A Dissertation for the Degree of Doctor of Philosophy in Pharmacy

Evolution of a Strategy For Concise Enantioselective Total Synthesis of the Salinosporamide Family of Natural Products

Salinosporamide 계열 천연물들의 효율적인 전합성 수행 및 이를 위한 비대칭 합성법 개발

February 2023

Graduate School of Pharmacy
Seoul National University
Pharmaceutical chemistry Major

Soojun Park

Evolution of a Strategy For Concise Enantioselective Total Synthesis of the Salinosporamide Family of Natural Products

by

Soojun Park

Under the guidance of Professor Sanghee Kim

Submitted to the Faculty of the College of Pharmacy

in Partial Fulfillment of the Requirements for the Degree of

DOCTOR OF PHILOSOPHY

December 2022

Pharmaceutical Chemistry Major, College of Pharmacy

Graduate School of Seoul National University

Seoul, Korea

A Dissertation Approved on

December 2022

by the following Dissertation Committee

Chair _____ (Seal)

Vice Chair _____ (Seal)

Committee Member _____ (Seal)

Committee Member _____ (Seal)

Committee Member _____ (Seal)

Abstract

Owing to their challenging structural features and significant biomedical properties, salinosporamides have attracted great interest from scientists within the chemical and medicinal research communities. This article reports the evolution of a synthetic strategy aimed at rapidly accessing highly functionalized pyrrolidinone cores with correct stereochemistries. Our first strategy involved combined use of memory of chirality and dynamic kinetic resolution principles in intramolecular aldol reactions of a 5-oxazolidinone aldol substrate, which was successful in terms of diastereoselectivity but ultimately unsuccessful with respect to enantioselectivity. This failure led us to the revised strategy, with which we installed the C-2 stereocenter prior to use of the intramolecular aldol reaction. The influence of the stereocenter in the 5-oxazolidinone enabled selective installation of the C-2 stereocenter. The intramolecular aldol reaction of the C-2 stereodefined 5-oxazolidinone aldol substrate was successful. An interesting and unexpected hydrolytic dynamic kinetic resolution was observed in hydrolyses of the 5-oxazolidinone/pyrrolidinone bicyclic aldol products. This unprecedented substrate-driven hydrolytic dynamic kinetic resolution was utilized in preparing the pyrrolidinone core with excellent efficiency. Through this strategy, a 9-step total synthesis of salinosporamide B and a 12-step synthesis of salinosporamide A were achieved with conciseness and high selectivity from silyl-protected serine as the only chiral source. In addition, the total syntheses of cinnabaramides A, E, and F were achieved by using the same chemistry.

Key word: Aldol cyclization, Salinosporamide, Hydrolytic dynamic kinetic resolution, 5-oxazolidinone, Total synthesis

Student Number: 2015-21874

Table of Contents

I. Introduction

Salinosporamides constitute a family of natural products produced by marine bacteria of the genus *Salinispora* (Figure 1). The characteristic structural feature of these compounds is a densely functionalized γ-lactam-β-lactone bicyclic core. The first and representative member of the salinosporamide family is salinosporamide A (**1**), which was isolated from *Salinispora tropica* by Fenical and coworkers in 2003.[1] Compound **1** is a highly potent irreversible inhibitor of the 20S proteasome and exhibits potent in vitro cytotoxicity. Due to its significant biomedical properties,[2] this compound was entered into human clinical trials under the name marizomib.[3] After the identification of **1**, several other salinosporamides were identified from *S. tropica*, including its deschloro analog salinosporamide B (**2**) and methyl congener salinosporamide D (**3**). C-2 epimers of **1** and **3** (salinosporamides F (**4**) and G (**5**), respectively) as well as the C-3 ethyl analog salinosporamide I (**6**) were also identified.[4] The salinosporamide family also encompasses chemically related terrestrial metabolites, cinnabaramides, isolated from a terrestrial strain of *Streptomyces*.[5] The structures of cinnabaramides basically differ from those of salinosporamides in possessing a hexyl substituent at C-2. Cinnabaramides A (**7**) and B (**8**) have bicyclic γ-lactam-β-lactone ring systems similar to those of salinosporamides, while cinnabaramides D (**9**) and E (**10**) are

seco-forms of the corresponding *β*-lactone moieties. Cinnabaramides F (**11**) and G (**12**) are thioester derivatives and are considered analogs of the natural product lactacystin. Interestingly, cinnabaramide A (**7**) strongly inhibited the 20S proteasome with a potency similar to that of **1**,[5] even though the former lacked the chlorine substituent essential for the strong activity of the latter.

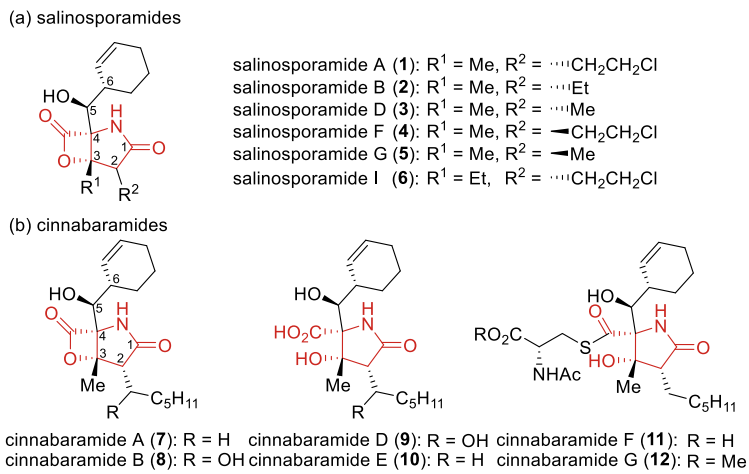


Figure 1. Structures of the salinosporamide family.

The challenging structural features of salinosporamides, which have a highly functionalized skeleton and five contiguous stereogenic centers, including adjacent quaternary centers, have attracted tremendous interest from the synthesis community. The first total synthesis of salinosporamide was achieved by Corey.[6a] To date, fifteen successful total syntheses of salinosporamide A (**1**) and seven formal syntheses have been reported.[6,7] Total syntheses of other salinosporamides

have not been reported. The synthesis of cinnabaramide A (**7**) has been reported once, by Romo.[6n] Most synthetic strategies differ in how they access the highly decorated pyrrolidinone core, as depicted in Figure 2. While Corey[6a] and Omura[6e] constructed the pyrrolidinone ring through a ring closure involving formation of a bond between C-2 and C-3, Borhan[6l] and Chida[6i] constructed the ring by joining the nitrogen function to C-1. An important approach to the pyrrolidinone ring involved bond formation between C-3 and C-4. In this regard, Burton[6k] and Hatakeyama[6d] employed oxidative cyclization and the Conia-Ene reaction of amidomalonate substrates, respectively. Moreover, several groups, including the Potts and Romo groups, used an intramolecular aldol reaction to connect C-3 and C-4.[6c,f,h,j,m]

It is surprising, considering the considerable recent advances in synthetic strategies and methods, that most syntheses of these comparably small but complex natural products have required more than 15 steps.[6a–e,g,i,k,l] Given our interest in asymmetric and concise total synthesis using a minimum number of chiral sources,[8,9] we sought a retrosynthetic scheme that would lead to the amino acid as the only chiral source in the synthesis of salinosporamides. Herein, we report concise total syntheses of salinosporamides A (**1**) and B (**2**) as well as cinnabaramides A (**7**), E (**10**), and F (**11**) from serine through a strategy that features a number of chirality induction processes.

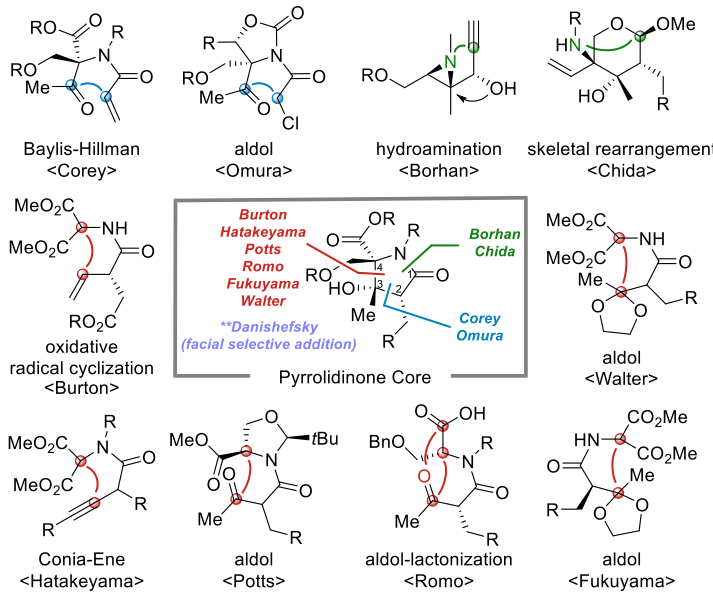


Figure 2. Previous strategies for preparing pyrrolidinone cores of salinosporamides.

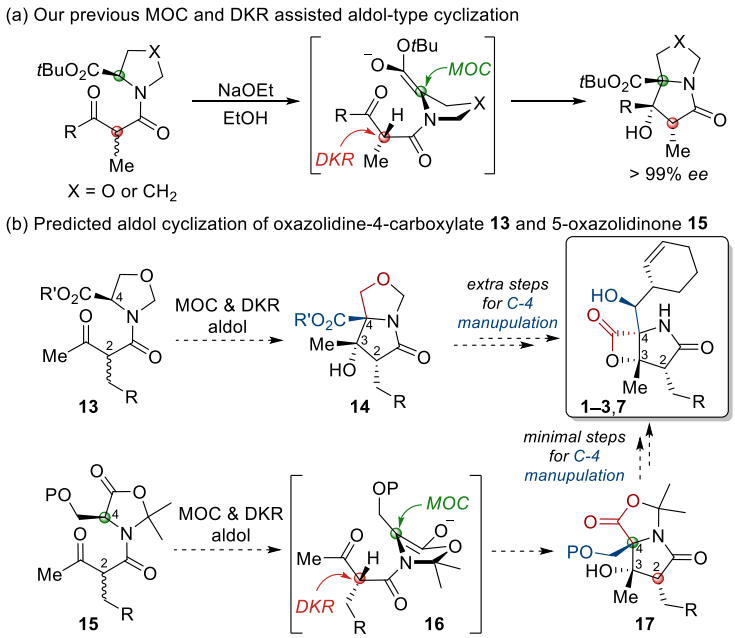
II. Results and Discussion

We previously reported an application of the principles of "memory of chirality" (MOC)[10] and "dynamic kinetic resolution" (DKR)[11] to intramolecular aldol reactions for asymmetric construction of the pyrrolidinone cores of some natural products by using simple amino acids as the only chiral source (Scheme 1a).[8] The excellent MOC and DKR outcomes were attained with the relatively weak base NaOEt in a protic solvent. Building on our previous work, we designed an approach that would implement the combined use of MOC and DKR for concise

synthesis of the salinosporamide family. As shown in Scheme 1b, we expected that the aldol reaction of d-serine derivative **13** would yield pyrrolidinone **14**. The predicted product **14** might have the C-2 and C-3 stereochemistries (natural product numbering) required for syntheses of the target salinosporamides. On the other hand, the configuration of the C-4 quaternary center was not suitable for concise synthesis. The oxidation levels of two substituents on the C-4 carbon should be reciprocally changed, which would make any given synthetic route longer. In fact, many previous syntheses of salinosporamides required several extra steps to adjust the oxidation levels of C-4 substituents or to differentiate two identical C-4 ester groups.[6b–d,j,l,m,o]

To shorten the synthesis by avoiding redox adjustment steps, we devised an alternate route involving l-serine-derived 5-oxazolidinone **15** (Scheme 1b). We envisioned that the intramolecular aldol reaction of **15** via enolate **16** might afford aldol product **17** with the proper configuration required to proceed swiftly to the salinosporamides. Although this stereochemical outcome was postulated on the basis of our previous MOC-DKR aldol reactions (Scheme 1a), there were several stereochemical concerns to be addressed. Two of the major questions were whether the axially chiral endocyclic enolate **16** was obtainable with appropriate selectivity and whether the resulting chiral enolate would have a sufficiently sizeable energy barrier for racemization to allow the MOC aldol reaction. Successful MOC

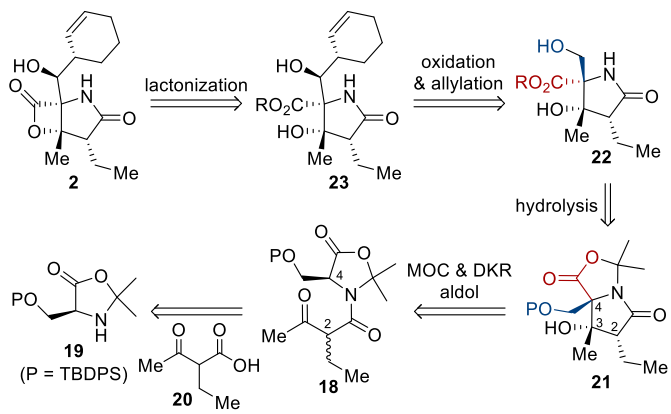
reactions via endocyclic enolates were reported by the Alezra group, who employed amino acid-derived 5-oxazolidinone with a bulky naphthyl amide moiety.[12] This bulky moiety was used to enhance the stability of the dynamic axial chirality in the endocyclic enolate. However, our designed aldol substrate **15** possesses a sterically less demanding alkyl amide group. Another major stereochemical concern was whether the DKR process would occur at the C-2 position of **15** during the aldol reaction. While a stereocenter adjacent to two carbonyl groups is generally readily epimerizable, the epimerization would not easily occur in some special systems, such as with Evans' 2-oxazolidinone-substituted β-ketoimides.[13] To the best of our knowledge, no study has reported epimerization of a 5-oxazolidinone-substituted β-ketoamide system.



Scheme 1. Implementation of the MOC and DKR strategy toward salinosporamides

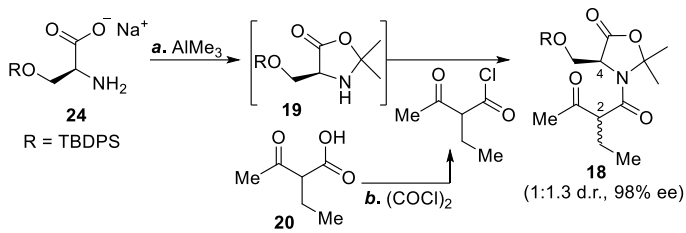
Despite these uncertainties, we decided to pursue the synthesis using 5-oxazolidinone **18** as a model study and a possible intermediate to salinosporamide B (**2**), as shown in retrosynthetic Scheme 2. If successful, this approach would enable total synthesis of the salinosporamide family with a minimum number of chiral sources and chemical steps. Specifically, aldol substrate **18** would be available by condensation of serine-derived oxazolidinone **19** with *β*-ketoacid **20**. We assumed that the C-2 stereocenter would not require installation because the DKR process might occur during the basic aldol reaction. The aforementioned MOC- and DKR-involved aldol reaction of **18** was envisioned to afford bicyclic

pyrrolidinone-oxazolidinone **21**. The resulting aldol product **21** might serve as an advanced intermediate en route to **2**. Attachment of the 2-cyclohexenyl group at the C-4 hydroxy methylene group in **22** was expected to proceed via Corey's protocol.[6a] Subsequent β-lactone ring formation with the two functional groups appropriately positioned in **23** would complete the total synthesis.



Scheme 2. Retrosynthetic analysis of salinosporamide B.

