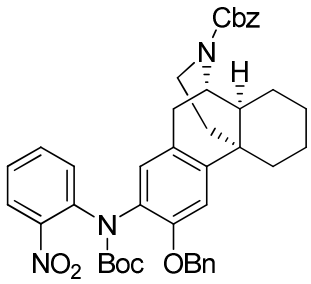
The title compound was obtained by repeating the procedure of Example 124.

^{1}H NMR (400 MHz, CD_3OD) δ 7.46 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.30 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.18-7.10 (m, 2H), 6.87 (s, 1H), 6.66 (s, 1H), 3.58 (q, *J* = 2.8 Hz, 1H), 3.15-3.04 (m, 5H), 2.77-2.73 (m, 2H), 2.58 (s, 3H), 2.39 (d, *J* = 10.4 Hz, 1H), 1.85 (d, *J* = 12.4 Hz, 1H), 1.77-1.72 (m, 2H), 1.58-1.36 (m, 6H), 1.09-1.01 (m, 1H).

MH+ 442.

Example 126 : Preparation of (+)-2-(2-(Dimethylamino)phenylamino)-3-hydroxymorphinan TFA salt

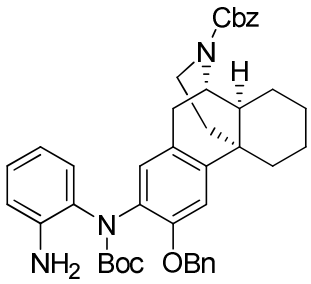
Step 1: Preparation of (+)-3-Benzyloxy-2-(2-nitrophenyl(*tert*-butyloxylcarbonyl)amino)-*N*-(benzyloxycarbonyl)morphinan



To a solution of (+)-3-benzyloxy-2-(4-nitrophenylamino)-*N*-(benzyloxycarbonyl)morphinan obtained in step 3 of Example 106 (9.01 g, 14.9 mmol) in THF (100 mL) were added di-*tert*-butyl dicarbonate (4.88 g, 22.4 mmol) and DMAP (2.18 g, 17.9 mmol) stepwisely. The resulting reaction mixture was heated at 70 ℃ overnight and evaporated to remove the solvent under vacuum. The residue was poured into water (300 mL) and extracted with EtOAc (150 mL X 2). The combined organic phase was dried over $MgSO_4$ and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (7.17 g, 68 %) as a red solid.

MH+ 704.

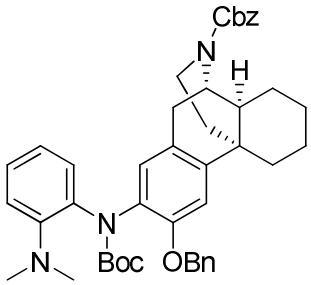
Step 2: Preparation of (+)-(2-Aminophenyl(*tert*-butyloxylcarbonyl)amino)-3-benzyloxy-*N*-(benzyloxycarbonyl)morphinan



To a solution of (+)-3-benzyloxy-2-(2-nitrophenyl(*tert*-butyloxylcarbonyl)amino)-*N*-(benzyloxycarbonyl)morphinan in step 1 (7.17 g, 10.2 mmol) and hydrazine hydrate (2.5 mL, 50.9 mmol) in MeOH (200 mL) was added Raney Ni (water solution, 1 mL) dropwise. The resulting reaction mixture was stirred at r.t. for 2 hrs and filtered to remove the catalyst. The filtrate was evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (6.24 g, 91 %) as a yellow solid.

MH+ 674.

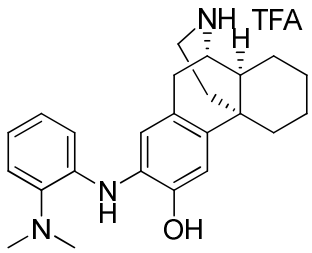
Step 3: Preparation of (+)-3-Benzyloxy-2- ((2-dimethylaminophenyl)(*tert*-butyloxylcarbonyl)amino)-*N*-(benzyloxycarbonyl)morphinan



To a solution of (+)-(2-aminophenyl(*tert*-butyloxylcarbonyl)amino)-3-benzyloxy-*N*-(benzyloxycarbonyl)morphinan obtained in step 2 (220 mg, 0.326 mmol) and formalin (1.2 mL, 16.3 mmol) in DCE (10 mL) was added $NaBH(OAc)_3$ (415 mg, 1.96 mmol) in a portion. The resulting reaction mixture was stirred at r.t. overnight and evaporated under vacuum. The residue was poured into water (50 mL) and extracted with EtOAc (20 mL X 2). The combined organic phase was dried over $MgSO_4$ and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (83 mg, 36 %) as a yellow solid.

MH+ 702.

Step 4: Preparation of (+)-2- ((2-dimethylaminophenyl)amino)-3-hydroxymorphinan TFA salt



To a solution of (+)-3-benzyloxy-2- ((2-dimethylaminophenyl)(*tert*-butyloxylcarbonyl)amino)-*N*-(benzyloxycarbonyl)morphinan obtained in step 3 (83 mg, 0.118 mmol) in DCM (10 mL) was added BBr_3 solution (1M in DCM, 0.4 mL, 0.40 mmol) at 0 ℃. The reaction was quenched by MeOH (2 mL) and the resulting

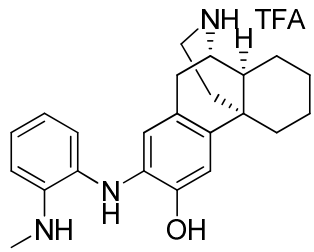
reaction mixture was evaporated under vacuum. The residue was purified by prep. reverse-phase HPLC (0.1 % TFA added) to provide the title compound (15 mg, 26 %) as a brown solid.

^{1}H NMR (400 MHz, CD_3OD) δ 7.74 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.44 (td, *J* = 7.6, 1.2 Hz, 1H), 7.38-7.33 (m, 2H), 6.81 (s, 1H), 6.55 (s, 1H), 3.60 (q, *J* = 2.8 Hz, 1H), 3.24 (s, 6H), 3.18-3.08 (m, 2H), 2.83-2.67 (m, 2H), 2.37 (d, *J* = 12.0 Hz, 1H), 1.89-1.68 (m, 3H), 1.58-1.28 (m, 6H), 1.18-1.09 (m, 1H).

MH+ 378.

The following compounds of Examples 127 to 131 were obtained by repeating the procedure of Example 126.

Example 127 : Preparation of (+)-3-Hydroxy-2-(2-(methylamino)phenylamino)morphinan TFA salt

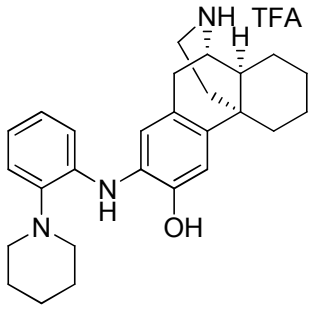


^{1}H NMR (400 MHz, CD_3OD) δ 7.35 (d, *J* = 8.0 Hz, 1H), 7.30-7.27 (m, 2H), 7.23-7.18 (m, 1H), 6.82 (s, 1H), 6.54 (s, 1H), 3.60 (q, *J* = 2.8 Hz, 1H), 3.17-3.06 (m, 2H),

3.02 (s, 3H), 2.82-2.74 (m, 2H), 2.38 (d, *J* = 12.4 Hz, 1H), 1.87 (d, *J* = 12.4 Hz, 1H), 1.78-1.69 (m, 2H), 1.58-1.37 (m, 6H), 1.16-1.12 (m, 1H).

MH+ 364.

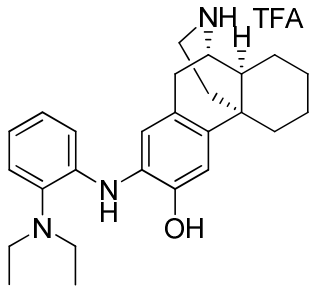
Example 128 : Preparation of (+)-3-Hydroxy-2-(2-(piperidin-1-yl)phenylamino)morphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.60 (d, *J* = 8.4 Hz, 1H), 7.36 (d, *J* = 3.6 Hz, 2H), 7.24-7.20 (m, 1H), 6.84 (s, 1H), 6.78 (s, 1H), 3.63 (q, *J* = 2.8 Hz, 1H), 3.53 (t, *J* = 4.8 Hz, 4H), 3.19 (dd, *J* = 19.2, 6.4 Hz, 1H), 3.11 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.85-2.78 (m, 2H), 2.39 (d, *J* = 12.8 Hz, 1H), 2.04-1.98 (m, 4H), 1.89 (d, *J* = 12.4 Hz, 1H), 1.83-1.72 (m, 4H), 1.60-1.33 (m, 6H), 1.18-1.14 (m, 1H).

MH+ 418.

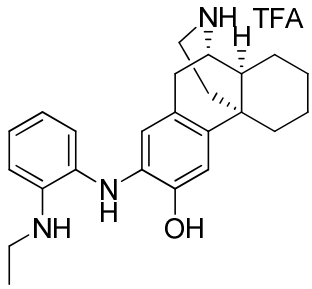
Example 129 : Preparation of (+)-2-(2-(Diethylamino)phenylamino)-3-hydroxymorphinan TFA salt



^{1}H NMR (400 MHz, CD_3OD) δ 7.68 (d, *J* = 8.4 Hz, 1H), 7.52 (td, *J* = 7.6, 1.6 Hz, 1H), 7.47-7.41 (m, 2H), 6.83 (s, 1H), 6.39 (s, 1H), 3.66 (q, *J* = 7.2 Hz, 4H), 3.59 (q, *J* = 2.8 Hz, 1H), 3.14-3.07 (m, 2H), 2.79-2.72 (m, 2H), 2.37 (d, *J* = 13.2 Hz, 1H), 1.87 (d, *J* = 12.4 Hz, 1H), 1.82-1.69 (m, 2H), 1.59-1.30 (m, 7H), 1.15 (t, *J* = 7.2 Hz, 6H).

MH+ 406.

Example 130 : Preparation of (+)-2-(2-(Ethylamino)phenylamino)-3-hydroxymorphinan TFA salt

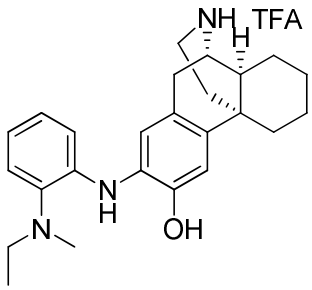


^{1}H NMR (400 MHz, CD_3OD) δ 7.40-7.30 (m, 3H), 7.22-7.18 (m, 1H), 6.83 (s, 1H), 6.59 (s, 1H), 3.60 (q, *J* = 2.8 Hz, 1H), 3.45 (q, *J* = 7.2 Hz, 2H), 3.17-3.07 (m, 2H), 2.83-2.72 (m, 2H), 2.38 (d, *J* = 12.4 Hz, 1H), 1.88 (d, *J* = 12.0 Hz, 1H), 1.82-1.69 (m, 2H),

1.59-1.37 (m, 6H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.18-1.09 (m, 1H).

MH+ 378.

Example 131 : Preparation of (+)-2-(2-(Ethyl(methyl)amino)phenylamino)-3-hydroxymorphinan TFA salt

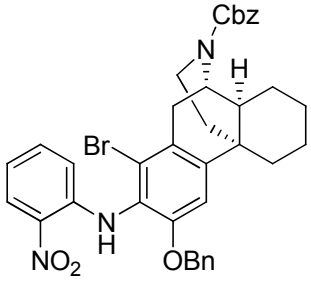


^{1}H NMR (400 MHz, CD_3OD) δ 7.71 (d, *J* = 8.4 Hz, 1H), 7.48 (td, *J* = 8.0, 1.2 Hz, 1H), 7.43-7.38 (m, 2H), 6.81 (s, 1H), 6.46 (s, 1H), 3.63-3.59 (m, 3H), 3.28 (s, 3H), 3.16-3.07 (m, 2H), 2.81-2.73 (m, 2H), 2.37 (d, *J* = 12.8 Hz, 1H), 1.87 (d, *J* = 12.4 Hz, 1H), 1.81-1.69 (m, 2H), 1.59-1.27 (m, 7H), 1.14 (t, *J* = 7.2 Hz, 3H).

MH+ 392.

Example 132 : Preparation of (+)-1-Bromo-3-hydroxy-2-(2-(methanesulfonamido)phenylamino)morphinan TFA salt

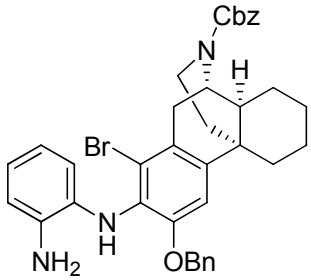
Step 1: Preparation of (+)-3-Benzyloxy-1-bromo-2-(2-nitrophenylamino)-*N*-(benzyloxycarbonyl)morphinan



A mixture of (+)-3-benzyloxy-2-(4-nitrophenylamino)-*N*-(benzyloxycarbonyl)morphinan obtained in step 3 of Example 106 (960 mg, 1.59 mmol) and pyridinium tribromide (560 mg, 1.75 mmol) in THF (15 mL) was heated at 60 ℃ overnight and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (950 mg, 88 %) as a brown solid.

MH+ 682.

Step 2: Preparation of (+)-2-(2-Aminophenylamino)-3-benzyloxy-1-bromo-*N*-(benzyloxycarbonyl)morphinan

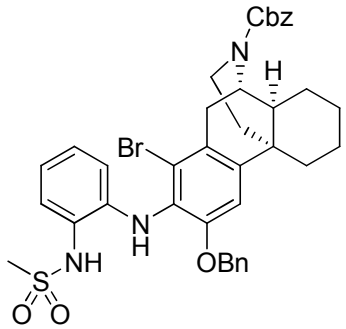


To a solution of (+)-3-benzyloxy-1-bromo-2-(2-nitrophenylamino)-*N*-(benzyloxycarbonyl)morphinan obtaine in step 2 (450 mg, 0.659 mmol) and hydrazine

hydrate (0.16 mL, 3.30 mmol) in MeOH (50 mL) was added Raney Ni (water solution, 1 mL) dropwise. The resulting reaction mixture was stirred at r.t. for 2 hr. and filtered to remove the catalyst. The filtrate was evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (267 mg, 62 %) as a brown solid.

MH+ 652.

Step 3: Preparation of (+)-3-Benzyloxy-1-bromo-2-(2-(methanesulfonamido)phenylamino)-*N*-(benzyloxycarbonyl)morphinan

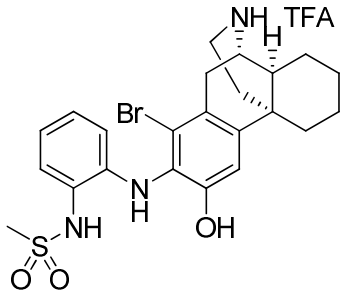


To a solution of (+)-2-(2-aminophenylamino)-3-benzyloxy-1-bromo-*N*-(benzyloxycarbonyl)morphinan obtained in step 2 (267 mg, 0.409 mmol) in DCM (10 mL) were added methanesulfonyl chloride (32 μL, 0.409 mmol) and TEA (86 μL, 0.614 mmol) at 0 ℃ stepwisely. The reaction mixture was stirred at rt overnight. Water (20 mL) was added and the mixture was extracted with DCM (20 mL X 2). The combined organics were dried over $MgSO_4$, filtered, and evaporated under vacuum.

The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (202 mg, 68 %) as a white solid.

MH+ 730.

Step 4: Preparation of (+)-1-Bromo-3-hydroxy-2-(2-(methanesulfonamido)phenylamino)morphinan TFA salt



To a solution of (+)-3-benzyloxy-1-bromo-2-(2-(methanesulfonamido)phenylamino)-*N*-(benzyloxycarbonyl)morphinan obtained in step 3 (202 mg, 0.276 mmol) in DCM (10 mL) was added BBr_3 solution (1M in DCM, 0.83 mL, 0.83 mmol) at 0 ^oC. After the reaction was completed, the reaction was quenched by MeOH (2 mL) evaporated under vacuum. The residue was purified by prep. reverse-phase HPLC (0.1 % TFA added) to provide the title compound (111 mg, 65 %) as a blue solid.

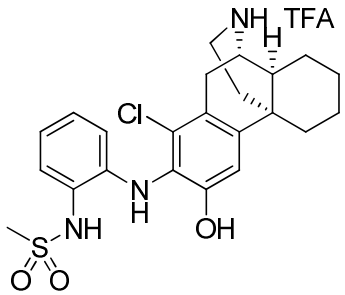
^1H NMR (400 MHz, CD_3OD) δ 7.28 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.02 (td, *J* = 8.0, 1.6 Hz, 1H), 6.98 (s, 1H), 6.80 (td, *J* = 7.6, 1.6 Hz, 1H), 6.34 (dd, *J* = 8.4, 1.2 Hz, 1H),

3.76 (q, *J* = 2.8 Hz, 1H), 3.16-3.08 (m, 2H), 3.07-2.97 (m, 4H), 2.74 (td, *J* = 13.6, 3.6 Hz, 1H), 2.43 (d, *J* = 13.6 Hz, 1H), 1.93 (dt, *J* = 12.4, 3.2 Hz, 1H), 1.83 (td, *J* = 13.6, 4.8 Hz, 1H), 1.73 (d, *J* = 12.8 Hz, 1H), 1.67-1.30 (m, 6H), 1.15-1.07 (m, 1H).