Our initial study began with the preparation of aldol substrate **18** (Scheme 3). First, oxazolidinone **19** was prepared from the sodium salt of silyl-protected serine **24**[14] by applying the procedure described by Alezra.[12] As this compound was unstable, it was coupled *in situ* with the known β-ketoacid **20** to afford **18** as a 1:1.3 mixture of C-2 diastereomers. During this operation, no epimerization occurred at the C-4 position.



Scheme 3. Synthesis of aldol substrate **18**. Reagents and conditions: (a) $AlMe_3$ (1.0 equiv), 4 Å molecular sieves (excess), acetone, rt, 16 h, then the acid chloride of 20 (1.5 equiv), rt, 2 h, 68%; (b) $(COCl)_2$ (1.2 equiv), cat. DMF, CH_2Cl_2, 0 °C to rt, 2 h. DMF = dimethylformamide.

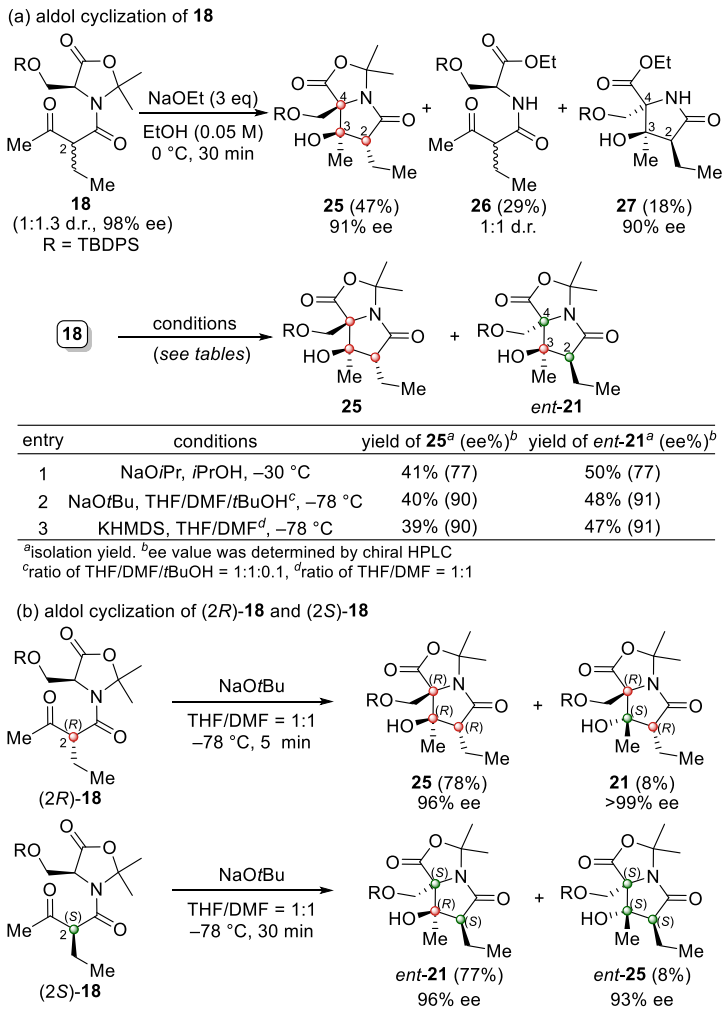
With a diastereomeric mixture of **18** in hand, we investigated the intramolecular aldol reaction. Initially, **18** was subjected to the previously established reaction conditions[8] (NaOEt in EtOH at 0 °C) for the MOC- and DKR-involved aldol reaction (Scheme 4). Unlike in our previous work,[8] the reaction of **18** was not selective and afforded three different products. The major product (47%) was bicyclic aldol product **25**, for which the enantiopurity was 91% ee. A structural determination by NMR showed that the C-3 stereocenter was epimeric to those of the target natural products, while two stereocenters at C-2 and C-4 had the desired configurations. Another product (29%) was acyclic compound **26**, which arose from the oxazolidinone ring-opening reaction of the starting substrate **18** with ethoxide. The other minor product was pyrrolidinone **27**, which was formed with a yield of 18% and enantiopurity of 90% ee. The relative stereochemistry of **27**, as determined by 2D NMR analysis, suggested first that **27** was derived from the

oxazolidinone ring-opening reaction of our initially envisioned bicyclic aldol product **21**. Later, it was found that **27** was derived from the ring-opening reaction of *ent*-**21**, not from the reaction of **21** (vide infra).[15]

Other sodium alkoxides with bulky organic substituents were employed to suppress ring-opening of the oxazolidinone moiety. NaO*i*Pr and NaO*t*Bu also afforded bicyclic **25** at low temperatures (Scheme 4a, table, entries 1–2). Instead of the oxazolidinone ring cleavage products **26** and **27**, these bases afforded another bicyclic aldol product. The obtained bicyclic species was not our initially envisioned aldol product **21**, but was, to our surprise, the enantiomer of **21** (*ent*-**21**).[16] The combined yield of the two aldol products **25** and *ent*-**21** was very high (ca. 90%), and the product ratio was 1:1.2. The enantiopurities of **25** and *ent*-**21** obtained from the reaction with NaO*t*Bu in THF/DMF/*t*BuOH were 90% and 91% ee, respectively. A sterically hindered strong organic base, KHMDS, also afforded the same two products with 90% ee and a yield and ratio similar to those of NaO*t*Bu (entry 3).

These results, including the similar diastereomeric ratios of the substrate and product, led us to suspect that the C-2 stereochemistry might be an important factor in determining the stereochemical outcome of the process. To comprehend the reaction, we performed additional experiments. When the two separated C-2 diastereomers of **18** were independently subjected to the aldol reaction conditions

with NaO*t*Bu in THF/DMF, each diastereomer produced a 9:1 mixture of diastereomeric aldol products (Scheme 4b). The (2*R*)-**18** isomer[17] rapidly produced (2*R*,3*R*,4*R*)-**25** as the major diastereomer along with its C-3 epimer **21**, while the reaction of the (2*S*)-**18** isomer less rapidly afforded *ent*-**21** with the (2*S*,*3R*,4*S*) configuration as the major isomer and its C-3 epimer *ent*-**25** as the minor isomer. The enantiopurities of the obtained isomers were excellent to very high. Conducting the reaction in the presence of a protic solvent resulted in a very similar outcome (see experimental section for details). These results explained the stereoselectivities obtained for the reaction with the C-2 diastereomeric mixture **18**. In addition, these results led us to conclude that the stereochemical outcome was controlled by the C-2 stereocenter rather than the envisioned MOC and DKR principles.



entry	conditions	yield of **25**[a] (ee%)[b]	yield of *ent*-**21**[a] (ee%)[b]
1	NaO*i*Pr, *i*PrOH, –30 °C	41% (77)	50% (77)
2	NaO*t*Bu, THF/DMF/*t*BuOH[c], –78 °C	40% (90)	48% (91)
3	KHMDS, THF/DMF[d], –78 °C	39% (90)	47% (91)

[a]isolation yield. [b]ee value was determined by chiral HPLC
[c]ratio of THF/DMF/*t*BuOH = 1:1:0.1, [d]ratio of THF/DMF = 1:1

Scheme 4. Aldol cyclization of 18.

At the outset of this study, we assumed that the configuration at the C-2 stereocenter would not be important because the DKR might occur at the epimerizable C-2 position. However, unlike our previous studies with oxazolidine-4-carboxylate,[8b,c] DKR was not operating with the 5-oxazolidinone substrate **18**. A

deuteration study of (2*S*)-**18** with NaOEt/EtOD at –40 °C showed a negligible level of deuterium incorporation at C-2 (Figure 3a). On the other hand, appreciable deuterium exchange was observed at C-4. Interestingly, the stereocenters of recovered (2*S*)-**18** were not racemized.[8a] The obtained aldol product showed no detectable deuterium incorporation at C-2 (see SI). The deuteration study of (2*R*)-**18** was aborted because of its very fast aldol reaction rate. However, it provided information indicating that the aldol product also did not contain deuterium at the C-2 position (see SI). These results implied a low kinetic acidity for the C-2 hydrogen atom of substrate **18** under the reaction conditions. One reasonable explanation for the low kinetic acidity exhibited by the hydrogen atom on C-2 adjacent to two carbonyl groups could be 1,3-allylic strain in the deprotonation transition state, which could arise from the presence of the 5-oxazolidinone amide group, as shown in the brackets.[13] This explanation was supported by the observation that oxazolidinone ring *seco* substrate **26** showed facile basic deuteration at C-2 (Figure 3b).

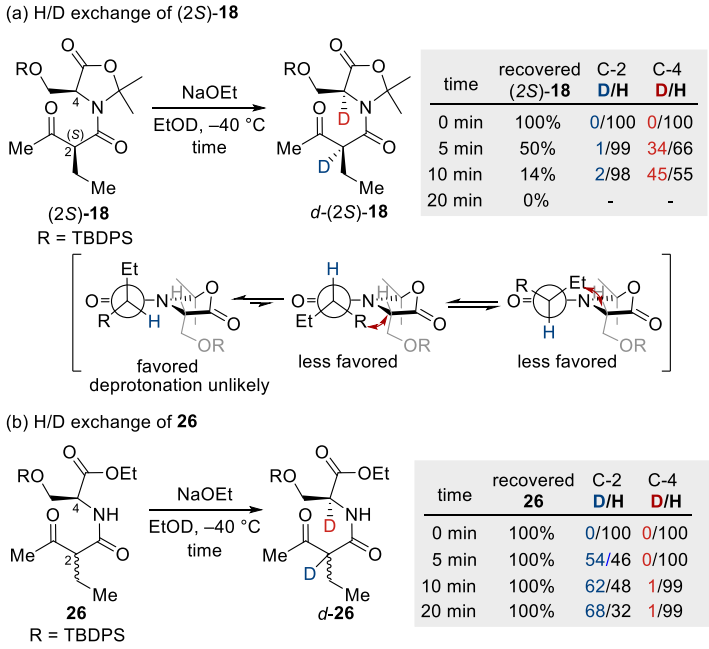
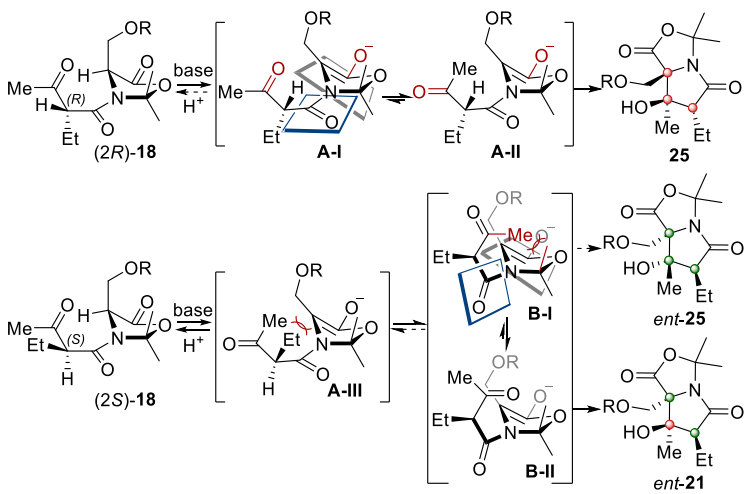


Figure 3. H/D exchange of **18** and **26** in EtOD.

Based on these results and our earlier reports, an aldol reaction mechanism of **18** was proposed, as shown in Scheme 5. An axially chiral enolate **A**, generated from the favored conformer (2*R*)-**18**, undergoes a rapid aldol reaction via conformer **A-II** to yield aldol product **25**. The reaction via conformer **A-I** would be less preferred because of the unfavorable dipole interaction between two carbon-oxygen bonds in a synclinal disposition. In the aldol reaction of (2*S*)-**18**, axial chiral enolate **A-III** was generated, similar to the reaction of (2*R*)-**18**. However, the C-2 alkyl group in **A-III** hinders enolate addition to the carbonyl group and prevents formation of the corresponding aldol product. Because the C-2 stereocenter of **18** is not readily epimerizable, (2*S*)-**18** takes an alternative reaction

pathway that involves epimerization of the chiral enolate. In this event, the C-2 alkyl group no longer blocks the enolate addition to the carbonyl group as shown in conformer **B**. The conformer **B-I** would suffer from a severe steric interaction between the methyl group and the gem-dimethyl moiety of the oxazolidinone ring. Thus, the aldol reaction of (2*S*)-**18** would proceed via conformer **B-II** to give *ent*-**21** despite the dipole interaction.



Scheme 5. Plausible aldol reaction mechanism of 18

We observed an interesting phenomenon in attempted basic hydrolyses of bicyclic aldol products. While hydrolysis of the oxazolidinone ring of *ent*-**21** with KOH in THF/water was very fast and gave the corresponding hydrolysis product *ent*-**28**, the hydrolysis of **25** was sluggish and produced the C-3 epimerized hydrolysis product

28 without loss of enantiopurity (Figure 4a). To understand this unexpected C-3 epimerization, we performed the basic hydrolysis of **25** in deuterated THF with D_2O (Figure 4b). Monitoring of the reaction by NMR indicated the presence of peaks for **21** or *ent*-**21**. Hydrolysis product **28** was progressively formed without detectable deuterium incorporation at C-2 as the reaction progressed. The ratio of **25** to **21** was unchanged (15:1) throughout the experimental period. These observations suggested that **21** was an intermediate for formation of **28** and was in equilibrium with **25** under basic conditions. To further understand this interesting phenomenon, the reaction of (2*R*)-**18** was monitored over time. As mentioned above, formation of the two bicyclic aldol products **25** and its C-3 epimer **21** was very fast. The product ratio was constant over time and favored **25** (Figure 4c).[18] This result suggested that **25** might be the thermodynamic and kinetic product of the reaction of (2*R*)-**18**. Our density functional theory (DFT) calculations using simplified enolate **29** supported the experimental suggestion. As shown in Figure 4d, formation of the (2*R*,3*R*,4*R*)-isomer was favored both thermodynamically and kinetically. The energy differences calculated for products **P1** and **P2** correlated well with the diastereomeric ratios obtained in the aldol reaction. Considering the low activation barriers, the aldol adducts might be in rapid equilibrium with each other.