MH+ 506.

The following compound of Example 133 was obtained by repeating the procedure of Example 132.

Example 133 : Preparation of (+)-1-Chloro-3-hydroxy-2-(2-(methanesulfonamido)phenylamino)morphinan TFA salt

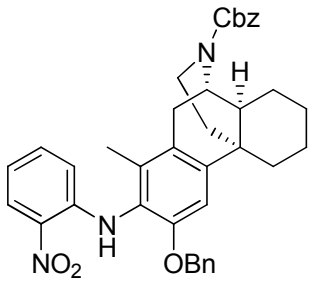


^{1}H NMR (400 MHz, CD_3OD) δ 7.28 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.03 (td, *J* = 8.0, 1.6 Hz, 1H), 6.93 (s, 1H), 6.81 (td, *J* = 7.6, 1.2 Hz, 1H), 6.37 (dd, *J* = 8.0, 1.2 Hz, 1H), 3.77 (q, *J* = 2.8 Hz, 1H), 3.15-3.09 (m, 2H), 3.05-2.97 (m, 4H), 2.76 (td, *J* = 13.6, 4.0 Hz, 1H), 2.42 (d, *J* = 14.0 Hz, 1H), 1.94 (dt, *J* = 12.8, 3.2 Hz, 1H), 1.83 (td, *J* = 13.6, 4.8 Hz, 1H), 1.73 (d, *J* = 12.4 Hz, 1H), 1.66-1.33 (m, 6H), 1.12-1.08 (m, 1H).

MH+ 462.

Example 134 : Preparation of (+)-3-Hydroxy-2-(2-(methanesulfonamido)phenylamino)-1-methylmorphinan TFA salt

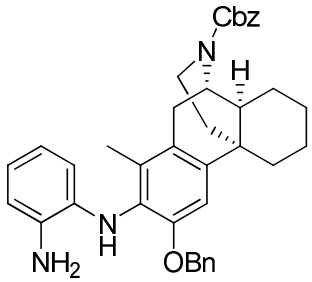
Step 1: Preparation of (+)-3-Benzyloxy-1-methyl-2-(2-nitrophenylamino)-*N*-(benzyloxycarbonyl)morphinan



To a solution of (+)-3-benzyloxy-1-bromo-2-(2-nitrophenylamino)-*N*-(benzyloxycarbonyl)morphinan obtained in step 1 of Example 132 (73) (500 mg, 0.732 mmol) in 1,4-dioxane (10 mL) were added trimethylboroxine (0.21 mL, 1.46 mmol), K_2CO_3 (405 mg, 2.93 mmol), and (dppf)$PdCl_2$.CH_2Cl_2 (59.8 mg, 0.0732 mmol). The resulting reaction mixture was heated at 100 ℃ overnight. After the reaction was completed, water (10 mL) was added thereto. The resulting mixture was extracted with EtOAc (15 mL X 2). The combined organic phase was dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (398 mg, 88 %) as a red solid.

MH+ 618.

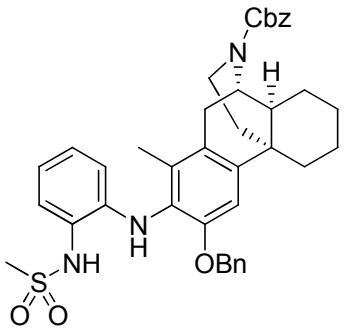
Step 2: Preparation of (+)-2-(2-Aminophenylamino)-3-benzyloxy-1-methyl-*N*-(benzyloxycarbonyl)morphinan



To a solution of (+)-3-benzyloxy-1-methyl-2-(2-nitrophenylamino)-*N*-(benzyloxycarbonyl)morphinan in step 1 (398 mg, 0.644 mmol) and hydrazine hydrate (0.16 mL, 3.22 mmol) in MeOH (50 mL) was added Raney Ni (water solution, 1 mL) dropwise. The resulting reaction mixture was stirred at r.t. for 2 hrs and filtered to remove the catalyst. The filtrate was evaporated under vacuum. The residue was further purified by flash column chromatography (Biotage SP1™) to provide the title compound (351 mg, 93 %) as a white solid.

MH+ 588.

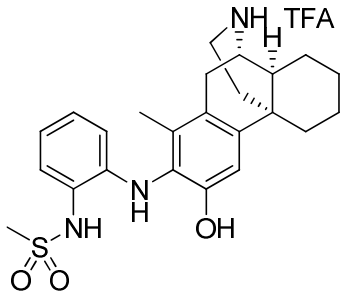
Step 3: Preparation of (+)-3-Benzyloxy-2-(2-(methanesulfonamido)phenylamino)-1-methyl-*N*-(benzyloxycarbonyl)morphinan



To a solution of (+)-2-(2-aminophenylamino)-3-benzyloxy-1-methyl-*N*-(benzyloxycarbonyl)morphinan obtained in step 2 (158 mg, 0.269 mmol) in DCM (10 mL) were added methanesulfonyl chloride (21 μL, 0.269 mmol) and TEA (56 μL, 0.404 mmol) at 0 ℃ stepwisely. The resulting reaction mixture was stirred at r.t. overnight. Water (20 mL) was added therteto and the mixture thus obtained was extracted with DCM (20 mL X 2). The combined organic phase was dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (174 mg, 97 %) as a white solid.

MH+ 666.

Step 4: Preparation of (+)-3-Hydroxy-2-(2-(methanesulfonamido)phenylamino)-1-methylmorphinan TFA salt

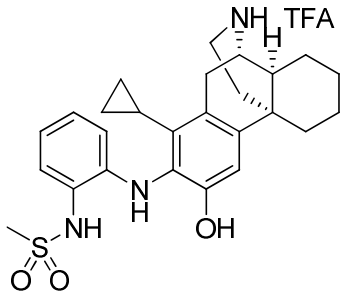


To a solution of (+)-3-benzyloxy-1-methyl-2-(2-(methanesulfonamido)phenylamino)-*N*-(benzyloxycarbonyl)morphinan obtained in step 3 (155 mg, 0.233 mmol) in DCM (10 mL) was added BBr_3 solution (1M in DCM, 0.7 mL, 0.70 mmol) at 0 ℃. The reaction was quenched by MeOH (2 mL) and the reevaporated under vacuum. The residue was purified by prep. reverse-phase HPLC (0.1 % TFA added) to provide the title compound (95 mg, 65 %) as a blue solid.

^{1}H NMR (400 MHz, CD_3OD) δ 7.24 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.01 (td, *J* = 8.0, 1.6 Hz, 1H), 6.83 (s, 1H), 6.72 (td, *J* = 8.0, 1.2 Hz, 1H), 6.20 (dd, *J* = 8.0, 1.2 Hz, 1H), 3.74 (q, *J* = 2.8 Hz, 1H), 3.13-3.04 (m, 5H), 2.82-2.75 (m, 2H), 2.43 (d, *J* = 12.8 Hz, 1H), 2.08 (s, 3H), 1.90 (dt, *J* = 12.4, 3.2 Hz, 1H), 1.80 (td, *J* = 13.6, 4.4 Hz, 1H), 1.72 (d, *J* = 11.6 Hz, 1H), 1.64-1.32 (m, 6H), 1.17-1.13 (m, 1H).

MH+ 442.

Example 135 : Preparation of (+)-1-Cylcopropyl-3-hydroxy-2-(2-(methanesulfonamido)phenylamino)morphinan TFA salt



The title compound was obtained by repeating the procedure of Example 134.

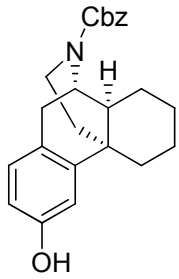
^{1}H NMR (400 MHz, CD_3OD) δ 7.16 (d, *J* = 15.6 Hz, 1H), 7.08 (d, *J* = 2.0 Hz, 1H), 7.92 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.78 (s, 1H), 6.68 (s, 1H), 3.58 (q, *J* = 2.8 Hz, 1H), 3.18-3.04 (m, 2H), 2.94 (s, 3H), 2.83-2.73 (m, 2H), 2.37 (d, *J* = 12.8 Hz, 1H), 2.08 (s, 3H), 1.91-1.83 (m, 2H), 1.75-1.71 (m, 2H), 1.55-1.27 (m, 6H), 1.17-1.13 (m, 1H), 0.95-0.90 (m, 2H), 0.65-0.61 (m, 2H).

MH+ 468.

4.4. Examples of polycycle derivaitves

Example 1 : (6*S*,6a*S*,10a*S*)-2,3,4,5,6,6a,7,8,9,10-Decahydro-6,10a-(epiminoethano)phenanthro[2,1-*b*][1,4]oxazin-12-ol TFA salt

Step 1: (4b*S*,8a*S*,9*S*)-Benzyl 3-hydroxy-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (2)

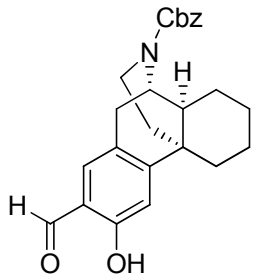


To a solution of (4b*S*,8a*S*,9*S*)-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthren-3-ol HBr (1) (50.0 g, 154 mmol) and sodium hydroxide (12.3 g, 308 mmol) in 1,4-dioxane (500 mL) and water (500 mL) was added Cbz-Cl (24.2 mL, 170 mmol) dropwise. The reaction mixture was stirred vigorously at r.t. overnight. After the reaction was completed, water (200 mL) was added. The mixture was extracted with diethyl ether (500 mL X 2). The combined organics were dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (54.6 g, 94 %) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.32 (m, 5H), 6.91m, 1H), 6.76 (s, 1H), 6.62 (m, 1H), 5.17-5.12 (m, 2H), 4.35 (d, *J* = 29.25 Hz, 1H), 3.92-3.82 (m, 1H), 3.11-3.03 (m, 1H), 2.72-2.56 (m, 2H), 2.31-2.28 (m, 1H), 1.63-1.26 (m, 10H), 1.11-1.00 (m, 1H).

MH+ 378.

Step 2: (4b*S*,8a*S*,9*S*)-Benzyl 2-formyl-3-hydroxy-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (3)

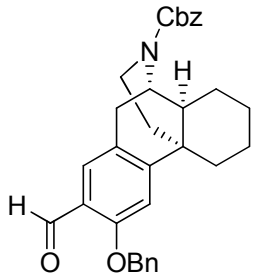


A mixture of (4b*S*,8a*S*,9*S*)-benzyl 3-hydroxy-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (2) (12.0 g, 31.8 mmol), paraformaldehyde (9.55 g, 318 mmol), $MgCl_2$ (4.54 g, 47.7 mmol) and TEA (11 mL, 79.5 mmol) in butyronitrile (80 mL) was heated at 120 ℃ for 8 days. The reaction mixture was evaporated to remove the solvent under vacuum. The residue was poured into water (300 mL) and extracted with EtOAc (300 mL X 3). The organic phase was dried over $MgSO_4$ and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (11.9 g, 92 %) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.73 (s, 1H), 9.83 (s, 1H), 7.38-7.26m, 5H), 6.95 (s, 1H), 5.18-5.13 (m, 2H), 4.41 (d, *J* = 44.8 Hz, 1H), 3.99-3.87 (m, 1H), 3.13 (td, *J* = 16.0, 5.6 Hz, 1H), 2.78-2.56 (m, 2H), 2.37 (d, *J* = 13.6 Hz, 1H), 1.76-1.54 (m, 5H), 1.49-1.18 (m, 4H), 1.07-0.97 (m, 1H).

MH+ 406.

Step 3: (4b*S*,8a*S*,9*S*)-Benzyl 3-(benzyloxy)-2-formyl-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (4)

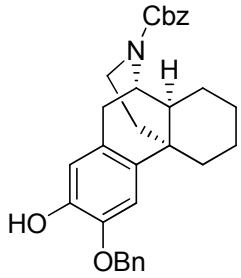


A mixture of (4b*S*,8a*S*,9*S*)-benzyl 2-formyl-3-hydroxy-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (3) (10.0 g, 24.7 mmol), benzyl bromide (3.5 mL, 29.6 mmol) and Cs_2CO_3 (12.1 g, 29.6 mmol) in DMF (100 mL) was stirred at r.t. overnight. The reaction mixture was evaporated to remove the solvent under vacuum. The residue was poured into water (300 mL) and extracted with EtOAc (200 mL X 2). The organic phase was dried over $MgSO_4$ and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (10.4 g, 85 %) as a yellow gum.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.50 (s, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.45-7.28 (m, 10H), 6.92 (s, 1H), 5.22-5.12 (m, 4H), 4.38 (d, *J* = 45.2 Hz, 1H), 3.97-3.84 (m, 1H), 3.09 (td, *J* = 18.0, 5.6 Hz, 1H), 2.75-2.56 (m, 2H), 2.26 (d, *J* = 13.6 Hz, 1H), 1.73-1.57 (m, 4H), 1.52-1.46 (m, 2H), 1.38-1.24 (m, 4H), 1.10-0.96 (m, 2H).

MH+ 409.

Step 4: (4b*S*,8a*S*,9*S*)-Benzyl 3-(benzyloxy)-2-hydroxy-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (5)

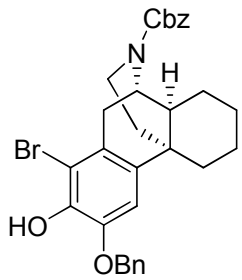


To a solution of (4b*S*,8a*S*,9*S*)-benzyl 3-(benzyloxy)-2-formyl-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (4) (1.64 g, 3.31 mmol) and 30 % H_2O_2 (1.5 mL, 14.7 mmol) in MeOH (100 mL) was added conc. H_2SO_4 (0.7 mL, 13.1 mmol) dropwise. The reaction mixture was stirred at r.t. overnight and evaporated under vacuum. The residue was poured into water (300 mL) and extracted with EtOAc (100 mL X 3). The organic phase was washed with sat. $NaHCO_3$ solution (80 mL X 3), dried over $MgSO_4$ and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (1.43 g, 89 %) as a yellow gum.

MH+ 484.

Step 5: (4b*S*,8a*S*,9*S*)-Benzyl 3-(benzyloxy)-1-bromo-2-hydroxy-6,7,8,8a,9,10-

hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (6)

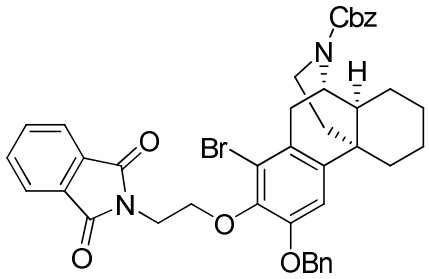


To a cooled solution of (4b*S*,8a*S*,9*S*)-benzyl 3-(benzyloxy)-2-hydroxy-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (5) (400 mg, 3.31 mmol) and NaOAc (135 mg, 1.65 mmol) in glacial AcOH (15 mL) was added Br_2 (85 μL, 1.65 mmol) dropwise. The reaction mixture was stirred at r.t. overnight and evaporated under vacuum. The residue was poured into water (50 mL) and extracted with EtOAc (30 mL X 2). The organic phase was washed with sat. $Na_2S_2O_3$ solution (20 mL X 2), dried over $MgSO_4$ and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (454 mg, 98 %) as a yellow gum.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.25 (m, 10H), 6.77 (s, 1H), 5.17-5.07 (m, 4H), 4.42 (d, *J* = 46.8 Hz, 1H), 3.89 (ddd, *J* = 33.6, 13.2, 4.0 Hz, 1H), 2.90 (td, *J* = 18.4, 6.0 Hz, 1H), 2.73-2.56 (m, 2H), 2.16 (d, *J* = 13.6 Hz, 1H), 1.67-1.49 (m, 3H), 1.46-1.39 (m, 2H), 1.33-1.23 (m, 3H), 1.08-0.95 (m, 2H).

MH+ 562.

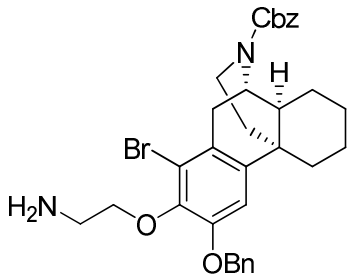
Step 6: (4b*S*,8a*S*,9*S*)-Benzyl 3-(benzyloxy)-1-bromo-2-(2-(1,3-dioxoisoindolin-2-yl)ethoxy)-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (8)



A mixture of (4b*S*,8a*S*,9*S*)-benzyl 3-(benzyloxy)-1-bromo-2-hydroxy-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (6) (800 mg, 1.42 mmol), *N*-(2-bromoethyl)phthalimide (7) (903 mg, 3.56 mmol) and Cs_2CO_3 (579 mg, 1.78 mmol) in DMF (10 mL) was heated at 60 ℃ overnight. The reaction mixture was evaporated to remove the solvent under vacuum. The residue was poured into water (50 mL) and extracted with EtOAc (30 mL X 2). The organic phase was dried over $MgSO_4$ and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (722 mg, 88 %) as a white solid.