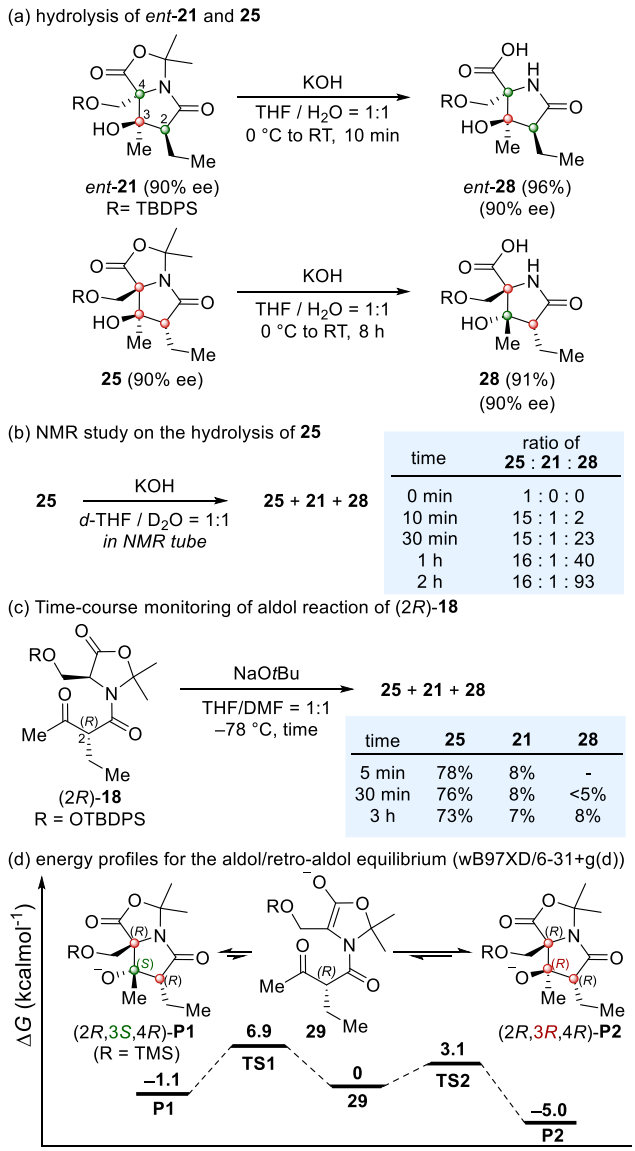
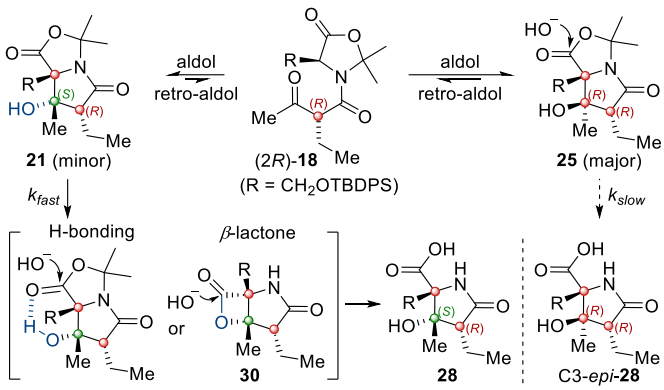


Figure 4. Hydrolysis of aldol products and mechanistic studies.

Based on the above experimental and computational studies, a hydrolytic C-3 epimerization mechanism of **25** was proposed, as shown in Scheme 6. Aldol product **25** is converted to its C-3 epimer **21** via a retroaldol–realdol process,[19] and

the two are in fast equilibrium with one another. The minor aldol product **21** would experience more rapid hydrolysis because its C-3 hydroxyl group is *syn* to the adjacent oxazolidinone ring. This proximal C-3 hydroxyl group can cooperate or be involved in hydrolysis of the oxazolidinone ring, thus accelerating the rate of hydrolysis.[20] One possible route for participation is through intramolecular hydrogen-bond formation to promote hydrolysis.[20a,d] The other possible participation route for this proximal group is irreversible formation of the reactive *β*-lactone intermediate **30**. Although we could hardly detect it via NMR monitoring, we found that *β*-lactone **30**, which was obtained by intramolecular cyclization of **28**, was hydrolyzed extremely rapidly to afford **28** under the above basic conditions (see SI). As a result of neighboring group participation by the C-3 hydroxyl group, the hydrolysis product distribution would not reflect the equilibrium distribution of the two aldol products, and the only hydrolytic product **28** arose from a minor component **21**. To the best of our knowledge, this type of substrate-driven hydrolytic DKR of diastereomers has not been reported thus far, although there are enzymatic or catalytic examples of hydrolytic DKR.[21]



Scheme 6. Plausible hydrolytic epimerization mechanism of **25**

The initially envisioned MOC- and DKR-involved aldol approach with C-2 diastereomeric mixture **18** proved to be unsuccessful, especially with respect to the enantioselectivity; (2*R*)-**18** produced the desired stereomer **28** after aldol reaction and consequent hydrolysis, while (2*S*)-**18** afforded *ent*-**28**. Thus, we developed a new synthetic approach, as shown in Scheme 7. The endgame disconnections of our revised synthetic plan remained identical and would lead to pyrrolidinone **28**, which would be accessible via an intramolecular aldol reaction and hydrolysis of oxazolidinone **18**. Central to the new approach was selective installation of the C-2 stereocenter prior to the intramolecular aldol reaction. We envisioned that diastereoselective 1,4-reduction of α,β-unsaturated 1,3-dicarbonyl substrate **31** could be achieved with control by the stereocenter in the 5-oxazolidinone ring to afford either (2*S*)-**18** or (2*R*)-**18**. Although no precedent for this type of selective

reduction has been reported, we deemed it possible based on Evans' oxazolidinone chemistry.[13]

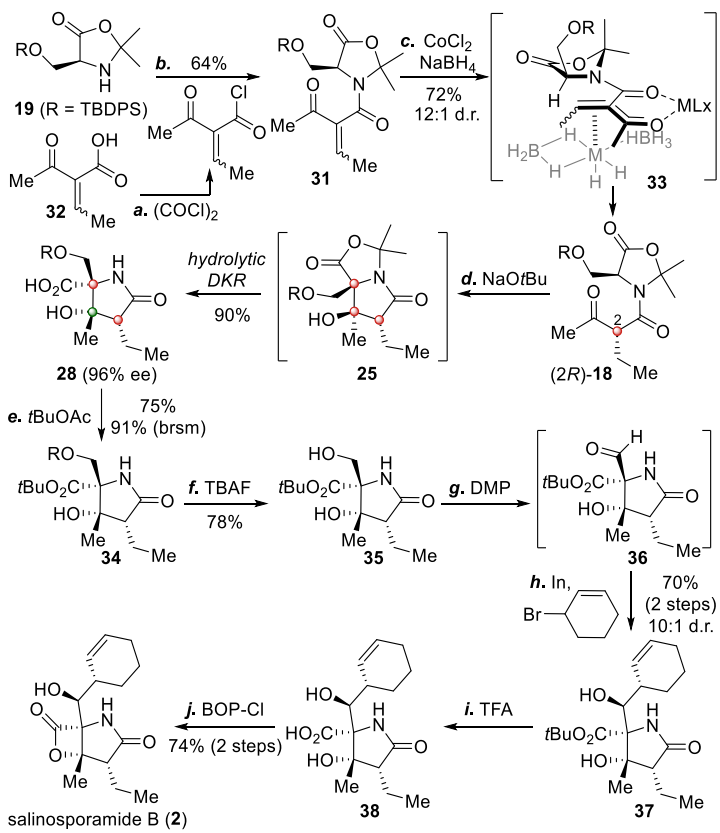
The required substrate **31** was prepared as a 1:1.5 mixture of *E*/*Z* isomers by condensation of oxazolidinone **19** with the known β-ketoacid **32**.[22] This mixture was subjected to various 1,4-reduction conditions. Gratifyingly, we found that reduction with $NaBH_4$ in the presence of $CoCl_2$ in methanol proceeded with high diastereoselectivity (12:1) to afford (2*R*)-**18** as a major isomer.[23] Based on the stereochemical outcome at the C-2 center, we proposed that the reduction proceeded through **33** involving chelation and minimized allylic strain wherein a substituent on the oxazolidinone ring blocked the approach of the reductant from the *re* face.

From our prior synthetic campaigns (Figure 4c),[18] it seemed that, under the correct conditions, the intramolecular aldol reaction of (2*R*)-**18** could occur in tandem with DKR hydrolysis. Thus, we sought reaction conditions for the one-pot tandem reaction. After some trials, we found that the reaction of (2*R*)-**18** with NaO*t*Bu in slightly wet *t*BuOH (~0.1% (v/v) water in *t*BuOH) at room temperature gave the desired pyrrolidinone **28** directly in 90% yield and with 96% ee. Increasing the water content was detrimental to the yield because excess water led to hydrolysis of the oxazolidinone ring prior to the aldol reaction.

Having achieved a selective route to **28**, the main task remaining for the total synthesis was attachment of the 2-cyclohexenyl group to the C-4 functional group with concomitant installation of the C-5 and C-6 stereogenic centers. We planned to achieve this goal by employing Corey's approach,[6a] which entailed the addition of a cyclohexenylzinc reagent to the C-4 aldehyde group. Corey's process is very commonly applied in syntheses of salinosporamides.[6a,b,d,e,i–k,m,o] However, success with this process required protection of the amide nitrogen, presumably due to the instability of the aldehyde intermediate and low diastereoselectivity.[6j,k] Only the Burton group has reported successful addition of the cyclohexenylzinc reagent to the unstable aldehyde substrate without a protecting group on the amide nitrogen, albeit in moderate yield.[6k] Encouraged by Burton's work, we proceeded to install the cyclohexene ring and stereocenters. To this end, the carboxylic acid in **28** was first converted to its *t*-butyl ester **34**, and the silyl protecting group was removed to afford **35**. Dess-Martin oxidation of **35** afforded the unstable aldehyde **36**, which was immediately subjected to the next reaction after filtration. The reaction of **36** with the cyclohexenylzinc reagent, which followed the Corey procedure,[6a,] gave a mixture of two diastereomers (5:1 d.r.) with desired isomer **37** as the major component, albeit in modest yield (54%). Alternatively, we found that indium-mediated Barbier-type allylation, which greatly simplified the experimental operation, afforded the desired product with much improved yield (70%) and

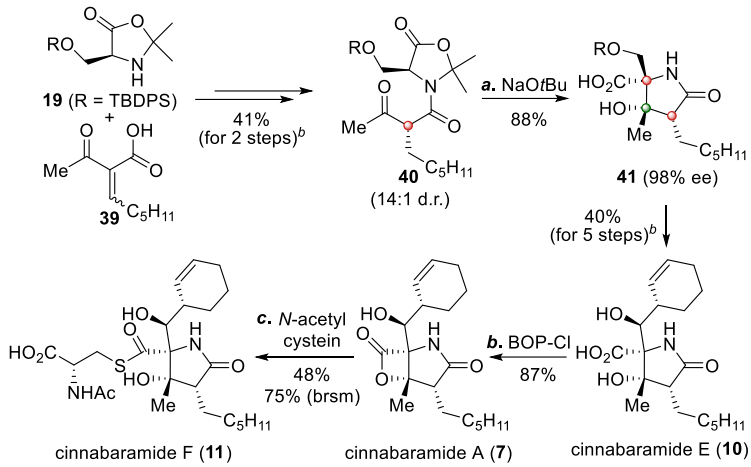
selectivity (10:1 d.r.). The best outcome was obtained when THF was employed as the solvent and ammonium chloride as an additive.

With a route to **37** secured, we proceeded to construct *β*-lactone ring with two substituents at C-3 and C-4. Toward this end, *t*-butyl ester was hydrolyzed with trifluroacetic acid (TFA) and the resulting crude acid **38** was treated with BOP–Cl and triethylamine to give salinosporamide B (**2**) in good yield. Overall, this asymmetric total synthesis was completed in only 9 steps from known silyl-protected serine **24** and 12% overall yield.



Scheme 7. Revised scheme for the total synthesis of salinosporamide B. Reagents and conditions: (a) $(COCl)_2$ (1.2 equiv), cat. DMF, CH_2Cl_2, 0 °C to rt, 2 h; (b) acid chloride of **32** (1.5 equiv), acetone, rt, 2 h, 64%; (c) $CoCl_2$ (4.0 equiv), $NaBH_4$ (5.0 equiv), MeOH, –78 °C to 0 °C, 1 h, 72% (12:1 d.r.); (d) NaO*t*Bu (5.0 equiv), *t*BuOH, rt, 30 min, 90% (96% ee); (e) 50% $HClO_4$ (aq)/*t*BuOAc (1:50), rt, 16 h, 75% (91% brsm); (f) TBAF (2.0 equiv), AcOH (4.0 equiv), THF, 0 °C to rt, 12 h, 78%; (g) Dess-Martin periodinane (1.2 equiv), CH_2Cl_2, rt, 2 h; (h) In (5.0 equiv), 3-bromocyclohexene (3.0 equiv), NH_4Cl (5.0 equiv), THF, rt, 6 h, 70% (10:1 d.r.) for 2 steps; (i) TFA/CH_2Cl_2, rt, 2 h; (j) BOP-Cl (3.0 equiv), Et_3N (6.0 equiv), CH_2Cl_2, rt, 10 h, 74% for 2 steps. TBAF = tetrabutylammonium fluoride, DMP = Dess–Martin periodinane; TFA = trifluoroacetic acid, BOP-Cl = bis(2-oxo-3-oxazolidinyl)phosphinic chloride.

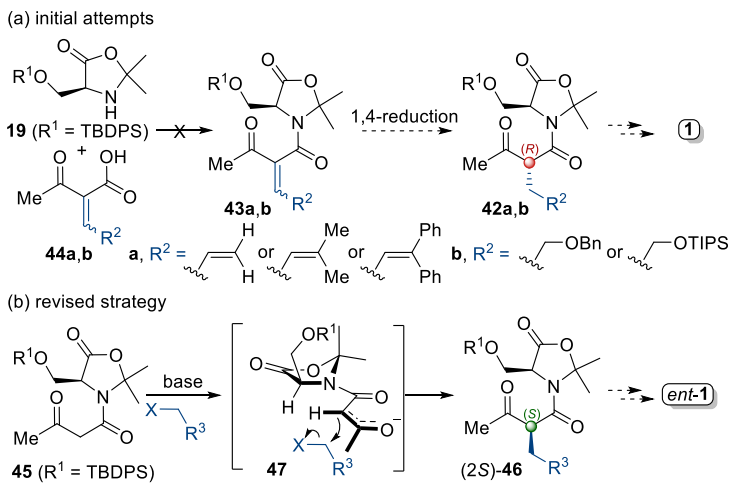
Using essentially the same chemistry described for the synthesis of **2**, we also accomplished the total syntheses of cinnabaramides, as briefly depicted in Scheme 8. The total synthesis of cinnabaramide A (**7**) was accomplished from **19** and **39** via the same process shown in Scheme 7. During this endeavor, cinnabaramide E (**10**) was obtained as a precursor to **7**, and cinnabaramide F (**11**) was derived from **7** by a reaction with *N*-acetylcysteine. The spectral data and optical rotations for the obtained cinnabaramides were in good agreement with those of the natural products,[5] thus confirming the structures of these natural products.



Scheme 7. Revised scheme for the total synthesis of salinosporamide B. Reagents and conditions: (a) NaO*t*Bu (5.0 equiv), *t*BuOH, rt, 30 min, 88% (98% ee); (b) BOP-Cl (3.0 equiv), Et_3N (6.0 equiv), CH_2Cl_2, rt, 10 h, 87%; (c) N-Acetyl-l-cycstein (1.0 equiv), Et_3N (3.0 equiv), CH_2Cl_2, rt, 12 h, 48% (75% brsm). [b]The synthesis was performed with the same procedure as in Scheme 7. For details, see the supporting information.

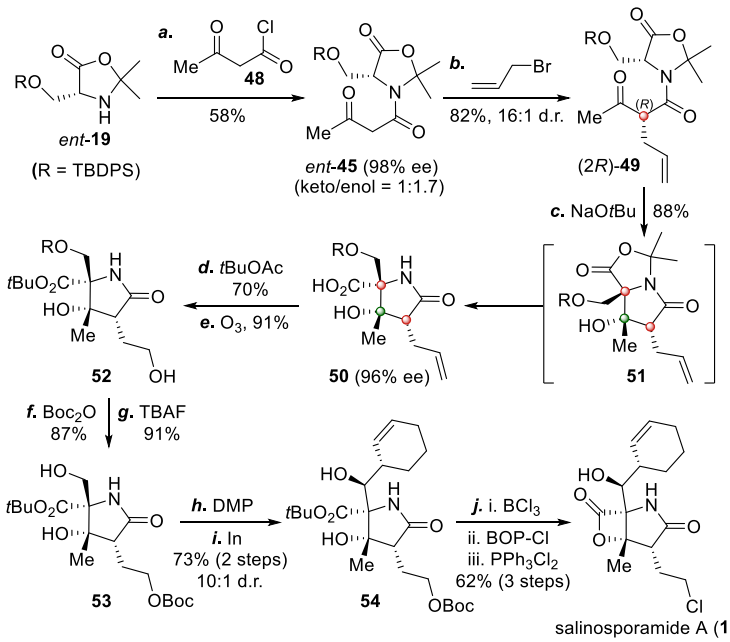
Having established a concise route to salinosporamide B and cinnabaramides, we turned our attention to the total synthesis of salinosporamide A (**1**). We anticipated that the synthesis would be achieved by using basically the same chemistry, although it would require additional steps due to the presence of a reactive chlorine substituent. To this end, several attempts were first made to prepare the C-2 stereodefined aldol substrate **42** from **19** with the same 1,4-reduction protocol used for (2*R*)-**18** (Scheme 9a). However, all attempts were unsuccessful, mainly due to the instabilities of reduction substrate **43a** and the required *β*-ketoacids **44b**.

As an alternate strategy, we envisioned that the reaction of **45** with an alkylating reagent could selectively afford **46** (Scheme 9b). A related system that used Evans' 2-oxazolidinones has been reported.[24] However, a base-mediated alkylation of the Evans' auxiliary substituted *β*-ketoimides afforded very poor diastereoselectivity, probably because exposure of the products to basic conditions during the long reaction time led to epimerization at the stereocenter adjacent to the two carbonyl groups. In light of the notable configurational stability observed for C-2 of the 5-oxazolidinone **18** under basic conditions, we hypothesized that it could be possible to obtain **46** without substantial epimerization at C-2. Thus, we investigated the diastereoselective alkylation of 5-oxazolidinone-substituted *β*-ketoamide **45**.



Scheme 9. Synthesis of the C-2 stereodefined aldol substrate for synthesis of salinosporamide A.

Given that the 5-oxazolidinone moiety in **45** effectively acts as a chiral auxiliary, the alkylation reaction would proceed via transition state **47**, and thus, the major product would have the 2*S* stereochemistry (Scheme 9b). Because the 2*S* stereoisomer would lead to synthesis of the enantiomer of natural **1**, d-serine-derived oxazolidinone *ent*-**19** was employed as the precursor to (–)-**1**. (Scheme 10). Condensation between *ent*-**19** and the known *β*-ketoacid chloride **48**[25] in the presence of pyridine provided *β*-ketoamide *ent*-**45** without epimerization at the C-4 position. Gratifyingly, the reaction of *ent*-**45** with allyl bromide afforded the C-2 allylated product (2*R*)-**49** in good yield and with high diastereoselectivity (>16:1 d.r.). Notably, the diastereo-selectivity reported for alkylation of Evans' auxiliary substituted *β*-ketoimide with allyl halide was very low (up to 2:1 d.r.),[24a,c] which suggested the potential utility of the 4-substituted 5-oxazolidinone moiety in asymmetric synthesis.



Scheme 7. Revised scheme for the total synthesis of salinosporamide B. Reagents and conditions: (a) 3-oxobutanoyl chloride (1.5 equiv), pyridine (2.5 equiv), acetone, rt, 2 h, 58% (98% ee); (b) allyl bromide (5.0 equiv), NaH (1.1 equiv), DMF, 0 °C, 30 min, 82% (16:1 d.r.); (c) NaO*t*Bu (5.0 equiv), *t*BuOH, rt, 30 min, 88% (96% ee); (d) 50% $HClO_4$ (aq)/*t*BuOAc (1:50), rt, 16 h, 70%; (e) O_3, CH_2Cl_2/MeOH (1:1), –78 °C, 10 min, then $NaBH_4$ (10 equiv), 0 °C, 2 h, 91%; (f) Boc_2O (5.0 equiv), VOF_3 (0.1 equiv), CH_2Cl_2, 50 °C, 48 h, 87%; (g) TBAF (2.0 equiv), AcOH (4.0 equiv), THF, 0 °C to rt, 12 h, 91%; (h) Dess-Martin periodinane (1.2 equiv), CH_2Cl_2, rt, 2 h; (i) In (5.0 equiv), 3-bromocyclohexene (3.0 equiv), NH_4Cl (5.0 equiv), THF, rt, 6 h, 73% (10:1 d.r.) for 2 steps; (j) i. BCl_3 (3.0 equiv), CH_2Cl_2, 0 °C, 1 h; ii. BOP-Cl (3.0 equiv), CH_2Cl_2/pyridine (2:1), rt, 8 h; iii. Ph_3PCl_2 (2.0 equiv), CH_3CN/pyridine (1:1), rt, 4 h, 62% for 3 steps.

The one-pot tandem aldol reaction and hydrolysis protocol was also successfully applied to (2*R*)-**49** to give the desired pyrrolidinone **50** (96% ee) via intermediate **51**. After conversion of the carboxylic acid moiety in **50** to the *t*-butyl ester, ozonolysis followed by reductive work-up yielded **52**. The primary hydroxyl group

in **52** was protected with a Boc group, and the silyl protecting group was removed to afford **53**. Dess-Martin oxidation of **53** and a subsequent indium-mediated Barbier-type allylation afforded **54** with a good two-step yield (73%) and high diastereoselectivity (10:1 d.r.). After removal of the two acid-labile protective groups, lactonization with BOP-Cl followed by chlorination with Ph_3PCl_2 afforded (–)-**1** in good overall yield. The spectral data and optical rotation obtained for **1** were in good agreement with those of natural salinosporamide A.[1,6]

III. Conclusion

In this article, we have described the evolution of an asymmetric total synthetic strategy for preparing salinosporamide natural products. Given the challenging structural features and significant biomedical properties, salinosporamides have attracted great interest from the synthetic community, and many elegant synthetic strategies have been reported. However, there is still room for more efficient and selective synthetic routes. Our endeavors resulted in a 9-step concise total synthesis of salinosporamide B (**2**) and a 12-step route to salinosporamide A (**1**) with excellent stereoselectivities from the known *O*-protected amino acid serine. In addition, the total syntheses of several natural congeners, including cinnabaramides A (**7**), E (**10**), and F (**11**) were achieved with the same chemistry, and this

confirmed their structures. Initially, we focused on an approach that would implement a combination of MOC and DKR principles in the intramolecular aldol reaction of a 5-oxazolidinone aldol substrate for rapid access to the highly decorated pyrrolidinone core. However, unlike our previous studies with oxazolidine-4-carboxylate, MOC and DKR did not operate with the 5-oxazolidinone substrate. Throughout this study, efforts were made to explore and exploit the innate properties of the 5-oxazolidinone moiety as a stereochemical inducer. Indeed, we have found that the 5-oxazolidinone moiety acts as in a manner similar to that of Evans' 2-oxazolidinone chiral auxiliary, and we utilized this moiety for selective installation of the C-2 stereocenter. In the revised synthetic approach, the C-2 stereocenter was installed prior to the intramolecular aldol reaction and was used to determine the stereochemical outcome of the aldol reaction. During our use of pyrrolidinone aldol products to synthesize the target products, we observed an interesting and unexpected hydrolytic DKR during hydrolyses of 5-oxazolidinone/pyrrolidinone bicyclic aldol products. This type of substrate-driven hydrolytic DKR with diastereomers has not been reported thus far and was utilized to prepare the pyrrolidinone core with excellent efficiency. Because of both the conciseness and potential modularity of this synthetic sequence, we anticipate that various analogs, including stereoisomers and congeners, will be easily accessible; this will provide a chance to achieve a greater

understanding of the biomedical properties of salinosporamide natural products and lead to new drug discovery. In addition, given the excellent stereochemical induction observed, we believe that the 4-substituted 5-oxazolidinone moiety might serve as an effective chiral auxiliary or substrate in asymmetric synthesis. Such investigations are underway in our laboratory.

IV. Experimental

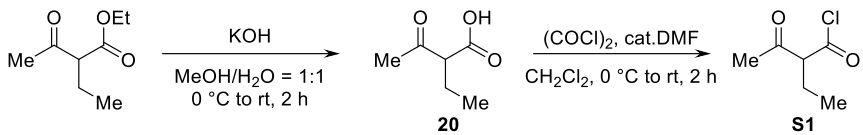
IV-1. General.

All chemicals were of reagent-grade and were used as purchased. All reactions were performed under an inert atmosphere of dry nitrogen using distilled dry solvents. The reactions were monitored with TLC analysis using silica gel 60 F-254 thin layer plates. Compounds on the TLC plates were visualized under UV light and by spraying with either potassium permanganate or anisaldehyde solutions. Flash column chromatography was conducted on silica gel 60 (230–400 mesh). Melting points were measured using a Buchi B-540 melting point apparatus without correction. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-ECZ400S (400 MHz) spectrometer at 278 K if not noted otherwise. Chemical shifts are reported in ppm (δ) units relative to the undeuterated solvent as a reference peak ($CDCl_3$–d_1: 7.24 ppm/^{1}H NMR, 77.16 ppm/^{13}C NMR; CD_3OD–d_4: 3.30 ppm/^{1}H NMR, 49.00 ppm/^{13}C NMR; DMSO-d_6: 2.50 ppm/^{1}H NMR, 39.52 ppm/^{13}C NMR). The following abbreviations are used to represent NMR peak multiplicities: s (singlet), d (doublet), t (triplet), m (multiplet), dd (doublet of doublets), dt (doublet of triplets), dq (doublet of quartets), td (triplet of doublets), and br (broad signal). The IR spectra were measured by an Agilent Technologies 5500 Series FT-IR spectrometer. The optical rotations were measured on a Jasco P-

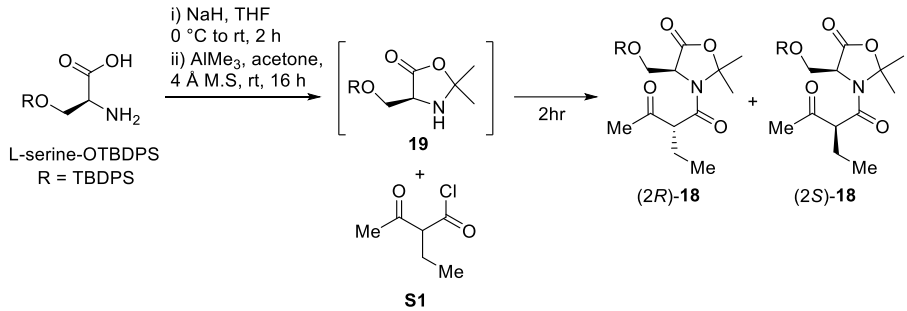
2000 Polarimeter using sodium light (D line 589.3 nm) and a 3.5 × 100 mm or 3.5 × 10 mm cell. The values are reported as the specific optical rotation with exact temperature, concentration (c (10 mg/mL)) and solvent. High-resolution mass spectra (HRMS) were recorded using fast atom bombardment (FAB) mass spectrometry.

IV-2. Experimental procedure and spectroscopic data analysis

IV-2-1. Exploratory studies to determine the mechanism of the aldol and hydrolysis reaction



Compound S1: To a solution of ethyl 2-ethylacetoacetate (5.00 g, 31.6 mmol) in MeOH (30 mL) and H_2O (30 mL), potassium hydroxide (5.32 g, 94.8 mmol) was added at 0 °C and stirred at room temperature for 2 h. Then, MeOH was removed under reduced pressure. The resulting mixture was cooled to 0 °C and acidified (ca. pH 2) with 1 n HCl aqueous solution, poured into water, extracted three times with EtOAc, dried over $MgSO_4$ and then concentrated *in vacuo* to provide carboxylic acid. The crude carboxylic acid and DMF (20 μL) was dissolved in CH_2Cl_2 (60 mL), 2.0 M oxalyl chloride solution in CH_2Cl_2 (19 mL, 38 mmol) was added at 0 °C and stirred for 2 h at room temperature. The reaction mixture was concentrated under reduced pressure to provide acid chloride **S1**. The crude mixture was used in next step without further purification.



Compound 18: To a solution of L-serine-OTBDPS (4.0 g, 11.6 mmol) in THF, NaH (310 mg, 90 wt. %, dry, 11.6 mmol) was added at 0 °C and stirred at room temperature for 2 h. The solvents were evaporated under low pressure to obtain sodium salt form of L-serine-OTBDPS. To stirred mixture of sodium salt of L-serine-OTBDPS and oven activated 4Å molecular sieves in dry acetone under nitrogen atmosphere was slowly added a solution of 2.0 M trimethylaluminium solution in hexane (5.8 mL, 11.6 mmol) at 0 °C. The mixture was slowly warmed to room temperature. After stirring for 16 h at the same temperature, acid chloride **S1** (17.4 mmol) was slowly added at 0 °C and stirred for 2 h at room temperature. The mixture was filtered through a pad of celite and silica, rinsed with EtOAc and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc = 5:1, *v*/*v*) to yield a 1:1.3 mixture of (2*R*)-**18** and (2*S*)-**18** (3.9 g, 68%) as a colorless oil. (2*R*)-**18** and (2*S*)-**18** were isolated from the mixture via recycling preparative HPLC (HPLC conditions: JAIGEL-ODS-AP-L (20 mm (i.d.) x 500 mm (l), 10 μm), H_2O/MeOH = 86:14, flow rate = 10 mL/min, λ = 225 nm).

(2*R*)-**18 :** R_f = 0.31 (hexane/EtOAc, 3:1); $[\alpha]^{20}_D$ +15.8 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, two rotamers in a 15:1 ratio) δ 7.66 – 7.54 (m, 4H), 7.48 – 7.31 (m, 6H), 4.51 (t, *J* = 2.2 Hz, 1H), 4.12 (dd, *J* = 11.2, 2.2 Hz, 1H), 3.84 (dd, *J* = 11.2, 2.2 Hz, 1H), 3.12 (dd, *J* = 8.0, 6.5 Hz, 1H), 2.10 (s, 3H), 2.02 – 1.87 (m, 1H), 1.92 (s, 3H), 1.85 – 1.75 (m, 1H), 1.78 (s, 3H), 1.02 (s, 9H), 0.74 (t, *J* = 7.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 204.7, 168.9, 166.1, 135.9 (2C), 135.6 (2 C), 132.3, 131.6, 130.3, 130.2, 128.1 (2C), 128.0 (2C), 99.0, 64.7, 62.3, 59.5, 26.9 (3C), 26.7, 26.2, 25.9, 22.1, 19.3, 12.1; IR (neat, cm^{-1}) υ_{max} 2962, 2933, 2860, 1794, 1656, 1366, 1262, 1105, 969, 821; HRMS (FAB): calcd. for $C_{28}H_{38}NO_5Si$ $[M+H]^+$ 496.2519, found 496.2517.

(2*S*)-**18 :** R_f = 0.31 (hexane/EtOAc, 3:1); $[\alpha]^{20}_D$ +27.4 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, two rotamers in a 8:1 ratio) δ = 7.59 (ddt, *J* = 16.3, 7.9, 1.4 Hz, 4H), 7.48 – 7.32 (m, 6H), 4.36 (t, *J* = 2.2 Hz, 1H), 4.11 (dd, *J* = 11.4, 1.8 Hz, 1H), 4.01 (dd, *J* = 11.3, 2.2 Hz, 2H), 3.05 (t, 7.2 H), 2.09 (s, 3H), 2.03 – 1.91 (m, 1H), 1.95 (s, 3H), 1.91 – 1.79 (m, 1H), 1.83 (s, 3H),1.03 (s, 9H), 0.87 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 203.8, 168.7, 167.6, 135.9 (2C), 135.6 (2C), 132.4, 131.8, 130.2 (2C), 128.0 (4C), 99.1, 64.8, 61.5, 60.1, 27.4, 26.9 (3C), 26.4, 26.0, 24.5, 19.3, 12.0; IR (neat, cm^{-1}) υ_{max} 2964, 2930, 2858, 1791, 1655, 1365, 1263, 1105, 969, 820; HRMS (FAB): calcd. for $C_{28}H_{38}NO_5Si$ $[M+H]^+$ 496.2519, found 496.2517.