MH+ 735.

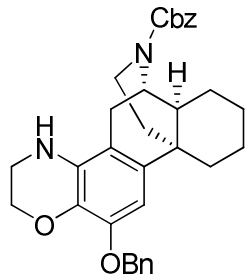
Step 7: (4b*S*,8a*S*,9*S*)-Benzyl 2-(2-aminoethoxy)-3-(benzyloxy)-1-bromo-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (9)



To a solution of (4b*S*,8a*S*,9*S*)-benzyl 3-(benzyloxy)-1-bromo-2-(2-(1,3-dioxoisoindolin-2-yl)ethoxy)-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (8) (722 mg, 0.981 mmol) in MeOH (20 mL) was added hydrazine hydrate (0.14 mL, 2.94 mmol). The reaction mixture was stirred at r.t. overnight and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (559 mg, 94 %) as a white solid.

MH+ 605.

Step 8: (6*S*,6a*S*,10a*S*)-Benzyl 12-(benzyloxy)-2,3,4,5,6,6a,7,8,9,10-decahydro-6,10a-(epiminoethano)phenanthro[2,1-*b*][1,4]oxazine-15-carboxylate (10)

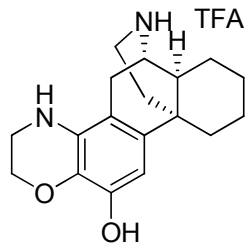


(4b*S*,8a*S*,9*S*)-Benzyl 2-(2-aminoethoxy)-3-(benzyloxy)-1-bromo-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (9) (81.1 mg, 0.134 mmol) was added to a microwave reactor containing a mixture of $Pd_2(dba)_3$ (12.3 mg, 0.0134 mmol), BINAP (12.5 mg, 0.0201 mmol) and Sodium *t*-butoxide (36.0 mg, 0.375 mmol) in THF (10 mL). The capped reactor was placed in a microwave reactor and the mixture was irradiated at 170 ℃ for 25 min. The reaction mixture was evaporated to remove the solvent under vacuum. The residue was poured into water (20 mL) and extracted with EtOAc (20 mL X 2). The organic phase was dried over $MgSO_4$ and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (52 mg, 73 %) as a yellow gum.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.23 (m, 10H), 6.26 (s, 1H), 5.18-5.06 (m, 4H), 4.41 (d, *J* = 42.8 Hz, 1H), 4.30 (br s, 2H), 3.90-3.79 (m, 1H), 3.46 (br s, 2H), 2.72-2.54 (m, 2H), 2.23 (t, *J* = 17.2 Hz, 1H), 2.11 (d, *J* = 13.6 Hz, 1H), 1.64-1.15 (m, 8H), 1.09-1.01 (m, 2H).

MH+ 525.

Step 9: (6*S*,6a*S*,10a*S*)-2,3,4,5,6,6a,7,8,9,10-Decahydro-6,10a-(epiminoethano)phenanthro[2,1-*b*][1,4]oxazin-12-ol TFA salt (11)



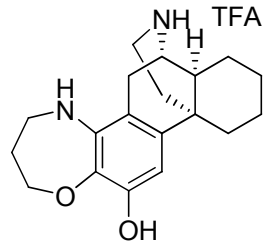
To a solution of (6*S*,6a*S*,10a*S*)-benzyl 12-(benzyloxy)-2,3,4,5,6,6a,7,8,9,10-decahydro-6,10a-(epiminoethano)phenanthro[2,1-*b*][1,4]oxazine-15-carboxylate (10) (120 mg, 0.229 mmol) in IPA (10 mL) was added 10 % Pd on charcoal (18 mg). The mixture was stirred under hydrogen atmosphere at r.t. overnight. The reaction mixture was filtered to remove the catalyst and evaporated under vacuum. The residue was further purified by prep. HPLC (Gilson, C18 column, 0.1 % TFA) to provide the title compound (77 mg, 81 %) as a white solid.

^{1}H NMR (400 MHz, CD_3OD) δ 6.27 (s, 1H), 4.19 (t, *J* = 4.4 Hz, 2H), 3.72-3.69 (m, 1H), 3.47-3.44 (m, 1H), 3.30-3.28 (m, 2H), 3.05 (dd, *J* = 12.8, 3.2 Hz, 1H), 2.85 (dd, *J* = 18.8, 6.4 Hz, 1H), 2.77 (td, *J* = 13.2, 3.6 Hz, 1H), 2.59 (d, *J* = 18.8 Hz, 1H), 2.33-2.31 (m, 1H), 1.85 (dt, *J* = 12.8, 3.2 Hz, 1H), 1.77-1.65 (m, 2H), 1.56-1.27 (m, 6H), 1.16-1.06 (m, 1H).

MH+ 301.

The following compound of Example 2 was obtained by repeating the procedure of Example 1 using *N*-(3-bromopropyl)phthalimide (13) instead of *N*-(2-bromoethyl)phthalimide (7).

Example 2 : (7*S*,7a*S*,11a*S*)-3,4,5,6,7,7a,8,9,10,11-Decahydro-2*H*-7,11a-(epiminoethano)phenanthro[2,1-*b*][1,4]oxazepin-13-ol TFA salt (12)



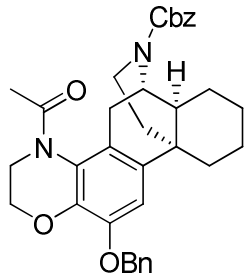
^{1}H NMR (400 MHz, CD_3OD) δ 4.14-4.13 (m, 1H), 4.07-4.06 (m, 1H), 3.74-3.72 (m, 1H), 3.35-3.33 (m, 2H), 3.06 (dd, *J* = 12.8, 2.8 Hz, 1H), 2.97-2.90 (m, 1H), 2.75 (td, *J* = 13.2, 3.6 Hz, 1H), 2.68-2.63 (m, 1H), 2.36-2.33 (m, 1H), 2.10-1.99 (m, 3H), 1.85 (dt, *J* = 12.4, 2.8 Hz, 1H), 1.78-1.65 (m, 2H), 1.58-1.45 (m, 4H), 1.42-1.21 (m, 4H), 1.16-1.06 (m, 1H).

MH+ 315.

Example 3 : 1-((6*S*,6a*S*,10a*S*)-12-Hydroxy-2,3,6,6a,7,8,9,10-octahydro-6,10a-

(epiminoethano)phenanthro[2,1-*b*][1,4]oxazin-4(5*H*)-yl)ethanone TFA salt (15)

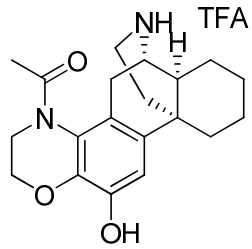
Step 1: (6*S*,6a*S*,10a*S*)-Benzyl 4-acetyl-12-(benzyloxy)-2,3,4,5,6,6a,7,8,9,10-decahydro-6,10a-(epiminoethano)phenanthro[2,1-*b*][1,4]oxazine-15-carboxylate (14)



To a solution of (6*S*,6a*S*,10a*S*)-benzyl 12-(benzyloxy)-2,3,4,5,6,6a,7,8,9,10-decahydro-6,10a-(epiminoethano)phenanthro[2,1-*b*][1,4]oxazine-15-carboxylate (10) (120 mg, 0.229 mmol), DMAP (33.6 mg, 0.275 mmol) and DIPEA (0.36 mL, 2.06 mmol) in DCM (20 mL) was added acetyl chloride (0.1 mL, 1.37 mmol) at 0 ℃. The reaction mixture was stirred at 50 ℃ overnight. The reaction mixture was evaporated to remove the solvent under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (96 mg, 74 %) as a brown gum.

MH+ 567.

Step 2: 1-((6*S*,6a*S*,10a*S*)-12-Hydroxy-2,3,6,6a,7,8,9,10-octahydro-6,10a-(epiminoethano)phenanthro[2,1-*b*][1,4]oxazin-4(5*H*)-yl)ethanone TFA salt (15)



To a solution of (6*S*,6a*S*,10a*S*)-benzyl 4-acetyl-12-(benzyloxy)-2,3,4,5,6,6a,7,8,9,10-decahydro-6,10a-(epiminoethano)phenanthro[2,1-*b*][1,4]oxazine-15-carboxylate (14) (96 mg, 0.169 mmol) in IPA (10 mL) was added 10 % Pd on charcoal (10 mg). The mixture was stirred under hydrogen atmosphere at r.t. overnight. The reaction mixture was filtered to remove the catalyst and evaporated under vacuum. The residue was further purified by prep. HPLC (Gilson, C18 column, 0.1 % TFA) to provide the title compound (35 mg, 45 %) as a yellow gum.

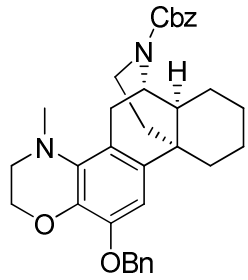
^{1}H NMR (400 MHz, CD_3OD) δ 6.75 (s, 1H), 4.59-4.55 (m, 1H), 4.37-4.26 (m, 2H), 3.64-3.56 (m, 1H), 3.51-3.45 (m, 1H), 3.19 (dd, *J* = 19.2, 6.4 Hz, 1H), 3.11-3.08 (m, 1H), 3.04-3.00 (m, 1H), 2.58 (td, *J* = 10.4, 3.6 Hz, 1H), 2.47 (d, *J* = 19.6 Hz, 1H), 2.36 (d, *J* = 12.8 Hz, 1H), 2.29-2.28 (m, 3H), 1.88-1.83 (m, 1H), 1.77-1.69 (m, 2H), 1.55-1.27 (m, 7H).

MH+ 343.

Example 4 : (6*S*,6a*S*,10a*S*)-4-Methyl-2,3,4,5,6,6a,7,8,9,10-decahydro-6,10a-

(epiminoethano)phenanthro[2,1-*b*][1,4]oxazin-12-ol TFA salt (17)

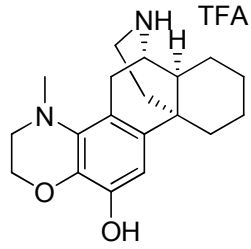
Step 1: (6*S*,6a*S*,10a*S*)-Benzyl 12-(benzyloxy)-4-methyl-2,3,4,5,6,6a,7,8,9,10-decahydro-6,10a-(epiminoethano)phenanthro[2,1-*b*][1,4]oxazine-15-carboxylate (16)



To a solution of (6*S*,6a*S*,10a*S*)-benzyl 12-(benzyloxy)-2,3,4,5,6,6a,7,8,9,10-decahydro-6,10a-(epiminoethano)phenanthro[2,1-*b*][1,4]oxazine-15-carboxylate (10) (148 mg, 0.282 mmol) and formalin (37 %, 1.1 mL, 14.1 mmol) in DCE (10 mL) was added sodium triacetoxyborohydride (179 mg, 0.846 mmol). The mixture was stirred at r.t. for 48 hours. The reaction mixture was evaporated to remove the solvent under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (67 mg, 44 %) as a brown gum.

MH+ 539.

Step 2: (6*S*,6a*S*,10a*S*)-4-Methyl-2,3,4,5,6,6a,7,8,9,10-decahydro-6,10a-(epiminoethano)phenanthro[2,1-*b*][1,4]oxazin-12-ol TFA salt (17)



To a solution of (6*S*,6a*S*,10a*S*)-benzyl 12-(benzyloxy)-4-methyl-2,3,4,5,6,6a,7,8,9,10-decahydro-6,10a-(epiminoethano)phenanthro[2,1-*b*][1,4]oxazine-15-carboxylate (16) (67 mg, 0.123 mmol) in IPA (10 mL) was added 10 % Pd on charcoal (7 mg). The mixture was stirred under hydrogen atmosphere at r.t. overnight. The reaction mixture was filtered to remove the catalyst and evaporated under vacuum. The residue was further purified by prep. HPLC (Gilson, C18 column, 0.1 % TFA) to provide the title compound (21 mg, 40 %) as a yellow gum.

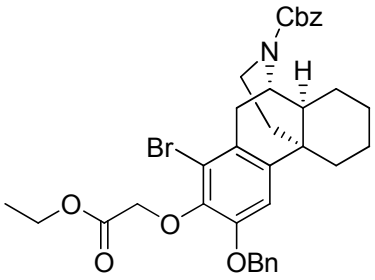
^{1}H NMR (400 MHz, CD_3OD) δ 6.59 (s, 1H), 4.29-4.27 (m, 2H), 3.72-3.70 (m, 1H), 3.19-3.09 (m, 3H), 3.06-2.95 (m, 3H), 2.74 (s, 3H), 3.64 (td, *J* = 13.2, 3.6 Hz, 1H), 2.36 (d, *J* = 13.2 Hz, 1H), 1.87 (dt, *J* = 12.8, 3.2 Hz, 1H), 1.77-1.69 (m, 2H), 1.56-1.50 (m, 3H), 1.44-1.26 (m, 3H), 1.20-1.14 (m, 1H).

MH+ 315.

Example 5 : (6*S*,6a*S*,10a*S*)-3,5,6,6a,7,8,9,10-Octahydro-2*H*-6,10a-(epiminoethano)phenanthro[1,2-*b*][1,4]dioxin-12-ol TFA salt (22)

Step 1: (4b*S*,8a*S*,9*S*)-Benzyl 3-(benzyloxy)-1-bromo-2-(2-ethoxy-2-oxoethoxy)-

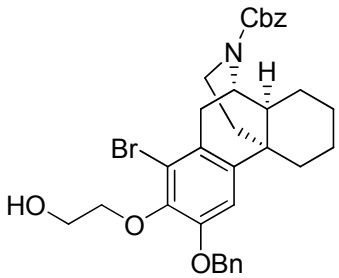
6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (18)



To a solution of (4b*S*,8a*S*,9*S*)-benzyl 3-(benzyloxy)-1-bromo-2-hydroxy-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (6) (500 mg, 0.889 mmol) and Cs_2CO_3 (579 mg, 1.78 mmol) in DMF (10 mL) was added ethyl bromoacetate (0.15 mL, 1.33 mmol). The reaction mixture was stirred at r.t. overnight and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (520 mg, 90 %) as a yellow gum.

MH+ 648.

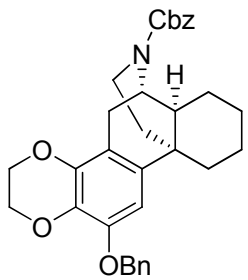
Step 2: (4b*S*,8a*S*,9*S*)-Benzyl 3-(benzyloxy)-1-bromo-2-(2-hydroxyethoxy)-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (19)



To a solution of (4b*S*,8a*S*,9*S*)-benzyl 3-(benzyloxy)-1-bromo-2-(2-ethoxy-2-oxoethoxy)-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (18) (683 mg, 1.05 mmol) in THF (10 mL) was added lithium borohydride (0.53 mL, 1.05 mmol) at 0 ℃. The reaction mixture was stirred at r.t. overnight and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (580 mg, 90 %) as a colorless gum.

MH+ 606.

Step 3: (6*S*,6a*S*,10a*S*)-Benzyl 12-(benzyloxy)-3,5,6,6a,7,8,9,10-octahydro-2*H*-6,10a-(epiminoethano)phenanthro[1,2-*b*][1,4]dioxine-15-carboxylate (21)

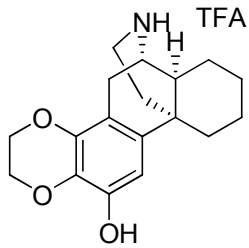


A mixture of (4b*S*,8a*S*,9*S*)-benzyl 3-(benzyloxy)-1-bromo-2-(2-hydroxyethoxy)-

6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (19) (300 mg, 0.495 mmol), $Pd_2(dba)_3$ (4.5 mg, 0.00495 mmol), 2-di-*t*-butylphosphino-2'-(*N*,*N*-dimethylamino)biphenyl (20) (3.4 mg, 0.00990 mmol) and sodium *t*-butoxide (71.4 mg, 0.743 mmol) in toluene (10 mL) was heated at 100 ℃ for 2 days and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (240 mg, 90 %) as a brown gum.

MH+ 526.

Step 4: (6*S*,6a*S*,10a*S*)-3,5,6,6a,7,8,9,10-Octahydro-2*H*-6,10a-(epiminoethano)phenanthro[1,2-*b*][1,4]dioxin-12-ol TFA salt (22)



To a solution of (6*S*,6a*S*,10a*S*)-benzyl 12-(benzyloxy)-3,5,6,6a,7,8,9,10-octahydro-2*H*-6,10a-(epiminoethano)phenanthro[1,2-*b*][1,4]dioxine-15-carboxylate (21) (237 mg, 0.495 mmol) in IPA (10 mL) was added 10 % Pd on charcoal (36 mg). The mixture was stirred under hydrogen atmosphere at r.t. overnight. The reaction mixture was filtered to remove the catalyst and evaporated under vacuum. The residue was further purified by prep. HPLC (Gilson, C18 column, 0.1 % TFA) to provide the title

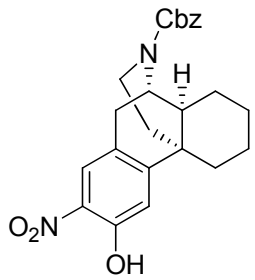
compound (19 mg, 9 %) as a colorless gum.