[Determination of the enantiomeric excess of **18**]

The enantiomeric purities of (2*R*)-**18** and (2*S*)-**18** were analyzed via chiral HPLC. The chiral HPLC chromatograms of (2*R*)-**18** and (2*S*)-**18** were compared with those of *rac*-(2*R*)-**18** and *rac*-(2*S*)-**18**. Based on this comparison, the enantiomeric purity of **18** was determined to be 98%.

HPLC conditions: CHIRALCEL AD-H (250 × 4.6 mm, 5 μm), hexane/2-propanol = 97:3 (*v*/*v*), flow rate = 0.7 mL/min, λ = 225 nm. The retention times are shown in Figure S1.

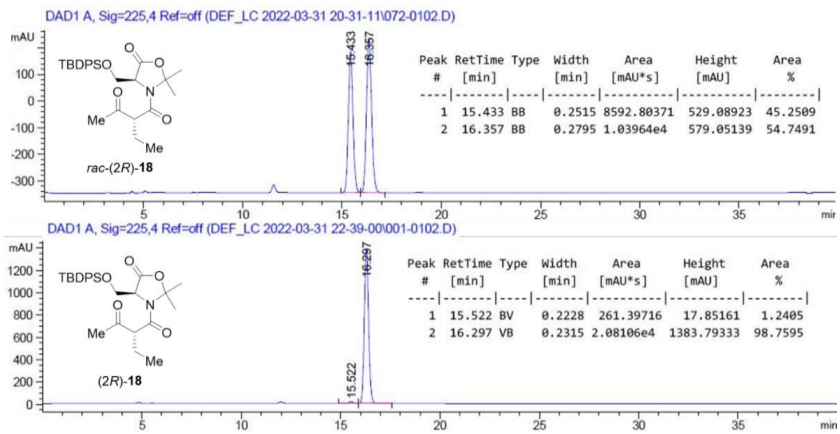


Figure S1. Chiral HPLC chromatograms of *rac*-(2*R*)-**18** and (2*R*)-**18**.

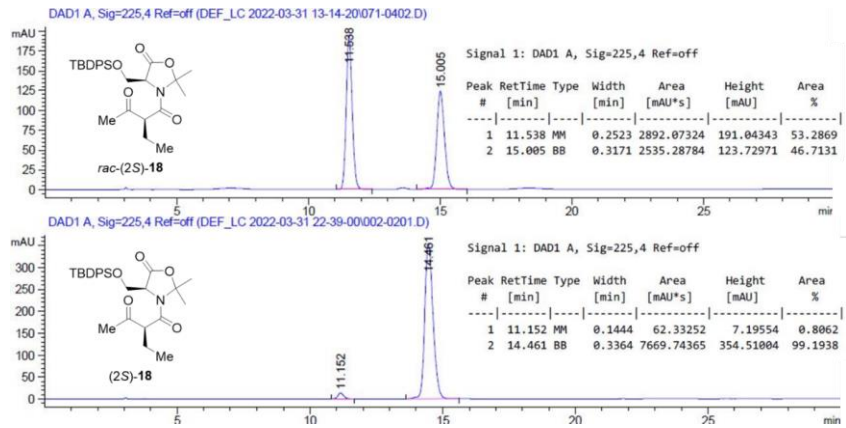
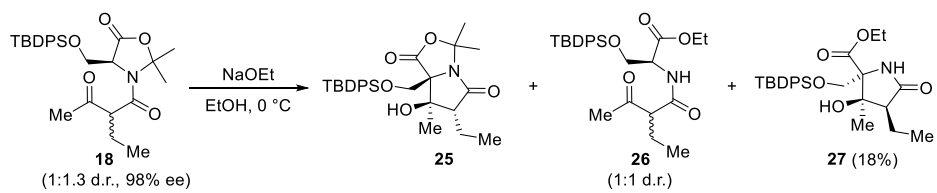


Figure S2. Chiral HPLC chromatograms of *rac*-(2*S*)-**18** and (2*S*)-**18**.



To a solution of **18** (50 mg, 0.10 mmol) in EtOH (2 mL), NaOEt (20 mg, 0.30 mmol) was added at 0 °C and stirred for 30 min at the same temperature. The reaction was quenched with saturated NH_4Cl aqueous solution and concentrated under reduced pressure to remove EtOH. The mixture was extracted with EtOAc three times and the combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (hexane/EtOAc = 5:1, *v*/*v*) to yield **25** (22 mg, 44%) as a colorless oil, **26** (16 mg, 33%, d.r. = 1:1) as a colorless oil, **27** (9 mg, 20%) as a colorless oil. The relative configuration of **25** and **27** were determined by NOESY experiments.

25 : R_f = 0.34 (hexane/EtOAc, 3:1); $[\alpha]^{20}_D$ – 48.5 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400

MHz, $CDCl_3$) δ = 7.65 – 7.55 (m, 4H), 7.53 – 7.32 (m, 6H), 4.22 (d, *J* = 11.4 Hz, 1H), 4.02 (d, *J* = 11.4 Hz, 1H), 2.96 (t, *J* = 7.1 Hz, 1H), 2.67 (s, 1H), 1.84 (s, 3H), 1.77 – 1.66 (m, 1H), 1.53 (s, 3H), 1.51 – 1.43 (m, 1H), 1.23 (s, 3H), 1.07 (t, *J* = 7.5 Hz, 3H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.2, 170.2, 135.9 (2C), 135.7 (2C), 132.1, 131.7, 130.4, 130.3, 128.17 (2C), 128.15 (2C), 96.7, 81.3, 74.6, 65.6, 55.6, 29.3, 27.0 (3C), 25.6, 19.3, 19.2, 17.8, 12.7; IR (neat, cm^{-1}) υ_{max} 3441, 2963, 2934. 2860, 1786, 1720, 1698, 1385, 1290, 1263, 1105, 822, 703; HRMS (FAB): calcd. for $C_{28}H_{38}NO_5Si$ $[M+H]^+$ 496.2519, found 496.28.

26 : R_f = 0.28 (hexane/EtOAc, 3:1); ^1H NMR (400 MHz, $CDCl_3$) δ = 7.68 – 7.50 (m, 4H), 7.44 – 7.32 (m, 6H), 7.05 – 6.95 (m, 1H), 4.63 (t, *J* = 2.9 Hz, 0.5 H), 4.61 (t, *J* = 2.9 Hz, 0.5H), 4.27 – 4.07 (m, 3H), 3.88 – 3.78 (m, 1H), 3.32 – 3.21 (m, 1H), 2.24 (s, 1.5H), 2.22 (s, 1.5H), 1.99 – 1.77 (m, 2H), 1.28 – 1.20 (m, 3H), 1.03 (s, 9H), 0.98 – 0.89 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 206.4, 170.2, 168.7, 135.6 (4C), (132.80, 132.78), 132.70, 130.10, 130.08, 128.0 (2C), 127.9 (2C), (64.3, 64.2), (62.9, 62.7), (61.8, 61.8), (54.3, 54.3), (29.6, 29.5), 26.8 (3C), (23.8, 23.6), 19.4, 14.3, (12.0, 11.9); IR (neat, cm^{-1}) υ_{max} 3332, 2961, 2933, 2859, 1743, 1722, 1665, 1515, 1428, 1359, 1197, 1104, 822, 736; HRMS (FAB): calcd. for $C_{27}H_{38}NO_5Si$ $[M+H]^+$ 484.2519, found 484.2527.

27 : R_f = 0.2 (hexane/EtOAc, 3:1); $[\alpha]^{20}_D$ – 67.4 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ = 8.74 (s, 1H), 7.65 (d, *J* = 7.0 Hz, 4H), 7.50 – 7.31 (m, 6H), 5.60

(s, 1H), 4.29 (dq, *J* = 11.0, 7.2 Hz, 1H), 4.13 (dd, *J* = 12.4, 8.3 Hz, 2H), .3.58 (d, *J* = 9.5Hz, 1H), 2.05 (t, *J* = 6.9 Hz, 1H), 1.78 (dq, *J* = 14.8, 7.4 Hz, 1H), 1.69 – 1.55 (m, 1H), 1.29 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.09 – 1.00 (m, 3H), 1.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.5, 171.4, 135.8 (4C), 132.9, 132.8, 130.0 (2C), 128.0 (2C), 127.9 (2C), 78.8, 76.0, 66.4, 62.1, 53.2, 26.7 (3C), 20.8, 19.3, 16.6, 14.3, 13.6; IR (neat, cm^{-1}) υ_{max} 3308, 2960, 2931, 2859, 1730, 1693, 1428, 1371, 1240, 1114, 823, 703; HRMS (FAB): calcd. for $C_{27}H_{38}NO_5Si$ $[M+H]^+$ 484.2519, found 484.2511.

[Determination of the enantiomeric excess of **25**]

The enantiomeric purity of **25** was analyzed via chiral HPLC. The chiral HPLC chromatogram of **25** was compared with that of *rac*-**25**. Based on this comparison, the enantiomeric purity of **25** was determined to be 96%.

HPLC conditions: CHIRALCEL AD-H (250 × 4.6 mm, 5 μm), hexane/2-propanol = 98:2 (*v*/*v*), flow rate = 1.0 mL/min, λ = 225 nm. The retention times are shown in Figure S3.

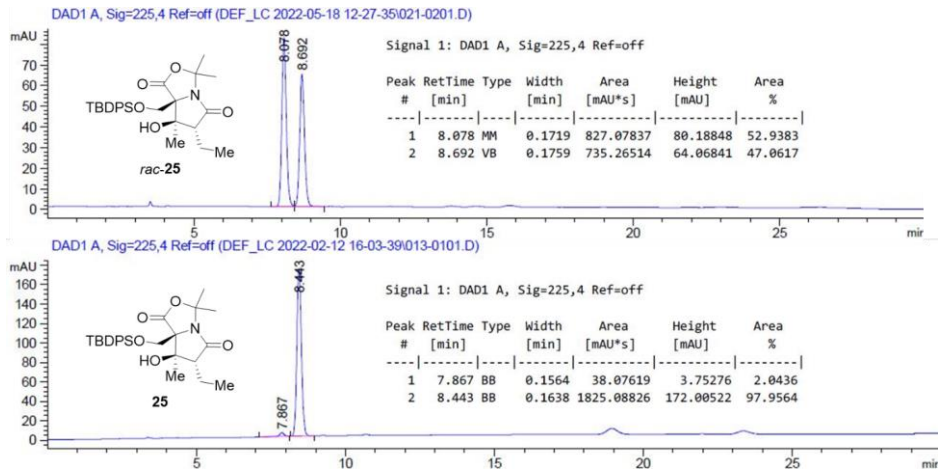


Figure S3. Chiral HPLC chromatograms of *rac*-**25** and **25**.

[Determination of the enantiomeric excess of **27**]

The enantiomeric purity of **27** was analyzed via chiral HPLC. The chiral HPLC chromatogram of **27** was compared with that of *rac*-**27**. Based on this comparison, the enantiomeric purity of **27** was determined to be 100%. However, the minor peak might be eclipsed by the major peak. Therefore, we also hydrolyzed **27** to obtain **28** and verify the ee value (see 'Procedure for the modification of **28** for determination of the enantiomeric excess of **28**' on page S19). The enantiomeric purity of **27** was determined to be 90%.

HPLC conditions: CHIRALCEL AD-H (250 × 4.6 mm, 5 μm), hexane/2-propanol = 93:7 (*v*/*v*), flow rate = 0.7 mL/min, λ = 225 nm. The retention times are shown in Figure S4.

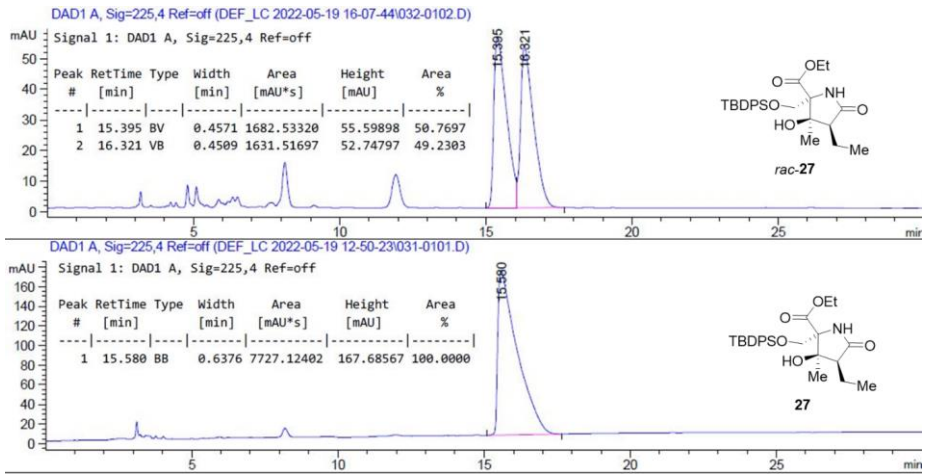
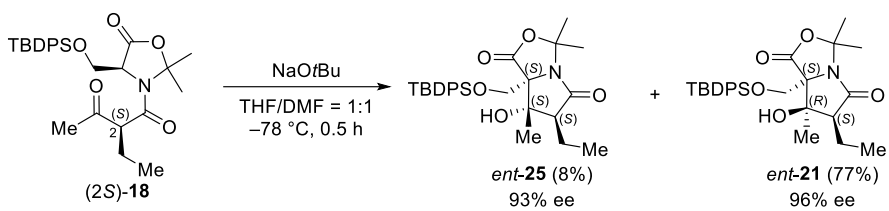


Figure S4. Chiral HPLC chromatograms of *rac*-**27** and **27**.



Compound *ent*-**21**: To a solution of (2*S*)-**18** (50 mg, 0.10 mmol) in THF (1 mL) and DMF (1 mL), sodium *tert*-butoxide (29 mg, 0.30 mmol) was added at –78 °C and stirred for 30 min at the same temperature. The reaction was quenched with 1 n HCl aqueous solution and warmed to room temperature. The mixture was extracted with EtOAc three times. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc = 5:1, *v*/*v*) to yield a 9.6:1 mixture of *ent*-**21** and *ent*-**25** (42 mg, 85%) as a colorless oil. *ent*-**21** and *ent*-**25** were isolated

from the mixture via flash chromatography on silica gel (CH_2Cl_2/EtOAc = 30:1, *v*/*v*). The relative configuration was determined by NOESY experiments.

ent-**21 :** R_f = 0.34 (hexane/EtOAc, 3:1); $[\alpha]^{20}_D$ – 63.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.69 – 7.57 (m, 4H), 7.48 – 7.32 (m, 6H), 3.95 (d, *J* = 11.1 Hz, 1H), 3.82 (d, *J* = 11.0 Hz, 1H), 2.72 (dd, *J* = 7.2, 5.7 Hz, 1H), 1.83 (s, 3H) 1.81 – 1.71 (m, 1H), 1.58 – 1.45 (m, 1H), 1.55 (s, 3H), 1.50 (s, 3H), 1.10 (t, *J* = 7.6 Hz, 3H), 1.04 (s, 9H).^{13}C NMR (100 MHz, $CDCl_3$) δ = 178.1, 170.1, 136.0 (2C), 135.7 (2C), 132.2, 131.7, 130.41, 130.36, 128.2 (2C), 128.1 (2C), 98.1, 80.8, 77.4, 65.0, 55.7, 29.5, 27.0 (3C), 24.9, 20.6, 19.3, 16.5, 13.5; IR (neat, cm^{-1}) υ_{max} 3442, 2961, 2933, 2860, 1782, 1703, 1462, 1428, 1385, 1270, 1112, 1071, 1030, 942, 822; HRMS (FAB): calcd. for $C_{28}H_{38}NO_5Si$ $[M+H]^+$ 496.2519, found 496.2531.

[Determination of the enantiomeric excess of *ent*-**21**]

The enantiomeric purity of *ent*-**21** was analyzed via chiral HPLC. The chiral HPLC chromatogram of *ent*-**21** was compared with that of *rac*-**21**. Based on this comparison, the enantiomeric purity of *ent*-**21** was determined to be 96%.

HPLC conditions: CHIRALCEL AD-H (250 × 4.6 mm, 5 μm), hexane/2-propanol = 98:2 (*v*/*v*), flow rate = 1.0 mL/min, λ = 225 nm. The retention times are shown in Figure S5.

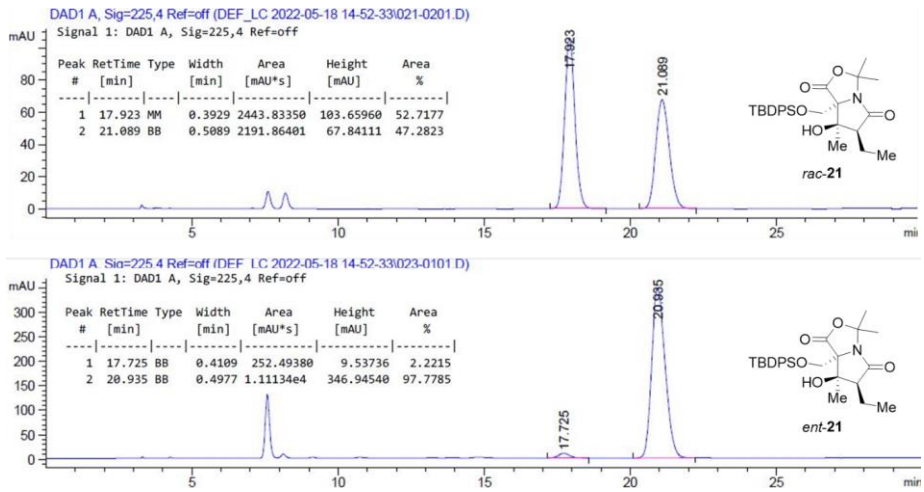
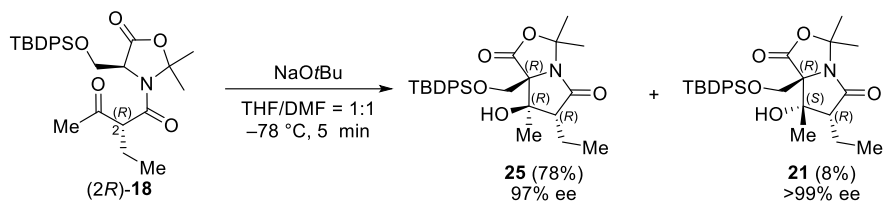


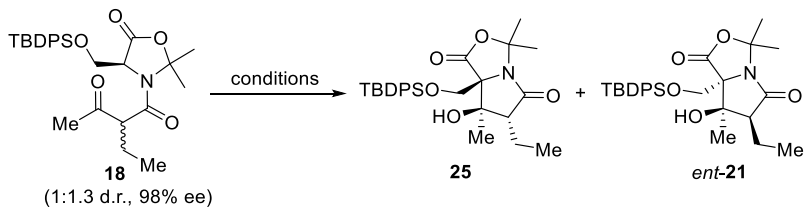
Figure S5. Chiral HPLC chromatograms of *rac*-**21** and *ent*-**21**.



To a solution of (2*R*)-**18** (50 mg, 0.10 mmol) in THF (1 mL) and DMF (1 mL), sodium *tert*-butoxide (29 mg, 0.30 mmol) was added at –78 °C and stirred for 30 min at the same temperature. The reaction was quenched with 1 n HCl aqueous solution and warmed to room temperature. The mixture was extracted with EtOAc three times. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc = 5:1, *v*/*v*) to yield a 9.8:1 mixture of **25** and **21** (43 mg, 86%) as a colorless oil. **25** and **21** were isolated from the mixture via flash

chromatography on silica gel (CH_2Cl_2/EtOAc = 30:1, *v*/*v*).

Table S1. Aldol cyclization of **18**[a]



18 (1:1.3 d.r., 98% ee) **25** *ent*-**21**

entry	reagent (equiv)	solvent (0.05 M)	tempera ture	time	yield of **23**[b] (ee %)[c]	yield of **24**[b] (ee %)[c]
1	NaO*i*Pr (3)	*i*PrOH	–30 °C	12 h	41% (77)	50% (77)
2	NaO*t*Bu (3)	THF/DMF/*t*BuOH = 10:10:1	–78 °C	0.5 h	40% (90)	48% (91)
3	KHMDS (3)	THF/DMF = 1:1	–78 °C	0.5 h	39% (90)	47% (91)
4[d]	NaO*t*Bu (3)	THF/DMF = 1:1	–78 °C	5 min	78% (96)	8% (-99)
5[d]	NaO*t*Bu (3)	THF/DMF/*t*BuOH = 10:10:1	–78 °C	5 min	77% (96)	9% (-96)
6[e]	NaO*t*Bu (3)	THF/DMF = 1:1	–78 °C	0.5 h	8% (-93)	77% (96)
7[e]	NaO*t*Bu (3)	THF/DMF/*t*BuOH = 10:10:1	–78 °C	0.5 h	8% (-92)	75% (96)

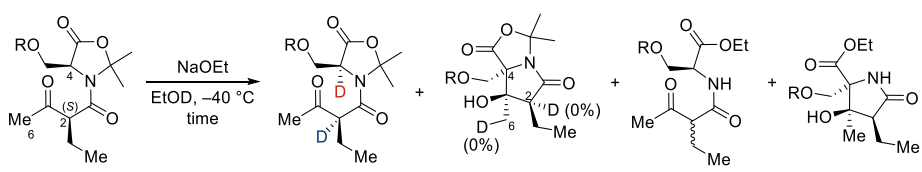
[a]Reactions were run with 0.1 mmol of **18** (1:1.3 d.r.). [b]Isolated yield. [c]ee value was determined by chiral HPLC. [d]Reactions were rim with 0.1 mmol of (2*R*)-**18**. [e]Reactions were performed with 0.1 mmol of (2*S*)-**18**.

General procedure for Table S1: To a solution of **18** (50 mg, 0.10 mmol) in solvent (0.05M), base (0.3 mmol) was added at above temperature and stirred for

time at the same temperature. The reaction was quenched with 1 n HCl aqueous solution and warmed to room temperature. The mixture was extracted with EtOAc three times. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc = 5:1, *v*/*v*) to yield **25** and *ent*-**21** as a colorless oil. **25** and *ent*-**21** were isolated from the mixture via flash chromatography on silica gel (CH_2Cl_2/EtOAc = 30:1, *v*/*v*).

Table S2. H/D exchange of (2*S*)-**18** with NaOEt/EtOD.[a]

H/D exchange rate of (2*S*)-**18**



entry	time (min)	% D at C-2 of (2*S*)-**18**[b]	% D at C-4 of (2*S*)-**18**[b]	yield[c] (%)			
				d-(2S)-**18**	*ent*-**21**	**26**	**27**
1	5	1	34	50	15	30	trace
2	10	2	45	14	20	45	7
3	20	-	-	0	10	57	12

[a]Reactions were run with 0.1 mmol of (2*S*)-**18** and NaOEt (20 mg, 0.3 mmol) in EtOD (2 mL).

[b]Determined by ^{1}H NMR. [c]Isolated yield.

Note: We conducted the intramolecular aldol reaction of (2*S*)-**18** in EtOD and analyzed the remaining deuterated (2*S*)-**18** in the incomplete reaction mixture (NaOEt/EtOD, –40 °C, quenched with saturated NH_4Cl(s) in D_2O solutions after 5

min, 10 min and 20 min) by ^{1}H NMR. The hydrogen at the α-carbon (C-4) of (2*S*)-**18** was gradually exchanged with deuterium over the course of the reaction. However, the hydrogen at C-2 of (2*S*)-**18** was hardly deuterated. This result showed a much less facile H/D exchange for the H-2 proton than the H-4 proton. The obtained aldol product *ent*-**21** showed no detectable deuterium incorporation at C-2 and C-6. The above result also suggested that C-4 of (2*S*, 4*S*)-**18** (starting material) was not racemized under reaction conditions since (2*S*, 4*R*)-**18** (enantiomer form of (2*R*, 4*S*)-**18**) was not detectable. To understand the rare racemization at the C-4 well, we performed an additional experiment.

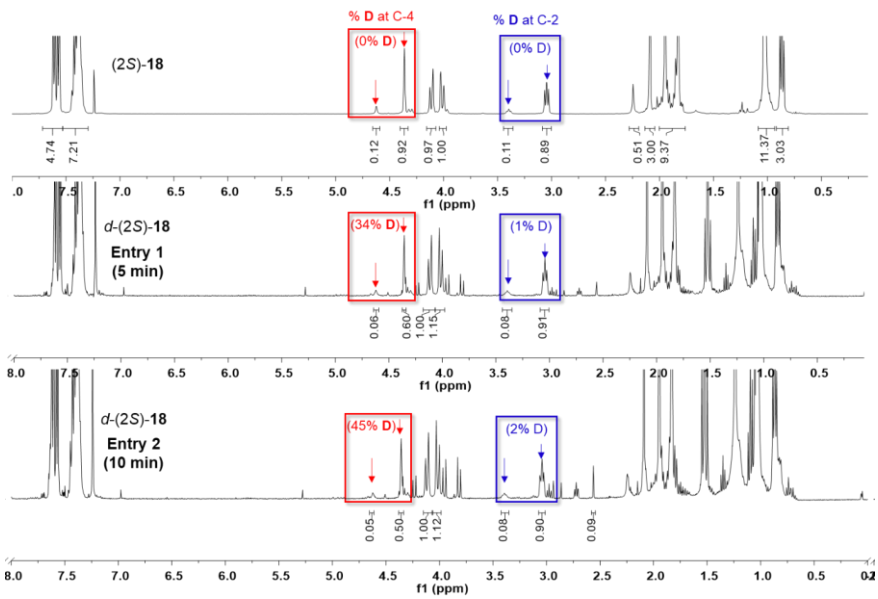
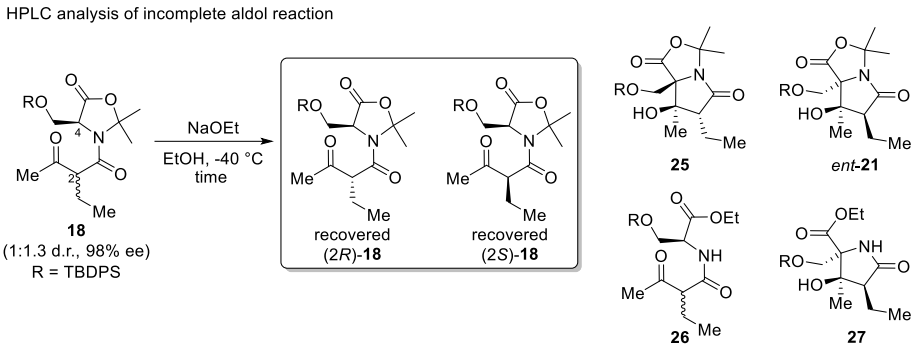


Figure S6. ^{1}H NMR spectra of (2*S*)-**18** and *d*-(2*S*)-**18** after the corresponding reaction times.

Table S3. Chiral HPLC analysis of **18** with NaOEt/EtOH.[a]



time	recovered (2*R*)-**18**		recovered (2*S*)-**18**		**25**[b]	*ent*-**21**[b]	**26**[b]	**27**[b]
	yield[b]	ee[c] (%)	yield[b]	ee[c] (%)				
3 min	10%	98	58%	98	35%	18%	24%	trace
10 min	0	-	15%	98	39%	16%	32%	8%
20 min	0	-	trace	-	40%	5%	35%	17%

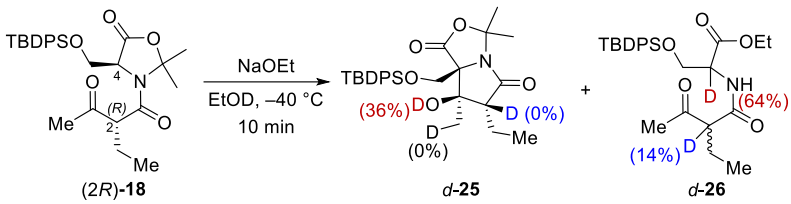
[a]Reactions were run with 0.2 mmol of **25** and NaOEt (40 mg, 0.6 mmol) in EtOH (4 mL). [b]Isolated yield. [c]Determined by chiral HPLC.

Procedure for Table S3: To a solution of **18** (100 mg, 0.2 mmol) in EtOH (4 mL), NaOEt (40 mg, 0.6 mmol) was added at –40 °C and stirred. A portion of mixture (1 mL) was quenched with saturated NH_4Cl aqueous solution at 3 min, 10 min and 20 min. Each mixture was concentrated under reduced pressure to remove EtOH. The mixture was extracted with EtOAc three times and the combined organic layer was dried over MgSO4 and concentrated *in vacuo.* The residue was purified by flash chromatography on silica gel (hexane/EtOAc = 5:1, *v*/*v*) to give recovered **18**, **25**, *ent*-**21**, **26** and **27**. (2*R*)-**18** and (2*S*)-**18** were isolated via Recycling preparative

HPLC (HPLC conditions: JAIGEL-ODS-AP-L (20 mm (i.d.) x 500 mm (l), 10 μm), water/MeOH = 86:14, flow rate = 10 mL/min, λ = 225 nm). The ee value of **18** was determined by 'Determination of the enantiomeric excess of **18** (Figure 1)'. The ee value of recovered (2*R*)-**18** and (2*S*)-**18** were not changed.

Note: Considering that H/D exchange occurred at C-4 of (2*S*)-**18**, as shown in Table S1, this suggested that even though deprotonation/reprotonation occurred at C-4 during the aldol reaction, the C-4 of **18** was not racemized. (if C-4 of (2*S*)-**18** or (2*R*)-**18** had been racemized, the ee value for recovered (2*S*)-**18** or (2*R*)-**18** should have been decreased.)

H/D exchange of (2*R*)-**18** with NaOEt/EtOD.



To a solution of (2*R*)-**18** (100 mg, 0.20 mmol) in EtOH (4 mL), NaOEt (41mg, 0.60 mmol) was added at –40 °C and stirred for 10 min at the same temperature. The mixture was quenched with saturated NH_4Cl aqueous solution and concentrated under reduced pressure to remove EtOH. The mixture was extracted with EtOAc three times and the combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (hexane/EtOAc = 5:1, *v*/*v*) to give *d*-**25** (42 mg, 42%), *d*-**26** (45 mg, 46%). The obtained aldol product *d*-**25** showed no detectable deuterium incorporation at C-2.