^{1}H NMR (400 MHz, CD_3OD) δ 6.41 (s, 1H), 4.30-4.24 (m, 4H), 3.67-3.65 (m, 1H), 3.08-3.04 (m, 1H), 2.96-2.90 (m, 1H), 2.82-2.75 (m, 2H), 2.33 (d, *J* = 12.0 Hz, 1H), 1.86-1.82 (m, 1H), 1.74-1.67 (m, 2H), 1.55-1.27 (m, 7H), 1.12-1.08 (m, 1H).

MH+ 302.

Example 6 : (6*S*,6a*S*,10a*S*)-2-Methyl-1,2,3,5,6,6a,7,8,9,10-decahydro-6,10a-(epiminoethano)phenanthro[1,2-*b*][1,4]oxazin-12-ol TFA salt (30)

Step 1: (4b*S*,8a*S*,9*S*)-Benzyl 3-hydroxy-2-nitro-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (23)



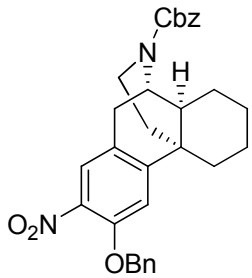
To a cooled solution of (4b*S*,8a*S*,9*S*)-benzyl 3-hydroxy-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (2) (7.46 g, 19.8 mmol) in formic acid (20 mL) was added nitric acid (65 %, 1.6 mL, 23.7 mmol) dropwise. The reaction mixture was stirred at r.t. overnight and evaporated to remove the solvent under vacuum. The residue was poured into water (300 mL) and extracted with EtOAc (300

mL X 3). The organic phase was washed with sat. $NaHCO_3$ solution (200 mL X 3), dried over $MgSO_4$ and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (5.26 g, 63 %) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.36 (s, 1H), 7.84 (s, 1H), 7.38-7.34m, 5H), 7.10 (s, 1H), 5.21-5.13 (m, 2H), 4.42 (d, *J* = 46.8 Hz, 1H), 4.00-3.8 (m, 1H), 3.12 (td, *J* = 16.0, 5.2 Hz, 1H), 2.79-2.54 (m, 2H), 2.36 (d, *J* = 13.6 Hz, 1H), 1.77-1.50 (m, 5H), 1.45-1.17 (m, 4H), 1.02-0.93 (m, 1H).

MH+ 423.

Step 2: (4b*S*,8a*S*,9*S*)-Benzyl 3-(benzyloxy)-2-nitro-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (24)



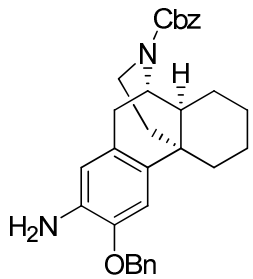
To a solution of (4b*S*,8a*S*,9*S*)-benzyl 3-hydroxy-2-nitro-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (23) (11.3 g, 26.7 mmol) and K_2CO_3 (7.38 g, 53.4 mmol) in DMF (100 mL) was added benzyl bromide (3.94 mL, 40.1 mmol). The reaction mixture was heated at 70 ℃ overnight and evaporated to

remove the solvent under vacuum. The residue was poured into water (300 mL) and extracted with EtOAc (150 mL X 2). The organic phase was dried over $MgSO_4$ and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (13.6 g, 99 %) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.45-1.29 (m, 10H), 6.96 (s, 1H), 5.26-5.12 (m, 4H), 4.39 (d, *J* = 46.0 Hz, 1H), 3.97-3.85 (m, 1H), 3.08 (td, *J* = 18.0, 5.6 Hz, 1H), 2.74-2.54 (m, 2H), 2.20 (d, *J* = 14.0 Hz, 1H), 1.73-1.57 (m, 3H), 1.53-1.44 (m, 2H), 1.38-1.24 (m, 3H), 1.02-0.93 (m, 2H).

MH+ 513.

Step 3: (4b*S*,8a*S*,9*S*)-Benzyl 2-amino-3-(benzyloxy)-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (25)



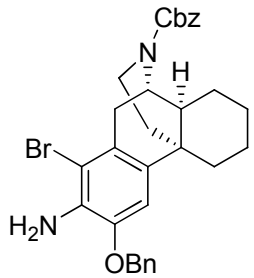
To a solution of (4b*S*,8a*S*,9*S*)-benzyl 3-(benzyloxy)-2-nitro-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (24) (13.6 g, 26.5 mmol) and hydrazine hydrate (12.9 mL, 265 mmol) in MeOH (200 mL) was added

Raney Ni (water solution, 1 mL) dropwise. The reaction mixture was stirred at r.t. for 2 hr. and filtered to remove the catalyst. The filtrate was evaporated under vacuum. The residue was further purified by flash column chromatography (Biotage SP1™) to provide the title compound (12.5 g, 98 %) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.30m, 10H), 6.69 (s, 1H), 6.45 (d, *J* = 10.8 Hz, 1H), 5.17-5.01 (m, 4H), 4.32 (d, *J* = 40.8 Hz, 1H), 3.96-3.82 (m, 1H), 3.72 (br s, 2H), 3.01 (td, *J* = 17.6, 5.6 Hz, 1H), 2.73-2.52 (m, 2H), 2.20 (d, *J* = 11.6 Hz, 1H), 1.66-1.06 (m, 10H).

MH+ 483.

Step 4: (4b*S*,8a*S*,9*S*)-Benzyl 2-amino-3-(benzyloxy)-1-bromo-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (26)



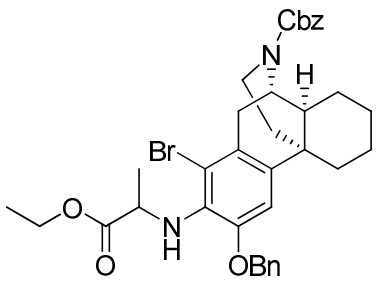
A mixture of (4b*S*,8a*S*,9*S*)-benzyl 2-amino-3-(benzyloxy)-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (25) (1.29 g, 2.67 mmol) and pyridinium tribromide (1.28 g, 4.01 mmol) in THF (30 mL) was heated at

60 ℃ overnight and evaporated under vacuum. The residue was further purified by flash column chromatography (Biotage SP1™) to provide the title compound (1.06 g, 71 %) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.30m, 10H), 6.70 (s, 1H), 5.17-5.01 (m, 4H), 4.41 (d, *J* = 44.8 Hz, 1H), 3.94-3.82 (m, 1H), 2.89 (td, *J* = 16.0, 5.6 Hz, 1H), 2.71-2.64 (m, 2H), 2.17 (d, *J* = 13.6 Hz, 1H), 1.62-1.1.25 (m, 8H), 1.15-0.97 (m, 2H).

MH+ 561.

Step 5: (4b*S*,8a*S*,9*S*)-Benzyl 3-(benzyloxy)-1-bromo-2-((1-ethoxy-1-oxopropan-2-yl)amino)-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (27)

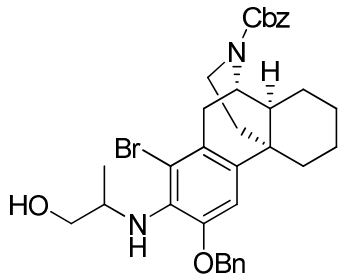


To a solution of (4b*S*,8a*S*,9*S*)-benzyl 2-amino-3-(benzyloxy)-1-bromo-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (26) (0.98 g, 1.75 mmol) and sodium iodide (0.34 g, 2.27 mmol) in DMF (10 mL) was added ethyl 2-bromoacetate (0.27 mL, 2.09 mmol). The reaction mixture was heated at

80 ℃ for 5 days and evaporated under vacuum. The residue was further purified by flash column chromatography (Biotage SP1™) to provide the title compound (0.58 g, 50 %) as a yellow gum.

MH+ 661.

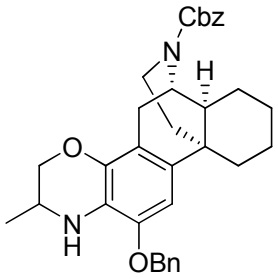
Step 6: (4b*S*,8a*S*,9*S*)-Benzyl 3-(benzyloxy)-1-bromo-2-((1-hydroxypropan-2-yl)amino)-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (28)



To a solution of (4b*S*,8a*S*,9*S*)-benzyl 3-(benzyloxy)-1-bromo-2-((1-ethoxy-1-oxopropan-2-yl)amino)-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (27) (0.58 g, 0.877 mmol) in THF (10 mL) was added lithium borohydride (0.88 mL, 1.75 mmol) at 0 ℃. The reaction mixture was stirred at r.t. overnight and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (0.27 g, 50 %) as a white solid.

MH+ 619.

Step 7: (6*S*,6a*S*,10a*S*)-Benzyl 12-(benzyloxy)-2-methyl-1,2,3,5,6,6a,7,8,9,10-decahydro-6,10a-(epiminoethano)phenanthro[1,2-*b*][1,4]oxazine-15-carboxylate (29)



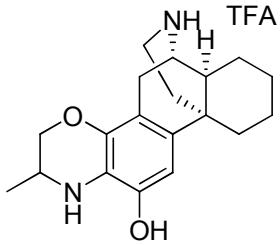
A mixture of (4b*S*,8a*S*,9*S*)-benzyl 3-(benzyloxy)-1-bromo-2-((1-hydroxypropan-2-yl)amino)-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (28) (270 mg, 0.436 mmol), $Pd_2(dba)_3$ (39.9 mg, 0.0436 mmol), 2-di-*t*-butylphosphino-2'-(*N*,*N*-dimethylamino)biphenyl (20) (29.8 mg, 0.0872 mmol) and sodium *t*-butoxide (62.8 mg, 0.654 mmol) in toluene (5 mL) was heated at 100 ℃ for 2 days and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (95 mg, 40 %) as a colorless gum.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.29m, 10H), 6.39 (d, *J* = 3.6 Hz, 1H), 5.16-5.01 (m, 4H), 4.37 (d, *J* = 43.2 Hz, 1H), 4.21 (d, *J* = 10.4 Hz, 1H), 3.90-3.76 (m, 2H), 3.47-3.45 (m, 1H), 2.79-2.71 (m, 2H), 2.65-2.61 (m, 1H), 2.20 (d, *J* = 10.8 Hz, 1H),

1.63-1.10 (m, 13H).

MH+ 539.

Step 8: (6*S*,6a*S*,10a*S*)-2-Methyl-1,2,3,5,6,6a,7,8,9,10-decahydro-6,10a-(epiminoethano)phenanthro[1,2-*b*][1,4]oxazin-12-ol TFA salt (30)



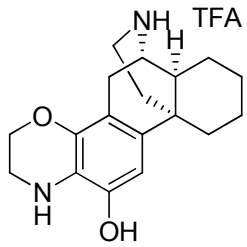
To a solution of (6*S*,6a*S*,10a*S*)-benzyl 12-(benzyloxy)-2-methyl-1,2,3,5,6,6a,7,8,9,10-decahydro-6,10a-(epiminoethano)phenanthro[1,2-*b*][1,4]oxazine-15-carboxylate (29) (54 mg, 0.101 mmol) in DCM (10 mL) was added BBr_3 (1M in DCM, 0.3 mL, 0.300 mmol) at 0 ℃. The mixture was stirred at r.t. overnight and quenched by MeOH (1 mL). The reaction mixture was evaporated under vacuum. The residue was further purified by prep. HPLC (Waters, C18 column, 0.1 % TFA) to provide the title compound (23 mg, 54 %) as a brown solid.

^{1}H NMR (400 MHz, CD_3OD) δ 6.62 (s, 1H), 4.57-4.52 (m, 1H), 4.12-4.04 (m, 1H), 3.82-3.74 (m, 2H), 3.12 (dd, *J* = 13.2, 4.0 Hz, 1H), 3.00-2.88 (m, 2H), 2.79-2.71 (m, 1H), 2.36 (d, *J* = 14.0 Hz, 1H), 1.97-1.93 (m, 1H), 1.84 (td, *J* = 13.6, 4.8 Hz, 1H), 1.67-1.39 (m, 9H), 1.28-1.18 (m, 1H), 1.05-1.01 (m, 1H).

MH+ 315.

The following compounds of Example 7 and 8 were obtained by repeating the procedure of Example 6.

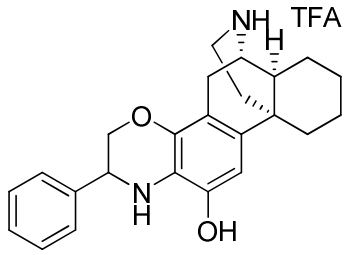
Example 7 : (6*S*,6a*S*,10a*S*)-1,2,3,5,6,6a,7,8,9,10-Decahydro-6,10a-(epiminoethano)phenanthro[1,2-*b*][1,4]oxazin-12-ol TFA salt (30a)



^{1}H NMR (400 MHz, CD_3OD) δ 6.37 (s, 1H), 4.73-4.71 (m, 1H), 4.35 (d, *J* = 12.0 Hz, 1H), 3.90 (m, 1H), 3.63-3.61 (m, 1H), 3.02-3.00 (m, 1H), 2.96-2.90 (m, 1H), 2.85-2.76 (m, 2H), 2.32-2.30 (m, 1H), 1.84-1.81 (m, 1H), 1.73-1.66 (m, 2H), 1.48-1.27 (m, 7H).

MH+ 301.

Example 8 : (6*S*,6a*S*,10a*S*)-2-Phenyl-1,2,3,5,6,6a,7,8,9,10-decahydro-6,10a-(epiminoethano)phenanthro[1,2-*b*][1,4]oxazin-12-ol TFA salt (30b)

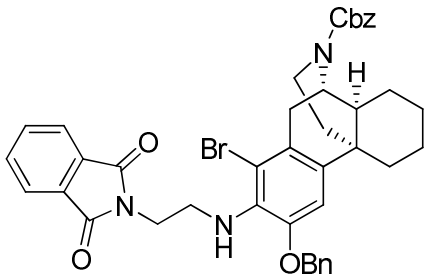


^{1}H NMR (400 MHz, CD_3OD) δ 7.46-7.31 (m, 5H), 6.43 (s, 1H), 4.49-4.45 (m, 1H), 4.37 (dd, *J* = 10.8, 2.8 Hz, 1H), 4.06 (dd, *J* = 10.8, 7.2 Hz, 1H), 3.68-3.66 (m, 1H), 3.08 (dd, *J* = 12.8, 3.2 Hz, 1H), 2.95 (dd, *J* = 19.2, 6.0 Hz, 1H) 2.85-2.79 (m, 2H), 2.35 (d, *J* = 10.4 Hz, 1H), 1.85 (d, *J* = 12.4 Hz, 1H), 1.79-1.70 (m, 2H), 1.57-1.37 (m, 6H), 1.20-1.12 (m, 1H).

MH+ 377.

Example 9 : (6*S*,6a*S*,10a*S*)-6,6a,7,8,9,10-Hexahydro-5*H*-6,10a-(epiminoethano)naphtho[2,1-*f*]quinoxalin-12-ol TFA salt (34)

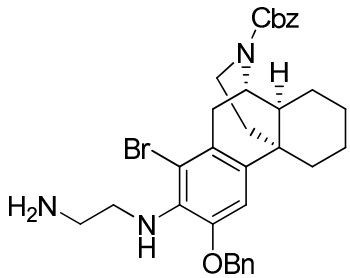
Step 1: (4b*S*,8a*S*,9*S*)-Benzyl 3-(benzyloxy)-1-bromo-2-((2-(1,3-dioxoisoindolin-2-yl)ethyl)amino)-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (31)



A mixture of (4b*S*,8a*S*,9*S*)-benzyl 2-amino-3-(benzyloxy)-1-bromo-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (26) (1.0 g, 1.78 mmol), *N*-(2-bromoethyl)phthalimide (7) (4.52 g, 17.8 mmol) and sodium iodide (2.67 g, 17.8 mmol) in DMF (20 mL) was heated at 60 ℃ for 7 days. The reaction mixture was evaporated to remove the solvent under vacuum. The residue was poured into water (100 mL) and extracted with EtOAc (50 mL X 2). The organic phase was dried over $MgSO_4$ and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (490 mg, 38 %) as a yellow solid.

MH+ 734.

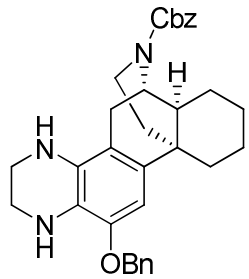
Step 2: (4b*S*,8a*S*,9*S*)-Benzyl 2-((2-aminoethyl)amino)-3-(benzyloxy)-1-bromo-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (32)



To a solution of (4b*S*,8a*S*,9*S*)-benzyl 3-(benzyloxy)-1-bromo-2-((2-(1,3-dioxoisoindolin-2-yl)ethyl)amino)-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (31) (490 mg, 0.670 mmol) in MeOH (15 mL) was added hydrazine hydrate (0.16 mL, 3.35 mmol). The reaction mixture was stirred at r.t. overnight and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (430 mg, 90 %) as a white solid.