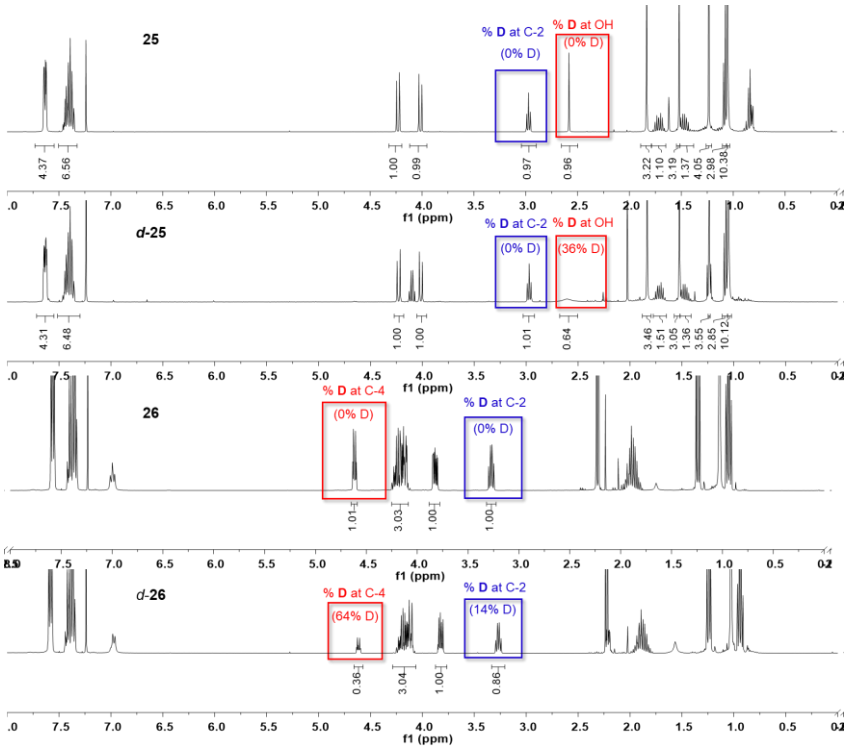
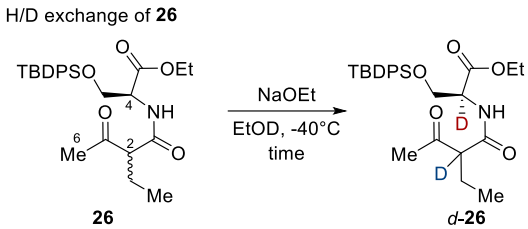


Figure S7. ^{1}H NMR spectra of **25**, *d*-**25, 26** and *d*-**26** after the reaction in EtOD (400 MHz, $CDCl_3$).

Table S4. H/D exchange of **26** with NaOEt/EtOD.[a]



entry	time	% D at C-2 of *d*-**26**[b]	% D at C-4 of *d*-**26**[b]	yield[c] [%]
1	5 min	32	0	100
2	10 min	54	0	100
3	20 min	62	0	100

[a]Reactions were run with 0.1 mmol of **26** and NaOEt (20 mg, 0.3 mmol) in EtOD (2 mL). [b]Determined by ^{1}H NMR. [c]Isolated yield.

Note: We conducted the H/D exchange reaction of **26** with NaOEt in EtOD at –40 °C. The reaction mixture was quenched with saturated NH_4Cl(s) in D_2O solutions after 5 min, 10 min and 20 min. The obtained *d*-**26** was analyzed by ^{1}H NMR. The hydrogen at C-2 of **26** was gradually exchanged with deuterium over the course of the reaction. However, the hydrogen at C-4 of **26** was not deuterated. This result suggested that the epimerization at C-2 of **26** was more facile than C-4 of **26**, unlike **18**. Even after 3 h, the deuterium content at C-2 of **26** was 60%. Partial deuterium/hydrogen exchange occurring during the work-up appears to be responsible for the incomplete deuteration at these positions. When the deuteration exchange reaction was conducted at room temperature, the hydrogens at C-2 and C-6 of **26** were deuterated; however, hydrogen at C-4 was not deuterated. This

result indicated that **26** rarely underwent aldol reaction under NaOEt/EtOH conditions.

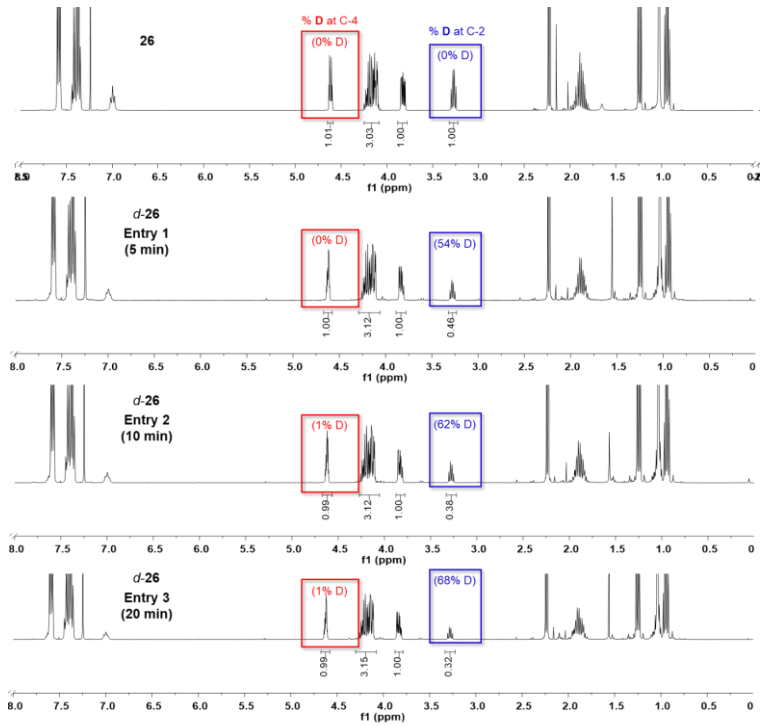
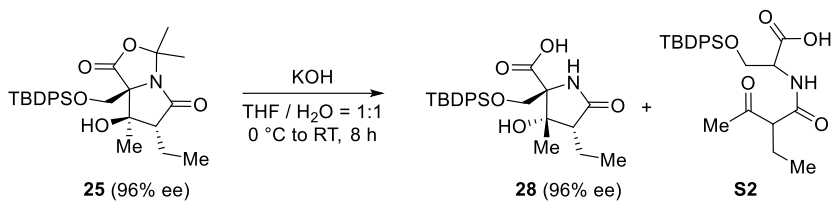


Figure S8. ^{1}H NMR spectra of **26** and *d*-**26** after the corresponding reaction times.

Procedure for the hydrolysis reaction of 25 and *ent*-21



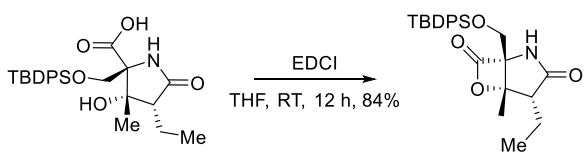
To a solution of **25** (50 mg, 0.10 mmol) in THF (1 mL) and H_2O (1 mL), potassium hydroxide (56 mg, 1.0 mmol) was added at 0 °C. The reaction was acidified (ca. pH 2) with 1 n HCl aqueous solution and warmed to room temperature. The mixture was extracted with EtOAc three times. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH/acetic acid = 20:1:0.2, *v*/*v*/*v*) to give **28** (41 mg, 91%) as a white solid and **S2** (3.6 mg, 8%, 1:1.1 d.r.) as a colorless oil.

28 : mp 184–188 °C; R_f = 0.3 (CH_2Cl_2/MeOH/acetic acid = 10:1:0.1, *v*/*v*/*v*); $[\alpha]^{20}_D$ +13.1 (*c* 0.5, MeOH); ^{1}H NMR (400 MHz, MeOD) 7.76 – 7.56 (m, 4H), 7.56 – 7.35 (m, 6H), 3.95 (d, *J* = 10.4 Hz, 1H), 3.85 (d, *J* = 10.4 Hz, 1H), 2.36 (t, *J* = 6.6 Hz, 1H), 1.77 – 1.66 (m, 1H), 1.66 – 1.54 (m, 1H), 1.50 (s, 3H), 1.10 (t, *J* = 7.6 Hz, 3H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 179.8, 172.6, 136.9 (2C), 136.7 (2C), 133.9, 133.6, 131.2, 131.1, 129.0 (2C), 128.9 (2C), 80.0, 75.6, 67.6, 54.9, 27.3 (3C), 21.1, 20.0, 17.9, 14.0; IR (neat, cm^{-1}) υ_{max} 3300, 2930, 2857, 1607, 1589, 1428, 1376, 1113, 825, 702; HRMS (FAB): calcd. for $C_{25}H_{34}NO_5Si$ $[M+H]^+$

456.2206, found 456.2207.

S2 (1:1.1 d.r.) **:** R_f = 0.3 (CH_2Cl_2/MeOH/acetic acid = 10:1:0.1, *v*/*v*/*v*); ^{1}H NMR (400 MHz, MeOD) δ = 7.73 – 7.60 (m, 4H), 7.49 – 7.36 (m, 6H), 4.66 – 4.52 (m, 1H), 4.14 – 4.05 (m, 1H), 3.99 – 3.89 (m, 1H), 2.23 (s, 3H, minor), 2.18 (s, 3H, major), 2.20 (s, 1H, minor), 2.01 (s, 1H, major), 1.94 – 1.74 (m, 2H), 1.05 (s, 9H), 0.96 – 0.89 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = (206.6, 206.4), 172.8, 171.8, 136.74 (2C), 136.69 (2C), 134.2, 134.0, 131.1 (2C), 128.90 (2C), 128.87 (2C), 65.0, (63.0, 62.9), 56.1, 29.1, 27.3 (3C), (23.3, 22.9), 20.1, (12.1, 12.0); IR (neat, cm^{-1}) υ_{max} 2960, 2930, 1735, 1654, 1522, 1427, 1202, 1112; HRMS (FAB): calcd. for $C_{25}H_{34}NO_5Si$ $[M+H]^+$ 456.2206, found 456.2204.

Procedure for the modification of 28 for determination of the enantiomeric excess of 28



28 **30**

Compound 30: To a solution of **28** (20 mg, 0.044 mmol) in THF (1 mL), EDC·HCl (17 mg, 0.089 mmol) was added at room temperature and stirred for 12 h. The mixture was extracted with EtOAc three times. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc = 4:1, *v*/*v*) to give

30 (16 mg, 82%) as a colorless oil.

30 : R_f = 0.3 (hexane/EtOAc = 4:1, *v*/*v*); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.70 – 7.57 (m, 4H), 7.53 – 7.33 (m, 6H), 5.97 (brs, 1H), 3.95 (d, *J* = 11.7 Hz, 1H), 3.84 (d, *J* = 11.9 Hz, 1H), 2.32 (dd, *J* = 9.6, 5.4 Hz, 1H), 1.98 – 1.86 (m, 1H), 1.82 – 1.70 (m, 1H), 1.78 (s, 3H), 1.14 (t, *J* = 7.5 Hz, 3H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.1, 168.0, 135.8 (2C), 135.7 (2C), 132.0, 131.9, 130.5, 130.4, 128.3 (2C), 128.2 (2C), 85.3, 76.0, 58.9, 50.5, 26.9 (3C), 20.5, 19.3, 19.1, 12.8; HRMS (FAB): calcd. for $C_{25}H_{32}NO_4Si$ $[M+H]^+$ 438.2101, found 438.2088.

[Determination of the enantiomeric excess of **30**]

The enantiomeric purity of I was analyzed by chiral HPLC. The chiral HPLC chromatogram of **30** was compared with that of *rac*-**30**. Based on this comparison, the enantiomeric purity of **30** was determined to be 96%.

HPLC conditions: CHIRALCEL AD-H (250 × 4.6 mm, 5 μm), hexane/2-propanol = 97:3 (*v*/*v*), flow rate = 0.7 mL/min, λ = 225 nm. The retention times are shown in Figure S9.

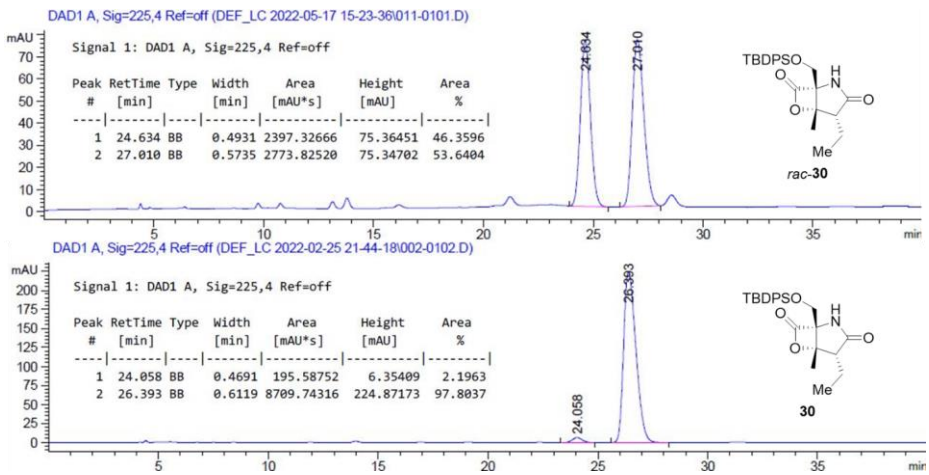
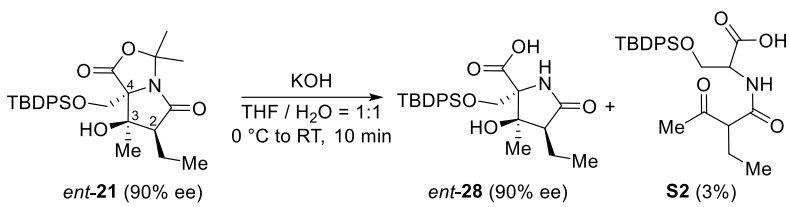
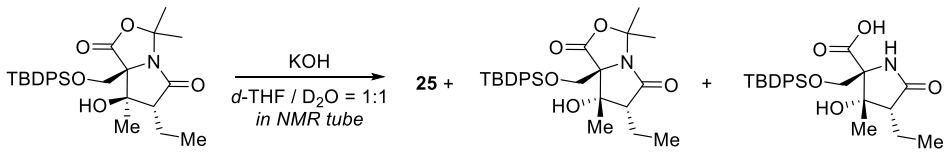


Figure S9. Chiral HPLC chromatograms of *rac*-**30** and **30**.



To a solution of *ent*-**21** (50 mg, 0.10 mmol) in THF (1 mL) and H_2O (1 mL), potassium hydroxide (56 mg, 1.0 mmol) was added at 0 °C. The mixture was slowly warm up to room temperature and stirred for 8 h. The reaction was acidified (ca. pH 2) with 1 n HCl aqueous solution and warmed to room temperature. The mixture was extracted with EtOAc three times. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH/acetic acid = 20:1:0.2, *v*/*v*/*v*) to give *ent*-**28** (44 mg, 96%) as a white solid and **S2** (1.3 mg, 3%) as a colorless oil.

Table S5. NMR study on the hydrolysis of **25.**[a] (Figure 4b in main text)



25 **21** **28**

entry	time	ratio[b] of **25**:**21**:**28**
1	10 min	15:1:2
2	30 min	15:1:23
3	1 h	16:1:40
4	2 h	16:1:93
5	3 h	1:0:39

[a]Reactions were run with 0.02 mmol of **25** and KOH (11.2 mg, 0.2 mmol) in *d*-THF (0.4 mL) and D_2O (0.4 mL). [b]Determined by ^1H NMR.

In an NMR tube, **25** (10mg, 0.02 mmol) was dissolved in *d*-THF (0.4 mL) and treated with potassium hydroxide (11 mg, 0.20 mmol) in D_2O (0.4 mL). ^1H NMR of the sample was checked at 10 min, 30 min, 1 h, 2 h and 3 h. The result shows the ratio of **25** and **21** was about 15:1 during the reaction.