MH+ 604.

Step 3: (6*S*,6a*S*,10a*S*)-Benzyl 12-(benzyloxy)-2,3,4,5,6,6a,7,8,9,10-decahydro-1*H*-6,10a-(epiminoethano)naphtho[2,1-*f*]quinoxaline-15-carboxylate (33)

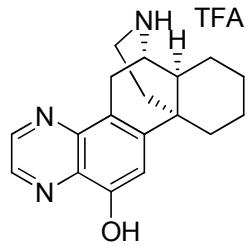


(4b*S*,8a*S*,9*S*)-Benzyl 2-((2-aminoethyl)amino)-3-(benzyloxy)-1-bromo-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (32) (38 mg, 0.0630 mmol) was added to a microwave reactor containing a mixture of $Pd_2(dba)_3$ (5.8 mg, 0.00630 mmol), BINAP (5.9 mg, 0.00945 mmol) and sodium *t*-butoxide (17.0 mg, 0.176 mmol) in THF (5 mL). The capped reactor was placed in a microwave reactor and the mixture was irradiated at 170 ℃ for 25 min. The reaction mixture was evaporated to remove the solvent under vacuum. The residue was poured into water (20 mL) and extracted with EtOAc (20 mL X 2). The organic phase was dried over $MgSO_4$ and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (27 mg, 81 %) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.29 (m, 10H), 6.29 (s, 1H), 5.16-5.11 (m, 2H), 5.01 (s, 2H), 4.41 (d, *J* = 41.2 Hz, 1H), 3.91-3.80 (m, 1H), 3.50 (br s, 2H), 3.39 (br s, 2H), 2.77-2.58 (m, 2H), 2.29-2.20 (m, 2H), 1.66-1.04 (m, 9H), 0.89-0.83 (m, 1H).

MH+ 524.

Step 4: (6*S*,6a*S*,10a*S*)-6,6a,7,8,9,10-Hexahydro-5*H*-6,10a-(epiminoethano)naphtho[2,1-*f*]quinoxalin-12-ol TFA salt (34)



To a solution of (6*S*,6a*S*,10a*S*)-benzyl 12-(benzyloxy)-2,3,4,5,6,6a,7,8,9,10-decahydro-1*H*-6,10a-(epiminoethano)naphtho[2,1-*f*]quinoxaline-15-carboxylate (33) (140 mg, 0.269 mmol) in IPA (10 mL) was added 10 % Pd on charcoal (14 mg). The mixture was stirred under hydrogen atmosphere at r.t. overnight. The reaction mixture was filtered to remove the catalyst and evaporated under vacuum. The residue was further purified by prep. HPLC (Gilson, C18 column, 0.1 % TFA) to provide the title compound (12 mg, 11 %) as a yellow solid.

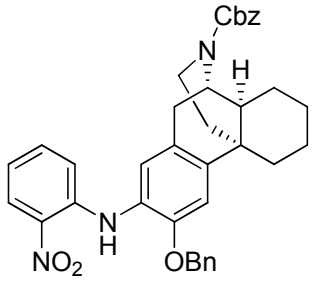
^{1}H NMR (400 MHz, CD_3OD) δ 8.82 (d, *J* = 2.0 Hz, 1H), 8.73 (d, *J* = 1.6 Hz, 1H), 7.15 (s, 1H), 3.80 (q, *J* = 3.6 Hz, 1H), 3.48 (d, *J* = 3.6 Hz, 2H), 3.02 (dd, *J* = 9.2, 3.2 Hz, 1H), 2.64 (td, *J* = 13.2, 4.0 Hz, 1H), 2.49 (d, *J* = 14.0 Hz, 1H), 1.95 (dt, *J* = 12.8, 3.2 Hz, 1H), 1.80 (td, *J* = 14.4, 4.8 Hz, 1H), 1.67-1.23 (m, 6H), 1.21-1.06 (m, 2H).

MH+ 296.

Example 10 : (4a*S*,14*S*,14a*S*)-2,3,4,13,14,14a-Hexahydro-1*H*-14,4a-(epiminoethano)naphtho[2,1-*a*]phenazin-6-ol TFA salt (40)

Step 1: (4b*S*,8a*S*,9*S*)-Benzyl 3-(benzyloxy)-2-((2-nitrophenyl)amino)-

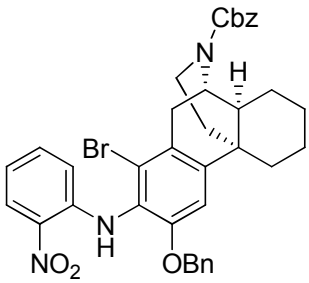
6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (36)



A mixture of (4b*S*,8a*S*,9*S*)-benzyl 2-amino-3-(benzyloxy)-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (25) (2.5 g, 5.18 mmol), 1-chloro-2-nitrobenzene (1.63 g, 10.4 mmol), $Pd(OAc)_2$ (350 mg, 0.518 mmol), BINAP (650 mg, 1.04 mmol) and sodium *t*-butoxide (1.00 g, 10.4 mmol) in toluene (15 mL) was heated at 110 ℃ overnight and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (2.4 g, 77 %) as a yellow solid.

MH+ 604.

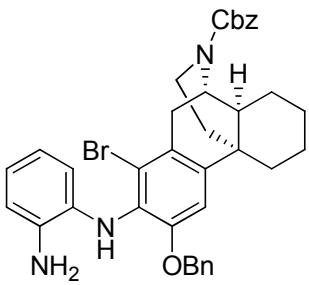
Step 2: (4b*S*,8a*S*,9*S*)-Benzyl 3-(benzyloxy)-1-bromo-2-((2-nitrophenyl)amino)-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (37)



A mixture of (4b*S*,8a*S*,9*S*)-benzyl 3-(benzyloxy)-2-((2-nitrophenyl)amino)-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (36) (1.05 g, 1.74 mmol) and pyridinium tribromide (1.11 g, 3.48 mmol) in THF (20 mL) was heated at 60 ℃ overnight and evaporated under vacuum. The residue was further purified by flash column chromatography (Biotage SP1™) to provide the title compound (0.99 g, 83 %) as a red solid.

MH+ 682.

Step 3: (4b*S*,8a*S*,9*S*)-Benzyl 2-((2-aminophenyl)amino)-3-(benzyloxy)-1-bromo-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (38)

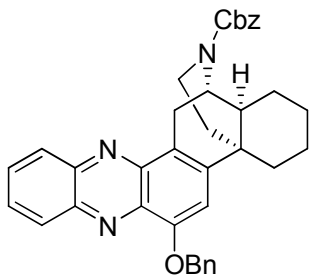


To a solution of (4b*S*,8a*S*,9*S*)-benzyl 3-(benzyloxy)-1-bromo-2-((2-

nitrophenyl)amino)-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (37) (410 mg, 0.601 mmol) and hydrazine hydrate (0.15 mL, 3.00 mmol) in MeOH (200 mL) was added Raney Ni (water solution, 1 mL) dropwise. The reaction mixture was stirred at r.t. for 2 hr. and filtered to remove the catalyst. The filtrate was evaporated under vacuum. The residue was further purified by flash column chromatography (Biotage SP1™) to provide the title compound (325 mg, 83 %) as a yellow solid.

MH+ 652.

Step 4: (4a*S*,14*S*,14a*S*)-Benzyl 6-(benzyloxy)-2,3,4,13,14,14a-hexahydro-1*H*-14,4a-(epiminoethano)naphtho[2,1-*a*]phenazine-15-carboxylate (39)



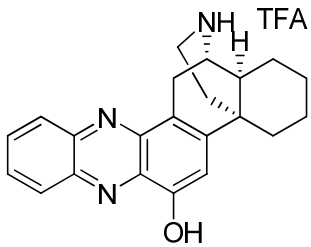
(4b*S*,8a*S*,9*S*)-Benzyl 2-((2-aminophenyl)amino)-3-(benzyloxy)-1-bromo-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (38) (47 mg, 0.0720 mmol) was added to a microwave reactor containing a mixture of $Pd_2(dba)_3$ (6.6 mg, 0.00720 mmol), BINAP (6.7 mg, 0.0108 mmol) and sodium *t*-

butoxide (13.8 mg, 0.144 mmol) in THF (5 mL). The capped reactor was placed in a microwave reactor and the mixture was irradiated at 170 ℃ for 40 min. The reaction mixture was evaporated to remove the solvent under vacuum. The residue was poured into water (20 mL) and extracted with EtOAc (20 mL X 2). The organic phase was dried over $MgSO_4$ and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (19 mg, 47 %) as a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 7.2 Hz, 1H), 8.22 (d, *J* = 10.0 Hz, 1H), 7.85-7.80 (m, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.43-7.26 (m, 10H), 6.97 (s, 1H), 5.62 (d, *J* = 13.2 Hz, 1H), 5.47 (d, *J* = 12.8 Hz, 1H), 5.20-5.08 (m, 2H), 4.60 (d, *J* = 44.8 Hz, 1H), 3.97-3.85 (m, 1H), 3.51-3.48 (m, 2H), 2.71-2.59 (m, 1H), 2.21-2.17 (m, 1H), 1.82-1.21 (m, 8H), 0.88-0.82 (m, 2H).

MH+ 570.

Step 5: (4a*S*,14*S*,14a*S*)-2,3,4,13,14,14a-Hexahydro-1*H*-14,4a-(epiminoethano)naphtho[2,1-*a*]phenazin-6-ol TFA salt (40)



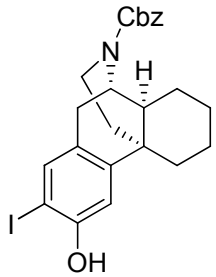
To a solution of (4a*S*,14*S*,14a*S*)-Benzyl 6-(benzyloxy)-2,3,4,13,14,14a-hexahydro-1*H*-14,4a-(epiminoethano)naphtho[2,1-*a*]phenazine-15-carboxylate (39) (120 mg, 0.211 mmol) in IPA (5 mL) was added 10 % Pd on charcoal (24 mg). The mixture was stirred under hydrogen atmosphere at r.t. overnight. The reaction mixture was filtered to remove the catalyst and evaporated under vacuum. The residue was further purified by prep. HPLC (Gilson, C18 column, 0.1 % TFA) to provide the title compound (27 mg, 28 %) as a brown solid.

^{1}H NMR (400 MHz, CD_3OD) δ 8.33-8.30 (m, 1H), 8.25-8.23 (m, 1H), 7.92-7.89 (m, 2H), 7.24 (s, 1H), 3.93 (d, *J* = 3.6 Hz, 1H), 3.71 (d, *J* = 3.2 Hz, 2H), 3.13 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.80 (td, *J* = 13.2, 4.0 Hz, 1H), 2.61 (d, *J* = 14.0 Hz, 1H), 2.07 (dt, *J* = 12.4, 3.2 Hz, 1H), 1.90 (td, *J* = 14.4, 4.8 Hz, 1H), 1.82-1.45 (m, 6H), 1.31-1.23 (m, 2H).

MH+ 346.

Example 11 : (4a*S*,13*S*,13a*S*)-1,2,3,4,7,12,13,13a-Octahydro-13,4a-(epiminoethano)naphtho[1,2-*c*]carbazole-6,8-diol TFA salt (45)

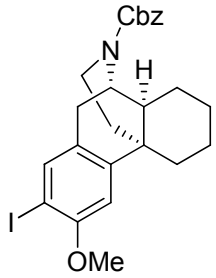
Step 1: (4b*S*,8a*S*,9*S*)-Benzyl 3-hydroxy-2-iodo-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (41)



A mixture of (4b*S*,8a*S*,9*S*)-benzyl 3-hydroxy-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (2) (10.0 g, 26.5 mmol) and iodine (13.4 g, 53.0 mmol) in pyridine (60 mL) was heated at 60 ℃ overnight and evaporated under vacuum. The residue was further purified by flash column chromatography (Biotage SP1™) to provide the title compound (12.9 g, 97 %) as a yellow solid.

MH+ 504.

Step 2: (4b*S*,8a*S*,9*S*)-Benzyl 2-iodo-3-methoxy-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (42)

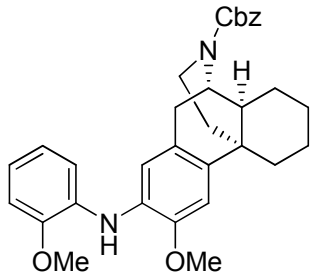


To a solution of (4b*S*,8a*S*,9*S*)-Benzyl 3-hydroxy-2-iodo-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (41) (12.9 g, 25.6 mmol) and

K_2CO_3 (5.31 g, 38.4 mmol) in acetone (100 mL) was added iodomethane (2.4 mL, 38.4 mmol). The reaction mixture was heated at 60 ℃ overnight and evaporated to remove the solvent under vacuum. The residue was poured into water (300 mL) and extracted with EtOAc (150 mL X 3). The organic phase was dried over $MgSO_4$ and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (12.2 g, 92 %) as a white solid.

MH+ 518.

Step 3: (4b*S*,8a*S*,9*S*)-Benzyl 3-methoxy-2-((2-methoxyphenyl)amino)-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (43)

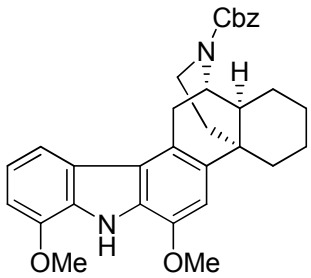


A mixture of (4b*S*,8a*S*,9*S*)-Benzyl 2-iodo-3-methoxy-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (42) (1.5 g, 2.90 mmol), *o*-anisidine (0.39 mL, 3.48 mmol), (dppf)$PdCl_2.CH_2Cl_2$ (94.7 mg, 0.116 mmol), dppf (175 mg, 0.348 mmol) and sodium *t*-butoxide (418 mg, 4.35 mmol) in toluene (15 mL) was heated at 100 ℃ overnight and evaporated under vacuum. The residue was purified

by flash column chromatography (Biotage SP1™) to provide the title compound (1.42 g, 96 %) as a yellow solid.

MH+ 513.

Step 4: (4a*S*,13*S*,13a*S*)-Benzyl 6,8-dimethoxy-1,2,3,4,7,12,13,13a-octahydro-13,4a-(epiminoethano)naphtho[1,2-*c*]carbazole-14-carboxylate (44)



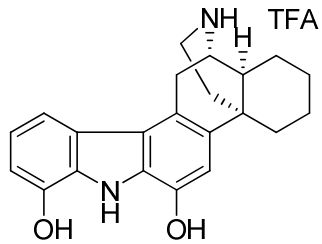
A mixture of (4b*S*,8a*S*,9*S*)-benzyl 3-methoxy-2-((2-methoxyphenyl)amino)-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene-11-carboxylate (43) (513 g, 1.00 mmol), $Pd(OAc)_2$ (202 mg, 0.300 mmol) and $Cu(OAc)_2$ (272 mg, 1.50 mmol) in glacial acetic acid (10 mL) was heated at 110 ℃ for 2 days and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (312 mg, 61 %) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.71 (dd, *J* = 32.4, 4.0 Hz, 1H), 7.44-7.25 (m, 4H), 7.14 (t, *J* = 8.0 Hz, 1H), 6.89 (s, 1H), 6.89 (d, *J* = 7.6 Hz, 1H), 6.82 (s, 1H), 5.24-5.09 (m, 2H), 4.59 (d, *J* = 44.8 Hz, 1H), 4.01 (s, 3H), 3.98 (s, 3H), 3.76-3.73

(m, 1H), 3.63-3.52 (m, 1H), 3.31 (t, *J* = 17.2 Hz, 1H), 2.74-2.62 (m, 1H), 2.46 (d, *J* = 12.0 Hz, 1H), 1.87-1.79 (m, 2H), 1.66-1.22 (m, 7H), 0.88-0.86 (m, 1H).

MH+ 511.

Step 5: (4a*S*,13*S*,13a*S*)-1,2,3,4,7,12,13,13a-Octahydro-13,4a-(epiminoethano)naphtho[1,2-*c*]carbazole-6,8-diol TFA salt (45)



To a solution of (4a*S*,13*S*,13a*S*)-benzyl 6,8-dimethoxy-1,2,3,4,7,12,13,13a-octahydro-13,4a-(epiminoethano)naphtho[1,2-*c*]carbazole-14-carboxylate (44) (84 mg, 0.165 mmol) in DCM (10 mL) was added BBr_3 (1M in DCM, 0.83 mL, 0.830 mmol) at 0 ℃. The mixture was stirred at r.t. overnight and quenched by MeOH (5 mL). The reaction mixture was evaporated under vacuum. The residue was further purified by prep. HPLC (Waters, C18 column, 0.1 % TFA) to provide the title compound (27 mg, 35 %) as a brown solid.

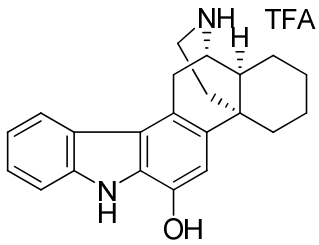
^{1}H NMR (400 MHz, CD_3OD) δ 7.59 (d, *J* = 8.0 Hz, 1H), 6.99 (t, *J* = 8.0 Hz, 1H), 6.84-6.81 (m, 2H), 3.86-3.84 (m, 1H), 3.70-3.56 (m, 2H), 3.47 (d, *J* = 19.2 Hz, 1H), 3.06 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.80 (td, *J* = 13.2, 4.0 Hz, 1H), 2.50 (d, *J* = 13.6 Hz,

1H), 1.97 (dt, *J* = 12.8, 3.6 Hz, 1H), 1.82 (td, *J* = 13.6, 4.8 Hz, 1H), 1.70-1.22 (m, 8H).

MH+ 349.

The following compounds of Example 12, 13 and 14 were obtained by repeating the procedure of Example 11.

Example 12 : (4a*S*,13*S*,13a*S*)-1,2,3,4,7,12,13,13a-Octahydro-13,4a-(epiminoethano)naphtho[1,2-*c*]carbazol-6-ol TFA salt (45a)

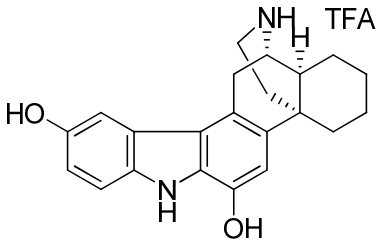


^{1}H NMR (400 MHz, CD_3OD) δ 8.08 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.15 (t, *J* = 8.0 Hz, 1H), 6.86 (s, 1H), 3.88-3.87 (m, 1H), 3.71 (dd, *J* = 18.8, 6.4 Hz, 1H), 3.49 (d, *J* = 18.8 Hz, 1H), 3.07 (dd, *J* = 13.2, 3.6 Hz, 1H), 2.80 (td, *J* = 13.2, 3.6 Hz, 1H), 2.51 (d, *J* = 14.0 Hz, 1H), 1.99 (d, *J* = 6.4 Hz, 1H), 1.83 (td, *J* = 13.6, 4.8 Hz, 1H), 1.67-1.20 (m, 8H).

MH+ 333.

Example 13 : (4a*S*,13*S*,13a*S*)-1,2,3,4,7,12,13,13a-Octahydro-13,4a-

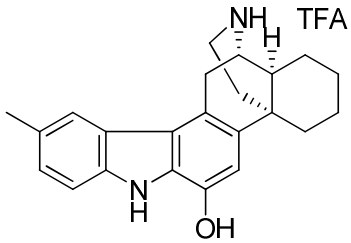
(epiminoethano)naphtho[1,2-*c*]carbazole-6,10-diol TFA salt (45b)



^{1}H NMR (400 MHz, CD_3OD) δ 7.49 (d, *J* = 2.0 Hz, 1H), 7.34 (d, *J* = 8.8 Hz, 1H), 6.93 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.81 (s, 1H), 3.87-3.85 (m, 1H), 3.66 (dd, *J* = 18.8, 6.4 Hz, 1H), 3.44 (d, *J* = 19.2 Hz, 1H), 3.07 (dd, *J* = 12.8, 3.2 Hz, 1H), 2.80 (td, *J* = 13.6, 3.6 Hz, 1H), 2.49 (d, *J* = 13.2 Hz, 1H), 1.97 (d, *J* = 12.4 Hz, 1H), 1.82 (td, *J* = 13.6, 4.8 Hz, 1H), 1.67-1.24 (m, 8H).

MH+ 349.

Example 14 : (4a*S*,13*S*,13a*S*)-10-Methyl-1,2,3,4,7,12,13,13a-octahydro-13,4a-(epiminoethano)naphtho[1,2-*c*]carbazol-6-ol TFA salt (45c)



^{1}H NMR (400 MHz, CD_3OD) δ 7.88 (s, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.20 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.84 (s, 1H), 3.88-3.86 (m, 1H), 3.70 (dd, *J* = 18.8, 6.4 Hz, 1H), 3.49 (d, *J* = 18.8 Hz, 1H), 3.07 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.80 (td, *J* = 13.2, 3.6 Hz,

1H), 2.52-2.50 (m, 4H), 1.99 (d, *J* = 12.0 Hz, 1H), 1.83 (td, *J* = 13.6, 4.8 Hz, 1H), 1.71-1.22 (m, 8H).

MH+ 347.

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Part II . Arylpiperazine-containing pyrimidine 4-carboxamide derivatives as a potential antidepressant

1. Introduction

1.1 Major depressive disorder (Depression) & SARI

Major depressive disorder is a mental disorder characterized by an all-encompassing low mood accompanied by low self-esteem and loss of interest or pleasure in normally enjoyable activities. There is a growing awareness that patients with depressive disorders often also suffer cognitive impairment, and some studies indicate that these deficits may persist even after remission.[1)] The monoaminergic hypothesis of depression assumes that depression is caused by the dysfunction of the serotonin (5-HT, SER), noradrenaline (NE) and/or dopamine (DA) neurotransmitter systems.[2)] This hypothesis has been used to explain the efficacy of existing antidepressant therapies. Among these available therapies, selective serotonin reuptake inhibitors (SSRIs) and more recently combined serotonin- and noradrenaline reuptake inhibitors (SNRIs) have become the standard treatment for depression.[3)]

In recent years, SARI (serotonin antagonist/reuptake inhibitor) drugs that block both the serotonin 5-HT_2 receptors and the serotonin transporters have been developed.[4)] YM-992 **1**, LY367265 **2**, Nefazodone **3**, and aripiprazole **4** are the typical examples of that series.[5)] Unlike most SSRIs, nefazodone is reported to have no negative effects on libido or sexual functioning. Nefazodone's claimed advantages over

other antidepressants include reduced possibility of disturbed sleep or sexual dysfunction, and ability to treat some patients who did not respond to other antidepressant drugs.[6] In this regard, there are still urgent medical needs on the development of novel drugs with better developability characteristics: improved pharmacologic properties and reduced side effects.

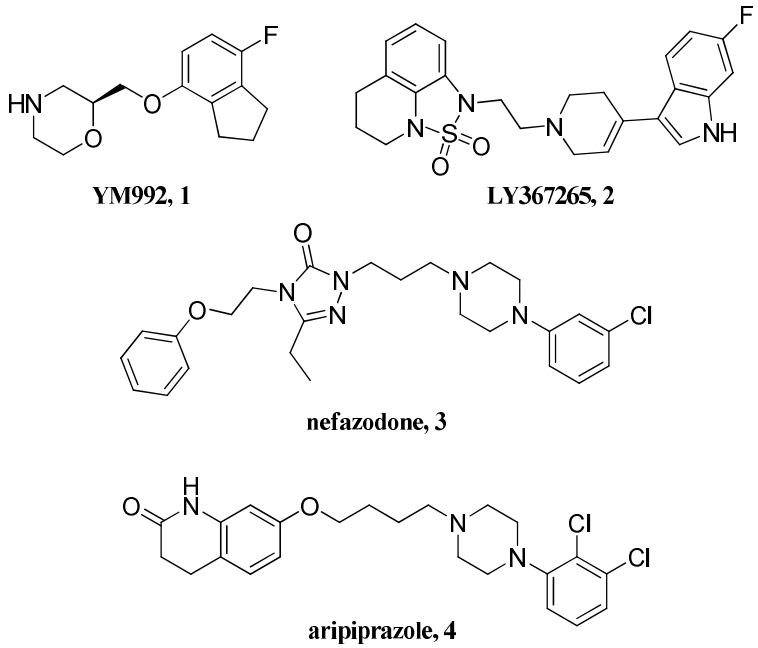
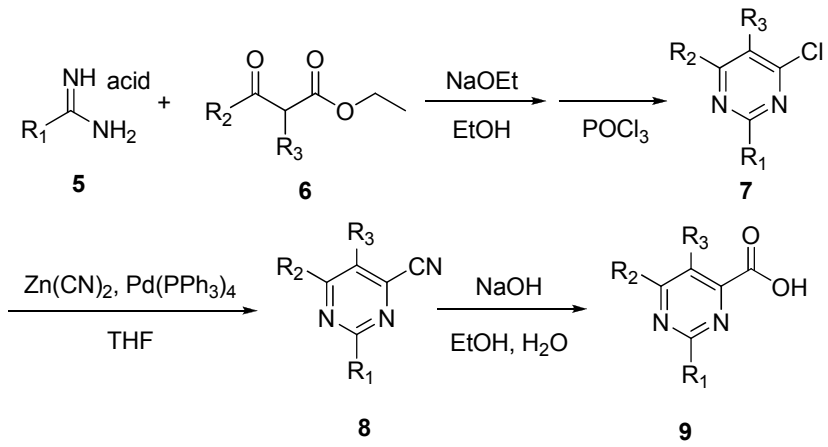


Figure 1. SARI drugs (serotonin antagonist/reuptake inhibitor)

2. Results and Discussion

2.1. Synthesis of pyrimidine 4-carboxamide derivatives

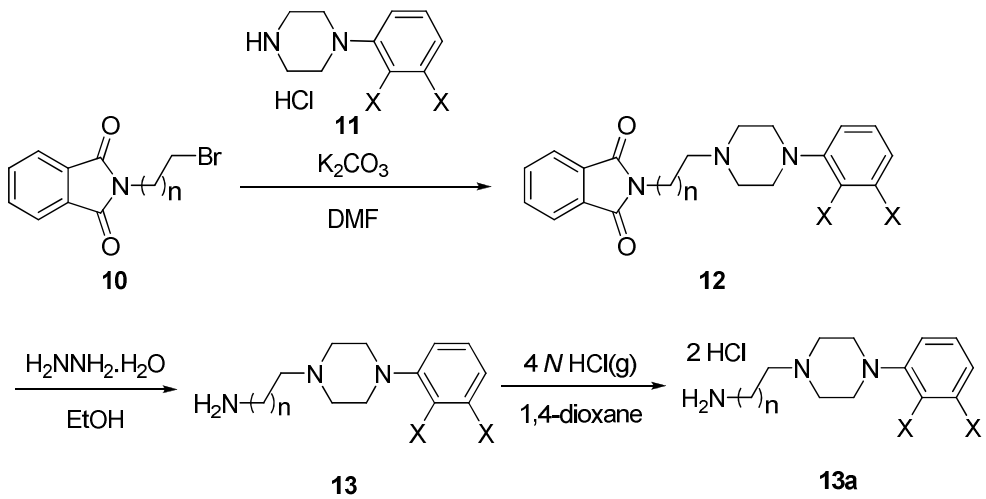
The carboxylic acid derivative **9** was prepared by a conventional method, for example, by reacting an amidine acid salt **4** with a keto-ester derivative **6** using sodium ethoxide, followed by chlorination using $POCl_3$ to produce a corresponding 4-chloropyrimidine **7**. Subsequent reaction of the resulting 4-chloropyrimidine **7** with zinc cyanide in the presence of $Pd(PPh_3)_4$ gave an intermediate 4-cyanopyrimidine **8**. An acid form **9** was transformed from the intermediate **8** using sodium hydroxide, followed by acidification, as shown in Scheme 1.



Scheme 1. Preparation of acid intermediate **9**

As shown in Scheme 2, preparation of aminoalkyl-arylpiperazine **13** started from

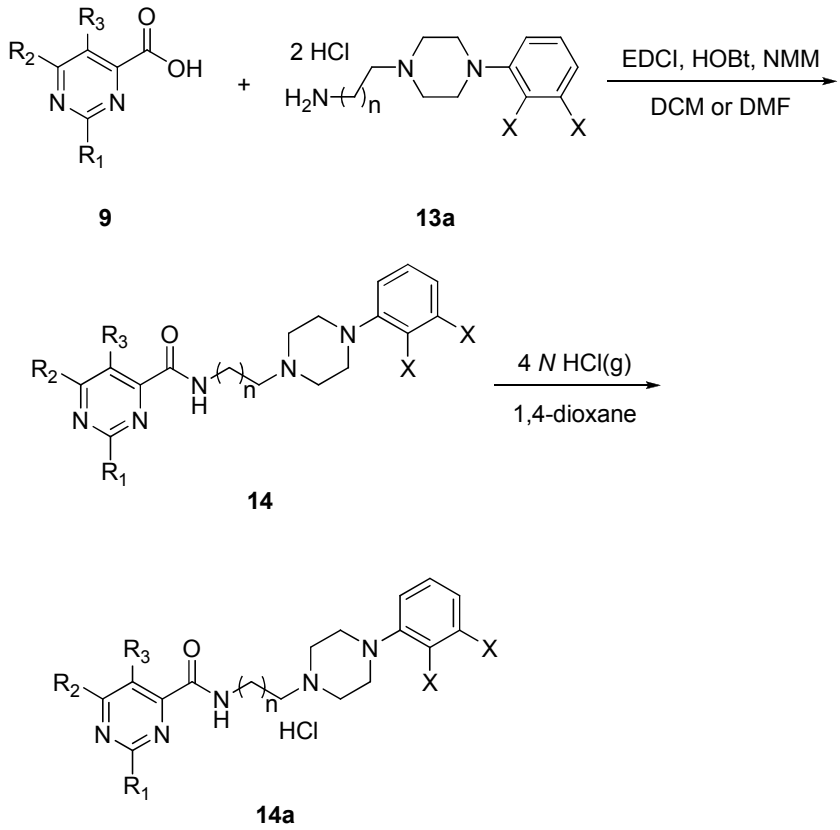
the corresponding bromoalkyl-phthalimide **10** and arylpiperazine **11**.[7] Treatment of bromoalkyl-phthalimide **10** with arylpiperazine hydrochloride **11** in the presence of potassium carbonate in DMF at room temperature afforded N-protected amine **12**. Compound **12** was then treated with hydrazine in ethanol to give amine **13**. For the sake of convenience of handling on scale, liquid amine **13** was transformed to hydrochloride salt form **13a** with 4 *N* HCl in dioxane.



Scheme 2. Preparation of amine intermediate **13a**

Finally, coupling reaction of acid **9** and aminoalkyl-arylpiperazine **13a** was conducted as shown in Scheme 3. With pyrimidine-4-carboxylic acid **9** and aminoalkyl-arylpiperazine dihydrochloride (**13a**) in hand, typical amide coupling was conducted under conditions involving EDCI, HOBT, and NMM in methylene chloride or DMF to

produce amide **14**. As reaction was completed, purification was performed using preparative reverse-phase HPLC with 0.1% TFA mixture of acetonitrile and water solution. The neutral form of product **14** was converted to HCl salt form **14a** to increase the overall solubility for biological evaluation.



Scheme 3. Preparation of pyrimidine 4-carboxamide derivative **14a**

2.2. Biological assay

2.2.1. Binding affinity evaluation

The binding affinity of current compounds against 5-HT_{2A}, 5-HT_{2C} receptor and serotonin transporter, stably expressed in CHO-K1 cells, were evaluated by displacement binding using [^{3}H]Ketanserin, [^{3}H]Mesulergine, and [^{3}H]Imipramine, respectively, as radioligands.[8)]

For serotonin 5-HT_{2A} receptor binding, an aliquot of frozen membrane from CHO-K1 cell line expressing the human recombinant 5- HT_{2A} receptor (PerkinElmer Life and Analytical Sciences, Boston, USA) and [^{3}H]Ketanserin 1 nM (PerkinElmer) were mixed in the presence of mianserin (20 μM) as nonspecific. The reaction mixture was incubated for 60 min at 27 ℃ using 50 mM Tris–HCl (pH 7.4) buffer containing 4 mM $CaCl_2$ and 0.1% ascorbic acid, and harvested through Filtermat A glass fiber filter presoaked in 0.5% PEI. The filter was covered with MeltiLex, sealed in a sample bag followed by drying in the microwave oven, and counted by MicroBeta Plus (Wallac, Finland). Competition binding studies were carried out with 5–6 varied concentrations of the test compounds run in duplicate tubes, and isotherms from three assays were calculated by computerized nonlinear regression analysis (GraphPad Prism, GraphPad Software, Inc., CA, USA) to yield IC_{50} values.

For 5-HT_{2C} binding, frozen membranes from stable CHO-K1 cell line expressing the human recombinant 5-HT_{2C} receptor (PerkinElmer) were used. [^{3}H]Mesulergine

(1.4 nM), receptor membrane and test compound were added into 50 mM Tris–HCl (pH 7.4) buffer containing 4 mM $CaCl_2$ and 0.1% ascorbic acid. Nonspecific binding was determined using 10 μM of methiothepin. The incubations were performed for 60 min at 27 ℃, and these were terminated by rapid filtration through Filtermat A glass fiber filter presoaked in 0.5% PEI.

Human serotonin transporter expressed in HEK293 (PerkinElmer) were used for serotonin transporter binding assays. For the binding, frozen membrane, 4 nM [^{3}H]Imipramine (PerkinElmer) and appropriate concentrations of test compounds were added to 0.25 mL assay buffer of 50 mM Tris–HCl (pH 7.4) containing 120 mM NaCl and 5 mM KCl. Incubations were carried out for 30 min at 27 ℃, and these were terminated by rapid filtration through Filtermat A glass fiber filter presoaked in 0.5% PEI. Imipramine (100 μM) was used as the nonspecific ligand 24.

2.2.2. Forced swimming test

To evaluate antidepressant activity of the interesting compounds, immobility in forced swimming test (FST) on mice were measured. Zoloft (sertraline) was used as a reference compound for comparison.

The forced swimming test was performed according to the modified methods described by Porsolt et al. (1978).[9] Each mouse was placed in a 25-cm glass cylinder

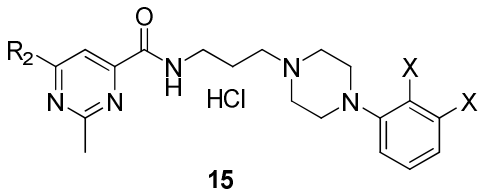
(10 cm diameter) containing 15 cm of water maintained at 23 ± 1 ℃, and was forced to swim for 10 min. Twenty-four hours later, the mouse was replaced 360 into the cylinder and the total duration of immobility was recorded during the last 5 min of the 6-min testing period. Mice are judged immobile when they float in an upright position and make only small movements to keep their head above water. Test compound (25 mg/kg) and sertraline (25 mg/kg) were suspended in 3%-Tween 80 solution, and administered (i.p.) 30 min before the testing.

3. Conclusion

The work was focused on exploration of the substitution group of pyrimidine moiety. 2-Methylpyrimidine derivatives and 2,3-dichlorophenyl- or 2,3-dimethylphenylpiperazine were connected with propyl-carboxamide as a linker.

The binding affinities of prepared compounds against the 5-HT_{2A}, 5-HT_{2C}, and SERT are shown in Table 1. Because these compounds would interact with multiple targets, it is not easy to evaluate prepared compounds following SARI (serotonin antagonist and reuptake inhibitor) mechanism. Initially, most compounds tested displayed IC_{50} <1 μM, implying that this series of arylpiperazinyl pyrimidine 4-carboxamide might hold promises as a potential antidepressant. The substituted R_2 group of pyrimidine showed a tendency of preference for bulky group. Also, it showed

considerable difference in binding affinity between 2,3-dichlorophenylpiperazinyl compounds and 2,3-dimethylphenylpiperazinyl compounds. In order to improve binding affinity against 5-HT_{2A}, 5-HT_{2C} receptors, and serotonin transporter, contraction of linker size was undertaken. For comparison, dimethylphenylpiperazinyl derivatives were synthesized and screened as shown in Table 2. In the case of 5-H pyrimidine (R_3 = H), 5-HT_{2A} and 5-HT_{2C} receptor binding affinities were increased when the length of the linker was shorten from C3 to C2. On the contrary, SERT binding affinities were decreased at the same conditions. In the case of 5-OMe pyrimidne (R_3 = OMe), the effect of the linker size on the binding affinities was not obvious (see Table 2).

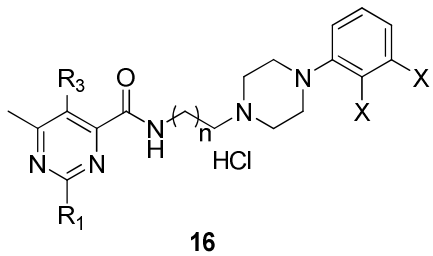


15

Compound	R_2	X	IC_{50} (nM)		
			5-HT_{2A}	5-HT_{2C}	SERT
15a	Me	Cl	166	610	289
15b	iPr	Cl	113	227	644
15c	Ph	Cl	35	30	588
15d	iPr	Me	490	1548	1213
15e	tBu	Me	458	575	730

Table 1. Binding affinities of pyrimidine 4-carboxamide derivatives **15**

Several compounds, like also trazodone and nefazodone, are metabolized into *meta*-chlorophenylpiperazine (m-CPP), a serotonin receptor agonist with high affinity to 5-HT_{2A} and even higher to 5-HT_{2C} receptor. This compound has itself anxiogenic-like and hypolocomotor effects. Furthermore, SSRIs through the increase of extracellular 5-HT concentration, activate at least 5-HT_{2C} receptors to induce anxiogenic-like and hypolocomotion effects which could be antagonised by subtype-selective 5-HT_{2C} receptor antagonists.[6)]



16

Compound	R_1	R_3	X	n	IC_{50} (nM)		
					5-HT_{2A}	5-HT_{2C}	SERT
16a	tBu	H	Me	2	274	2688	537
16b	tBu	H	Me	1	69	494	6374
16c	SMe	H	Me	2	54	1170	394
16d	SMe	H	Me	1	47	148	1014
16e	SMe	H	Cl	1	55	81	881
16f	cPr	H	Me	2	256	1178	347
16g	Me	OMe	Me	2	744	2049	892

16h	Me	OMe	Me	1	842	1266	2096
16i	Me	OMe	Cl	1	263	135	646

Table 2. Binding affinities of pyrimidine 4-carboxamide derivatives **16**

The forced swimming test results are shown in Figure **2**.

Compared with Zoloft, dichlorophenylpiperazine compounds with C3 linker size (**15a**, **15b**) showed more potent *in vivo* efficacy in animal model. In the case of 2-SMe series (R_1 = SMe), the C2 linker size compounds (**16d**, **16e**) appeared to be more efficacious than C3 linker size compound (**16c**). 5-OMe substituted compounds (R_3 = OMe) also showed a similar trend of results in immobility test.

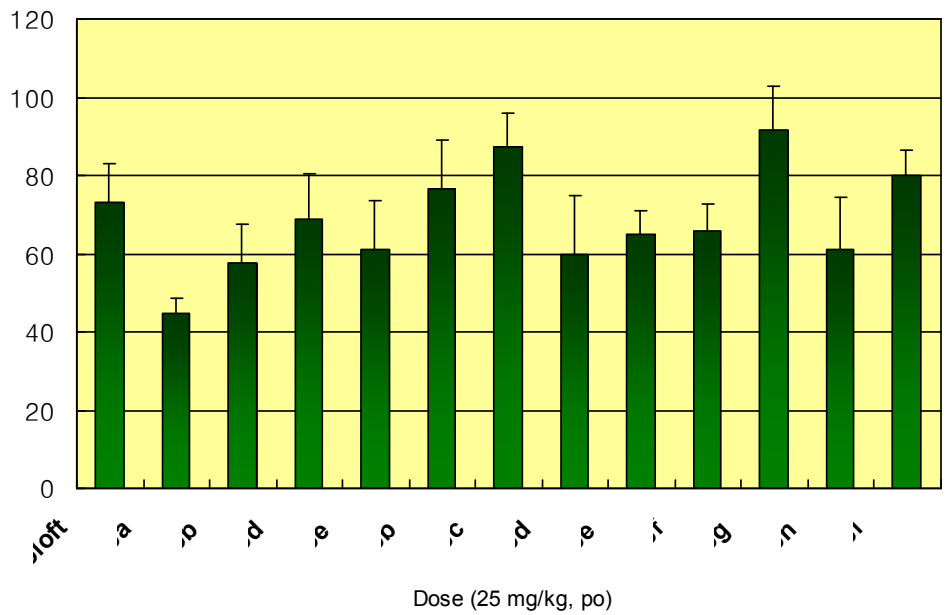


Figure 2. Immobility of pyrimidine 4-carboxamide derivatives in forced swimming test

To distinguish antidepressant effect from hyperactivity of animal, spontaneous locomotor activity tests were conducted in mice. As a result, **15a** compound showed hyperactivity, while **16g** compound showed hypoactivity. Therefore, the efficacy in immobility of **15a** compound was caused by hyperactivity of animal, that is, false positive result. The results of the other compounds fell within the normal range (Fig. **3**).

Off target activity of selected compounds was briefly evaluated. The activity of **16d** in the hERG potassium channel assay was determined to be greater than 10 μM IC_{50} (Table 3). Compound **16d** also showed no appreciable inhibition against CYP1A2, CYP2D6, CYP2C9, and CYP3A4, showing IC_{50} > 20 μM.

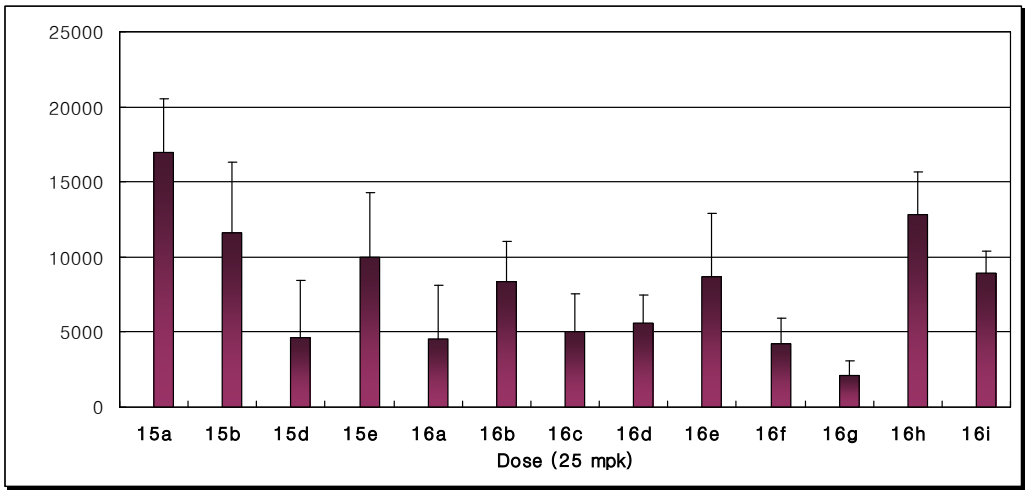
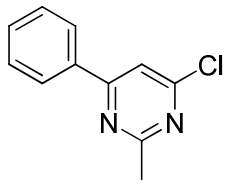


Figure 2. Locomotor activities of pyrimidine 4-carboxamide derivatives

4. Experimentals

^{1}H and ^{13}C NMR spectra were recorded on Varian 400-MR spectrometer. Chemical shifts were expressed in parts per million (ppm, δ units). Coupling constants are in units of hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Mass spectra were obtained with either a Agilent®, 1100LC/6110MSD.

1. Preparation of 4-chloro-2-methyl-6-phenylpyrimidine (7a)



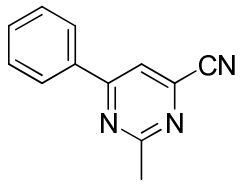
To a solution of ethyl benzoylacetate (10 mL, 58.1 mmol) and acetamdine hydrochloride (8.24 g, 87.2 mmol) in EtOH (80 ml) was added K_2CO_3 (16.1 g, 116 mmol) at rt. The reaction mixture was refluxed for 18 hr. and evaporated to remove the solvent under vacuum. The residue was poured into water (100 mL) and extracted with EtOAc (100 mL × 3). The organic layer was dried with $MgSO_4$ and evaporated under vacuum. To the residue was added $POCl_3$ (80 mL). The reaction mixture was refluxed for 12 hr. and poured into ice-water (400 g) followed by extraction with DCM (100 mL × 2). The organic layer was dried with $MgSO_4$ and evaporated under vacuum. The

residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (6.12 g, 52 %) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07-8.05 (m, 2H), 7.55 (s, 1H), 7.53-7.48 (m, 3H), 2.78 (s, 3H).

MH+ 205.

2. Preparation of 2-methyl-6-phenylpyrimidine-4-carbonitrile (8a)

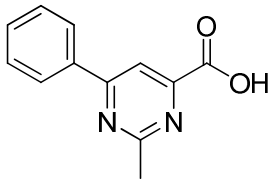


To a microwave reactor containing $Zn(CN)_2$ (1.73 g, 14.8 mmol) and tetrakis(triphenylphosphine)palladium(0) (853 mg, 0.738 mmol) in THF (15 mL) was added 4-chloro-2-methyl-6-phenylpyrimidine (**7a**) (1.51 g, 7.38 mmol). The capped reactor was placed in a microwave reactor and the mixture was irradiated at 165 ℃ for 30 min. The residue was poured into water (30 mL) and extracted with EtOAc (30 mL × 2). The organic layer was dried with $MgSO_4$ and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (0.91 g, 63 %) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11-8.09 (m, 2H), 7.84 (s, 1H), 7.60-7.52 (m, 3H), 2.85 (s, 3H).

MH+ 196.

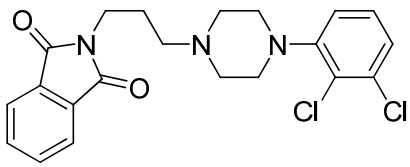
3. Preparation of 2-methyl-6-phenylpyrimidine-4-carboxylic acid (9a)



To a solution of 2-methyl-6-phenylpyrimidine-4-carbonitrile (**8a**) (615 mg, 3.15 mmol) in EtOH (20 mL) and water (20 mL) was added NaOH (378 mg, 9.45 mmol) at rt. The reaction mixture was refluxed for 18 hr. and evaporated under vacuum. 1 N HCl solution was added to aqueous layer until pH < 2. And extraction was accomplished with EtOAc. The organic layer was dried with $MgSO_4$ and evaporated under vacuum to provide the title compound (651 mg, 96 %) as a white solid. Without further purification, acid was used for the reaction of amide coupling.

MH+ 215.

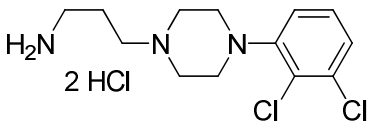
4. Preparation of 2-(3-(4-(2,3-dichlorophenyl)piperazin-1-yl)propyl)isoindoline-1,3-dione (12a)



1-(2,3-Dichlorophenyl)piperazine hydrochloride (3.16 g, 11.8 mmol) and potassium carbonate (4.08 g, 29.5 mmol) were added to the solution of 2-(3-bromopropyl)isoindoline-1,3-dione (3.16 g, 11.8 mmol) in DMF (20 ml). The reaction mixture was stirred for 18 hr. at rt. The residue was poured into water (40 ml) and extracted with EtOAc (30 mL × 3). The organic layer was dried with $MgSO_4$ and evaporated under vacuum. The residue was purified by flash column chromatography (Biotage SP1™) to provide the title compound (4.00 g, 81 %) as a white solid.

MH+ 418.

5. Preparation of 3-(4-(2,3-dichlorophenyl)piperazin-1-yl)propan-1-amine dihydrochloride (13a)

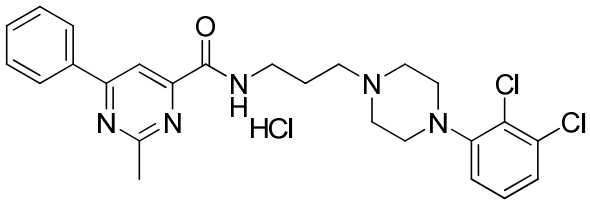


To a stirred solution of 2-(3-(4-(2,3-dichlorophenyl)piperazin-1-yl)propyl)isoindoline-1,3-dione (**12a**) (4.00 g, 9.57 mmol) in ethanol (50 ml) was added hydrazine monohydrate (3 ml) at rt. The reaction mixture was stirred at 80 ^{o}C for 18 hr. The resulting solution was cooled down to rt, and the volatiles were evaporated under vacuum. The residue was extracted with EtOAC and saturated sodium bicarbonate solution. After evaporation of organic layer under vacuum, it was poured into 1N HCl

solution. The aqueous solution was washed with ethyl ether, and then basified with aqueous ammonia. DCM was used for work-up organic layer, dried with $MgSO_4$. After solvent was removed under vacuum, 4N HCl in dioxane (5 ml) was added at 0 ^oC and stirred 10 min to produce HCl salt form. Light yellow solid title compound (3.08 g, 89 %) was obtained by evaporation and drying *in vacuo* volatile compounds.

MH+ 288.

6. Preparation of *N*-(3-(4-(2,3-dichlorophenyl)piperazin-1-yl)propyl)-2-methyl-6-phenylpyrimidine-4-carboxamide hydrochloride (15c)



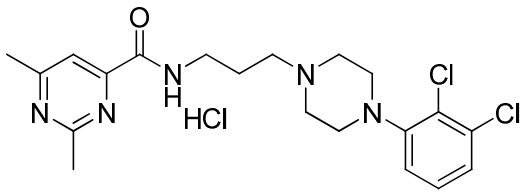
To the mixture of 2-methyl-6-phenylpyrimidine-4-carboxylic acid (**9a**) (163 mg, 0.76 mmol) and 3-(4-(2,3-dichlorophenyl)piperazin-1-yl)propan-1-amine dihydrochloride (**13a**) (274 mg, 0.76 mmol) in DCM (10 ml) was added EDCI (291 mg, 1.52 mmol), HOBT (205 mg, 1.52 mmol) and NMM (330 μl, 3.04 mmol) continuously. After stirring for 18 hr at rt, MeOH was added to the resulting solution, and filter off. After evaporation under vacuum, the residue was purified by reverse phase preparative HPLC. After solvent was removed under vacuum, 4N HCl in dioxane (5 ml) was added at 0 ^oC and stirred 10 min to produce HCl salt form. White solid title compound (202

mg, 51 %) was obtained by evaporation and drying *in vacuo* volatile compounds.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (br s, 1H), 8.36 (s, 1H), 8.19-8.16 (m, 2H), 7.54-7.49 (m, 3H), 7.18-7.13 (m, 2H), 6.99-6.94 (m, 1H), 3.64 (q, *J* = 6.4 Hz, 2H), 3.17 (br s, 4H), 2.79 (s, 3H), 2.70 (br s, 4H), 2.62 (t, *J* = 6.4 Hz, 2H), 1.88 (quint, *J* = 6.4 Hz, 2H).

MH+ 484.

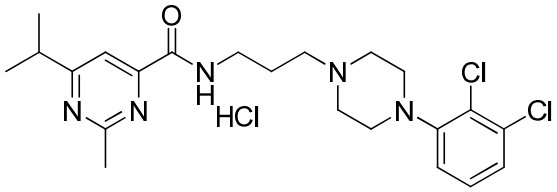
7. Preparation of *N*-(3-(4-(2,3-dichlorophenyl)piperazin-1-yl)propyl)-2,6-dimethylpyrimidine-4-carboxamide hydrochloride (15a)



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (br s, 1H), 7.79 (s, 1H), 7.17-7.12 (m, 2H), 6.96-6.93 (m, 1H), 3.60 (q, *J* = 6.4 Hz, 2H), 3.15 (br s, 4H), 2.70 (br s, 7H), 2.61-2.58 (m, 5H), 1.85 (quint, *J* = 6.4 Hz, 2H).

MH+ 422.

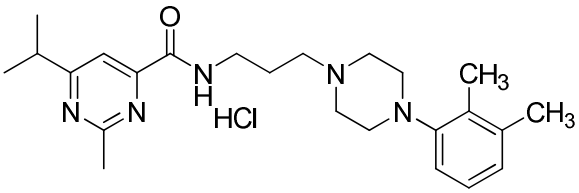
8. Preparation of *N*-(3-(4-(2,3-dichlorophenyl)piperazin-1-yl)propyl)-6-isopropyl-2-methylpyrimidine-4-carboxamide hydrochloride (15b)



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (br s, 1H), 7.17-7.12 (m, 2H), 6.96-6.94 (m, 2H), 3.60 (t, *J* = 6.4 Hz, 2H), 3.14 (br s, 4H), 3.05 (quint, *J* = 7.2 Hz, 1H), 2.70 (br s, 7H), 2.59 (t, *J* = 7.2 Hz, 2H), 1.85 (quint, *J* = 6.4 Hz, 2H), 1.31 (d, *J* = 7.2 Hz, 6H).

MH+ 450.

9. Preparation of *N*-(3-(4-(2,3-dimethylphenyl)piperazin-1-yl)propyl)-6-isopropyl-2-methylpyrimidine-4-carboxamide hydrochloride (15d)

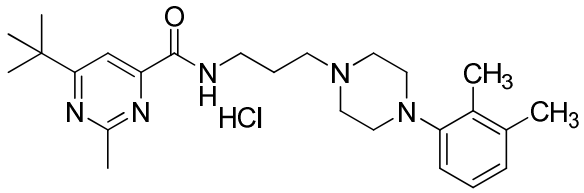


^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (br s, 1H), 7.81 (s, 1H), 7.08 (t, *J* = 8.0 Hz, 1H), 6.91 (dd, *J* = 8.0, 4.8 Hz, 2H), 3.60 (q, *J* = 6.4 Hz, 2H), 3.05 (quint, *J* = 7.2 Hz, 1H), 2.97 (t, *J* = 4.8 Hz, 4H), 2.73 (s, 3H), 2.66 (br s, 4H), 2.59 (t, *J* = 6.4 Hz, 2H), 2.27 (s, 3H), 2.22 (s, 3H), 1.86 (quint, *J* = 6.4 Hz, 2H), 1.31 (d, *J* = 6.8 Hz, 6H).

MH+ 410.

10. Preparation of 6-*tert*-butyl-*N*-(3-(4-(2,3-dimethylphenyl)piperazin-1-

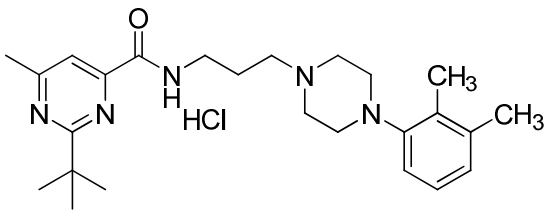
yl)propyl)-2-methylpyrimidine-4-carboxamide hydrochloride (15e)



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (br s, 1H), 7.93 (s, 1H), 7.08 (t, *J* = 7.6 Hz, 1H), 6.91 (t, *J* = 7.6 Hz, 2H), 3.60 (q, *J* = 6.4 Hz, 2H), 2.97 (t, *J* = 4.8 Hz, 4H), 2.72 (s, 3H), 2.65 (br s, 4H), 2.58 (t, *J* = 6.4 Hz, 2H), 2.27 (s, 3H), 2.21 (s, 3H), 1.86 (quint, *J* = 6.4 Hz, 2H), 1.35 (s, 9H).

MH+ 424.

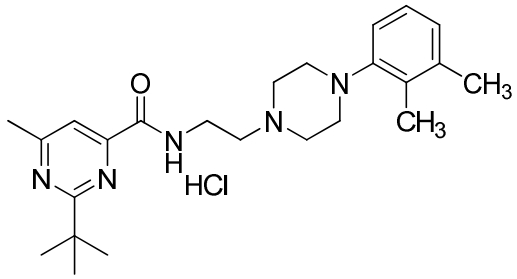
11. Preparation of 2-*tert*-butyl-*N*-(3-(4-(2,3-dimethylphenyl)piperazin-1-yl)propyl)-6-methylpyrimidine-4-carboxamide hydrochloride (16a)



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (br s, 1H), 7.74 (s, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.91 (t, *J* = 7.6 Hz, 2H), 3.57 (q, *J* = 6.4 Hz, 2H), 2.92 (t, *J* = 4.8 Hz, 4H), 2.64 (br s, 4H), 2.58 (s, 3H), 2.53 (t, *J* = 7.2 Hz, 2H), 2.26 (s, 3H), 2.21 (s, 3H), 1.88 (quint, *J* = 7.2 Hz, 2H), 1.42 (s, 9H).

MH+ 424.

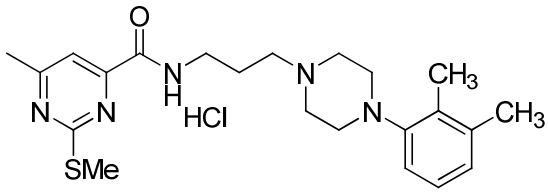
12. Preparation of 2-*tert*-butyl-*N*-(2-(4-(2,3-dimethylphenyl)piperazin-1-yl)ethyl)-6-methylpyrimidine-4-carboxamide hydrochloride (16b)



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (br s, 1H), 7.73 (s, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 6.92 (d, *J* = 7.6 Hz, 2H), 3.59 (q, *J* = 5.6 Hz, 2H), 2.95 (t, *J* = 4.4 Hz, 4H), 2.72-2.69 (m, 6H), 2.59 (s, 3H), 2.28 (s, 3H), 2.23 (s, 3H), 1.44 (s, 9H).

MH+ 410.

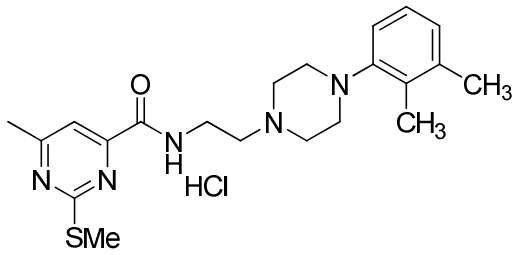
13. Preparation of *N*-(3-(4-(2,3-dimethylphenyl)piperazin-1-yl)propyl)-6-methyl-2-(methylthio)pyrimidine-4-carboxamide hydrochloride (16c)



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (br s, 1H), 7.60 (s, 1H), 7.06 (t, *J* = 7.6 Hz, 1H), 6.90 (d, *J* = 7.6 Hz, 2H), 3.58 (q, *J* = 6.4 Hz, 2H), 3.00 (br s, 4H), 2.76-2.68 (m, 6H), 2.58 (s, 3H), 2.54 (s, 3H), 2.26 (s, 3H), 2.20 (s, 3H), 1.92 (br s, 2H).

MH+ 414.

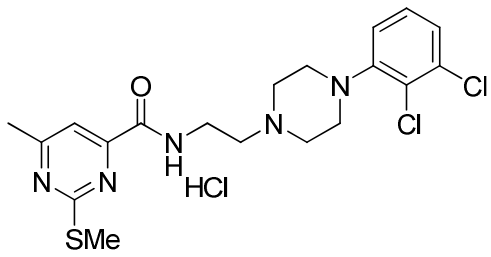
14. Preparation of *N*-(2-(4-(2,3-dimethylphenyl)piperazin-1-yl)ethyl)-6-methyl-2-(methylthio)pyrimidine-4-carboxamide hydrochloride (16d)



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (br s, 1H), 7.62 (s, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 6.92-6.90 (m, 2H), 3.59 (q, *J* = 6.0 Hz, 2H), 2.93 (t, *J* = 4.4 Hz, 4H), 2.70-2.67 (m, 6H), 2.64 (s, 3H), 2.55 (s, 3H), 2.27 (s, 3H), 2.23 (s, 3H).

MH^+ 400.

15. Preparation of *N*-(2-(4-(2,3-dichlorophenyl)piperazin-1-yl)ethyl)-6-methyl-2-(methylthio)pyrimidine-4-carboxamide hydrochloride (16e)

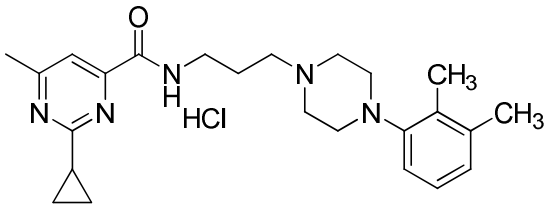


^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (br s, 1H), 7.62 (s, 1H), 7.17 (m, 2H), 6.95 (dd, *J* =

6.8, 3.2 Hz, 1H), 3.60 (q, *J* = 6.0 Hz, 2H), 3.09 (m, 4H), 2.73-2.69 (m, 6H), 2.62 (s, 3H), 2.56 (s, 3H).

MH^+ 440.

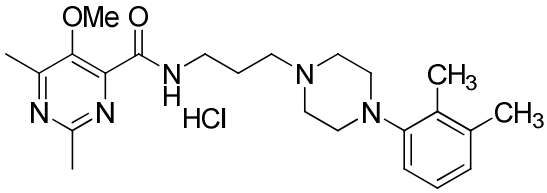
16. Preparation of 2-cyclopropyl-*N*-(3-(4-(2,3-dimethylphenyl)piperazin-1-yl)propyl)-6-methylpyrimidine-4-carboxamide hydrochloride (16f)



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (br s, 1H), 7.70 (s, 1H), 7.04 (t, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 2H), 3.59 (q, *J* = 6.4 Hz, 2H), 2.97 (t, *J* = 4.4 Hz, 4H), 2.64 (br s, 4H), 2.57 (t, *J* = 6.4 Hz, 2H), 2.52 (s, 3H), 2.29-2.24 (m, 4H), 2.21 (s, 3H), 1.85 (quint, *J* = 6.4 Hz, 2H), 1.14-1.11 (m, 2H), 1.03-0.98 (m, 2H).

MH+ 408.

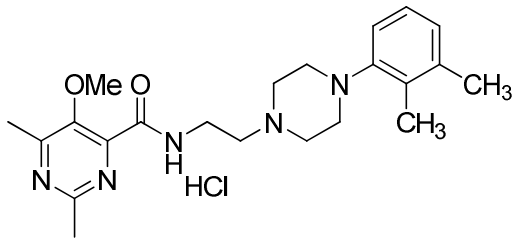
17. Preparation of *N*-(3-(4-(2,3-dimethylphenyl)piperazin-1-yl)propyl)-5-methoxy-2,6-dimethylpyrimidine-4-carboxamide hydrochloride (16g)



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (br s, 1H), 7.06 (t, *J* = 7.6 Hz, 1H), 6.87 (dd, *J* = 20.8, 7.6 Hz, 2H), 3.93 (s, 3H), 3.57 (q, *J* = 6.4 Hz, 2H), 2.88 (t, *J* = 4.8 Hz, 4H), 2.67-2.64 (m, 7H), 2.56 (t, *J* = 6.4 Hz, 2H), 2.53 (s, 3H), 2.26 (s, 3H), 2.21 (s, 3H), 1.85 (quint, *J* = 6.4 Hz, 2H).

MH+ 412.

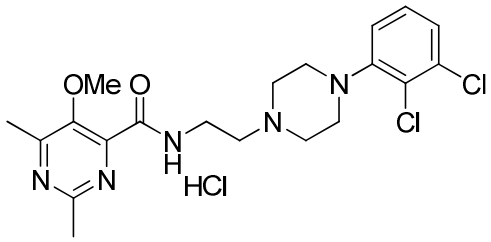
18. Preparation of *N*-(2-(4-(2,3-dimethylphenyl)piperazin-1-yl)ethyl)-5-methoxy-2,6-dimethylpyrimidine-4-carboxamide hydrochloride (16h)



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (br s, 1H), 7.08 (t, *J* = 7.6 Hz, 1H), 6.91 (t, *J* = 7.2 Hz, 2H), 3.93 (s, 3H), 3.59 (q, *J* = 6.4 Hz, 2H), 2.93 (t, *J* = 4.8 Hz, 4H), 2.70-2.68 (m, 9H), 2.54 (s, 3H), 2.27 (s, 3H), 2.23 (s, 3H).

MH^+ 398.

19. Preparation of *N*-(2-(4-(2,3-dichlorophenyl)piperazin-1-yl)ethyl)-5-methoxy-2,6-dimethylpyrimidine-4-carboxamide hydrochloride (16i)



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16-7.14 (m, 2H), 6.95 (dd, *J* = 6.8, 2.8 Hz, 2H), 3.98 (s, 3H), 3.59 (t, *J* = 6.4 Hz, 2H), 3.09 (br s, 4H), 2.72-2.67 (m, 9H), 2.54 (s, 3H).

MH^+ 438.

5. References

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국문초록

파킨슨병은 신경퇴행장애의 일종으로 도파민계 신경의 파괴에 의해 나타나는 질병이다. 이 병을 치료하기 위한 방법으로 신경보호 활성을 보이는 물질의 개발이 활발히 이루어지고 있는데, (+)-3-HM은 파킨슨병 동물모델에서 신경보호 활성이 있는 것으로 나타났다. 이 (+)-3-HM은, 오랜 기간 진해거담제로 사용되어 오던 DM의 대사체로 체내 안전성이 확인되었기 때문에 약물로 개발하는 것이 유망하지만, 경구투여시 체내 흡수가 낮아 어려움이 있었다. 이러한 문제를 해결하기 위해 (+)-3-HM의 전구약물을 연구하여 GCC1290K를 발굴하였고 미국 FDA 임상2상 시험을 진행하고 있다.

HT-22 세포에서 글루타민산염 독성 시험을 하여 신경보호 활성 측정지표를 확보한 후에 (+)-3-HM의 유도체 합성을 통해 신경보호 효과가 개선된 물질을 찾고자 연구를 진행하였고, 유도체 합성에 주요하게 쓰인 반응은 Suzuki-Miyaura cross-coupling 반응과 Buchwald-Hartwig cross-coupling 반응이다. 이 반응으로 신경보호 활성을 갖는 DF의 유도체를 합성하였고, 친전자성 방향족 치환반응 (electrophilic aromatic substitution reaction)을 통해 (+)-3-HM의 1번과 2번 위치에 치환기를 도입한 후 새로운 링을 만들어서 polycycle 유도체를 합성하였다.

우울증은 전반적인 정신기능이 저하된 상태로 인지장애를 동반하기도 하는 질병이다. 항우울제는 신경전달물질의 수용기나 수송기에 작용하는 약물

인데, SARI 작용기전을 갖는 화합물 개발을 위해 arylpiperazine이 포함된 pyrimidine 4-carboxamide 유도체를 합성하였다. 이 유도체 합성은 pyrimidine링과 페닐링의 치환체 변화 및 linker의 길이 변화를 통해 이루어졌으며, 세로토닌 수용기 및 수송기 친화력 측정 및 강제수영시험, 그리고 자발적 활동항진증 시험을 통해 선도물질을 발굴해냈다.

주요어 : 파킨슨병, 신경보호 활성, (+)-3-HM, GCC1290K, cross-coupling, 글루타민산염 독성 시험, 항우울제, 세로토닌, pyrimidine, 강제수영시험, 활동항진증

학번 : 2008-30479