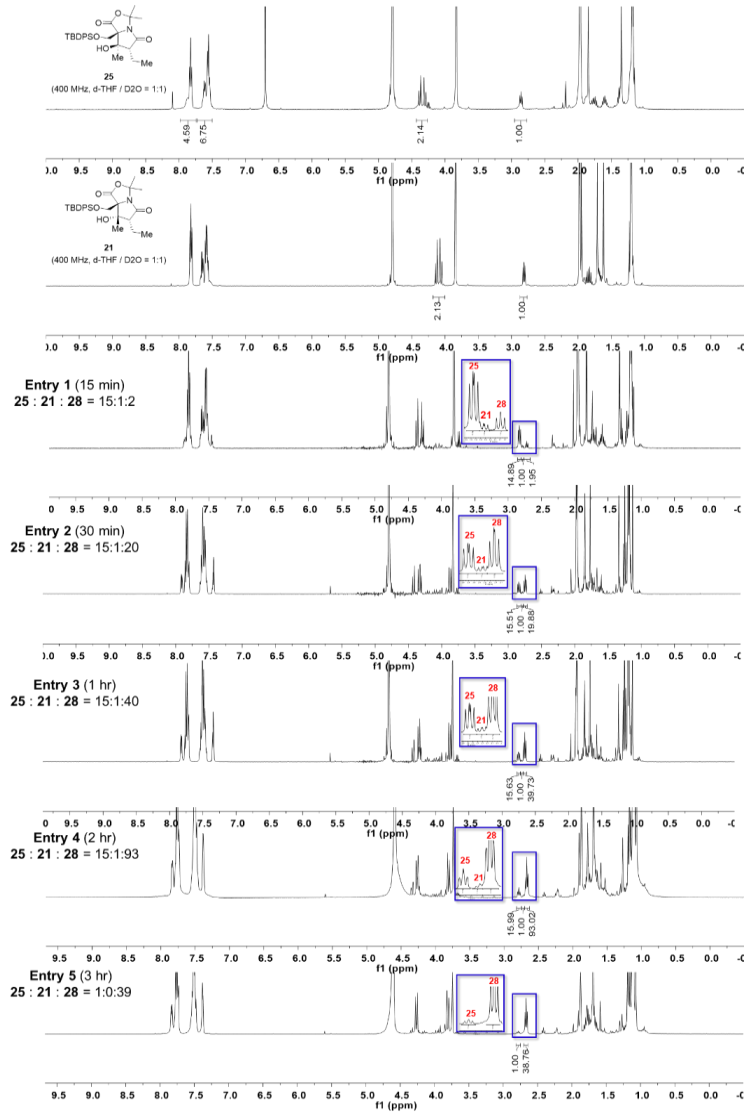
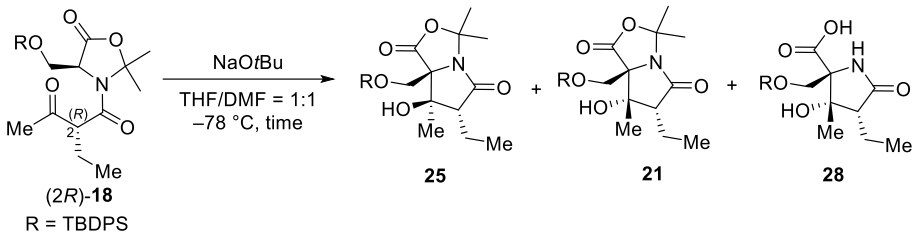


Figure S10. ^{1}H NMR spectra of reaction mixture at corresponding reaction times (400 MHz, D_2O, *d*-THF).

Table S6. Time-course monitoring of aldol reaction of (2*R*)-**18**.[a] (Figure 4c in main text)

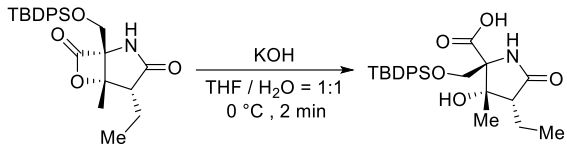


entry	time	yield of **25**[b]	yield of **21**[b]	yield of **28**[b]
1	5 min	78	8	-
2	30 min	76	8	4%
3	3 h	73	7	8%

[a]Reactions were run with 0.1 mmol of (2*R*)-**18** and NaO*t*Bu (20 mg, 0.3 mmol) in THF/DMF = 1:1 (2 mL). [b]Isolated yield.

To a solution of (2*R*)-**18** (50 mg, 0.10 mmol) in THF (1 mL) and DMF (1 mL), sodium *tert*-butoxide (29 mg, 0.30 mmol) was added at –78 °C and stirred for certain time (5 min, 30 min, 3 h) at the same temperature. The reaction was acidified (ca. pH 2) with 1 n HCl aqueous solution and warmed to room temperature. The mixture was extracted with EtOAc three times. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc = 5:1, *v*/*v* to CH_2Cl_2/MeOH/acetic acid = 20:1:0.2, *v*/*v*/*v*) to give mixture of **25** and **21** as a colorless oil and **28** as a white solid. The mixture of **25** and **21** were isolated from the mixture via flash chromatography on silica gel (CH_2Cl_2/EtOAc = 20:1, *v*/*v*).

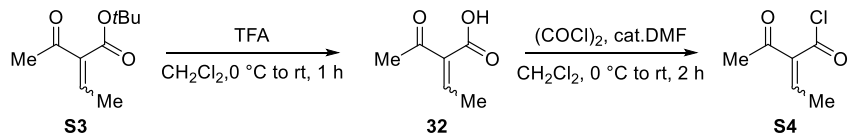
Procedure for the hydrolysis reaction of 30



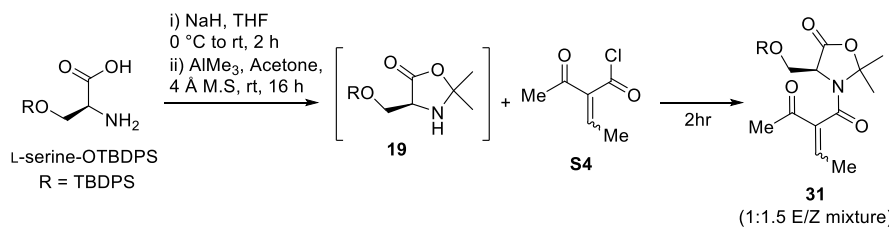
30 **28**

To a solution of **30** (30 mg, 0.07 mmol) in THF (0.7 mL) and H_2O (0.7 mL), potassium hydroxide (39 mg, 0.70 mmol) was added at 0 ℃ and stirred for 2 min at the same temperature. The reaction was acidified (ca. pH 2) with 1 n HCl aqueous solution at 0 °C and extracted with EtOAc three times. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH/acetic acid = 20:1:0.2, *v*/*v*/*v*) to give **28** (30 mg, 94%) as a white solid.

IV-2-2. Total synthesis of salinosporamide B (2)



Compound S4: To a solution of E/Z mixture (~1:1) of **S3**[1] (4.0 g, 22 mmol) in CH_2Cl_2 (30 mL), TFA (10 mL) was added at 0 °C slowly and stirred at room temperature for 1 h. TFA was removed by co-evaporation with toluene in vacuo to provide carboxylic acid. The crude carboxylic acid and DMF (20 μL) was dissolved in CH_2Cl_2 (44 mL), oxalyl chloride in CH_2Cl_2 (13 mL, 26 mmol) was added at 0 °C and stirred for 2 h at room temperature. The reaction mixture was concentrated under reduced pressure to provide acid chloride **S4**. The crude mixture was used in next step without further purification.



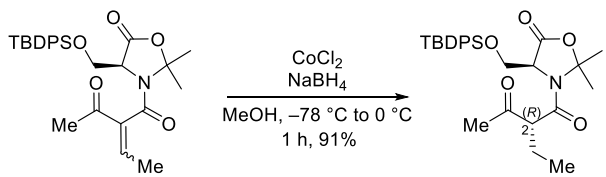
Compound 31: To a solution of l-serine-OTBDPS (4.0 g, 11.6 mmol) in THF, NaH (310 mg, 90 wt. %, dry, 11.6 mmol) was added at 0 °C and stirred at room temperature for 2 h. The solvents were evaporated under low pressure to obtain sodium salt form of l-serine-OTBDPS. To stirred mixture of sodium salt of l-serine-OTBDPS and oven activated 4Å molecular sieves in dry acetone under

nitrogen atmosphere was slowly added a solution of trimethylaluminium in hexane (5.8 mL, 11.6 mmol) at 0 °C. The mixture is slowly warmed to room temperature. After stirring for 16 h at the same temperature, acid chloride **S4** was slowly added at 0 °C and stirred for 2 h at room temperature. The mixture was filtered through a pad of celite and silica, rinsed with EtOAc and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to (hexane/EtOAc = 3:1, *v*/*v* to hexane/EtOAc = 1:1, *v*/*v*) to yield a 1:1.5 E/Z mixture of **31** (3.6 g, 64%) as yellowish oil. The minor form of **31** was slowly transformed to major form of **31** or decomposed.

31 (major) **:** R_f = 0.38 (hexane/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.63 – 7.55 (m, 4H), 7.45 – 7.33 (m, 6H), 6.66 (q, *J* = 7.1 Hz, 1H), 4.03 (t, *J* = 2.1 Hz, 1H), 3.98 (dd, *J* = 11.0, 2.0 Hz, 1H), 3.50 (dd, *J* = 11.0, 2.2 Hz, 1H), 2.14 (s, 3H), 2.00 (s, 3H), 1.92 (s, 3H), 1.70 – 1.62 (m, 3H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 195.2, 169.2, 164.7, 141.3, 136.1 (2C), 135.9 (2C), 135.6, 132.6, 131.7, 130.2 (2C), 127.9 (4C), 99.0, 63.6, 59.8, 26.9 (5C), 26.3, 25.9, 19.2; IR (neat, cm^{-1}) υ_{max} 2932, 2858, 1791, 1650, 1589, 1392, 1369, 1293, 1260, 1105, 1046, 968, 940, 885; HRMS (FAB): calcd. for $C_{28}H_{36}NO_5Si$ $[M+H]^+$ 494.2363, found 494.2382.

31 (minor) **:** R_f = 0.5 (hexane/EtOAc, 1:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.57 (dt, *J* = 8.1, 1.5 Hz, 4H), 7.46 – 7.34 (m, 6H), 6.11 (q, *J* = 7.3 Hz, 1H), 4.21 – 4.11 (m, 1H), 4.02 (d, *J* = 11.0 Hz, 1H), 3.77 – 3.69 (m, 1H), 2.19 (s, 3H), 1.96 (s, 3H),

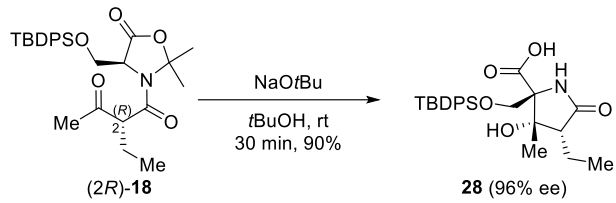
1.84 (s, 3H), 1.82 – 1.77 (m, 3H), 1.02 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 196.7, 169.1, 164.7, 141.7, 136.1 (2C), 135.9 (2C), 135.7, 132.6, 131.7, 130.3, 130.2 128.02 (2C), 127.95 (2C), 99.0, 63.6, 60.1, 30.5, 26.93 (2C), 26.87 (3C), 25.9, 19.2; IR (neat, cm^{-1}) υ_{max} 2934, 2859, 1793, 1696, 1654, 1395, 1368, 1105, 1045, 966, 938, 884; HRMS (FAB): calcd. for $C_{28}H_{36}NO_5Si$ $[M+H]^+$ 494.2363, found 494.2375.



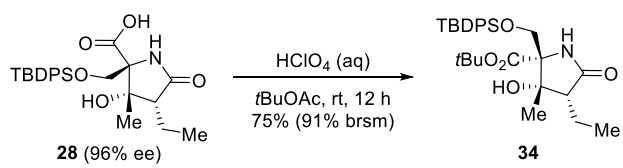
31
(1:1.5 E/Z mixture)

(2*R*)-**18**
d.r. = 12:1

Compound (2*R*)-**18**: To a solution of **31** mixture (3.0 g, 6.1 mmol) in MeOH (122 ml), $CoCl_2$-$6H_2O$ (5.8 g, 24.4 mmol) and $NaBH_4$ (1.1 g, 30 mmol) was added at –78 °C. The mixture was slowly warm up to 0 °C and stirred for 1 h. The reaction mixture was concentrated under reduced pressure to remove MeOH. The mixture was filtered through a pad of celite and silica, rinsed with EtOAc and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc = 5:1, *v*/*v*) to yield a 12:1 mixture of (2*R*)-**18** and (2*S*)-**18** (2.7 g, 91%) as a colorless oil. (2*R*)-**18** and (2*S*)-**18** were isolated from the mixture via recycling preparative HPLC (HPLC conditions: JAIGEL-ODS-AP-L (20 mm (i.d.) x 500 mm (l), 10 μm), water/MeOH = 86:14, flow rate = 10 mL/min, λ = 225 nm).



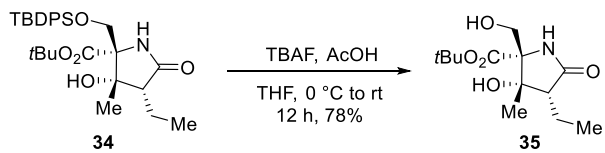
Compound 28: To a stirred solution of (2*R*)-**18** (2.5 g, 5.0 mmol) in *t*BuOH (100 mL), Sodium *tert*-butoxide (2.4 g, 25 mmol) was added at room temperature. The mixture was stirred at room temperature for 30 min and quenched with 1 n HCl aqueous solution and extracted with EtOAc three times. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH/acetic acid = 20:1:0.2, *v*/*v*/*v*) to give **28** (2.1 g, 90%) as a white solid. The enantiomeric excess of **28** was determined to be 96%.



Compound 34: To a solution of **28** (2.0 g, 4.4 mmol) in *tert*-Butyl acetate (44 mL), aqueous 50% $HClO_4$ (880 μL) was added at room temperature. The mixture was stirred at room temperature for 16 h and quenched with saturated $NaHCO_3$ aqueous solution at 0 °C. The mixture was extracted with EtOAc three times, and the combined organic fraction was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel

(hexane/EtOAc = 4:1, *v*/*v*) to yield **34** (1.7 g, 75%) as a colorless oil, and **28** (320 mg, 16%) was recovered.

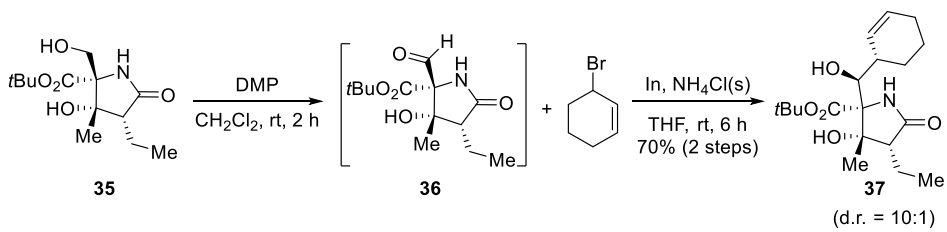
34 : R_f = 0.31 ((hexane/EtOAc = 4:1, *v*/*v*); $[\alpha]^{20}_{D}$ – 44.4 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 8.57 (s, 1H), 7.81 – 7.57 (m, 4H), 7.51 – 7.31 (m, 6H), 4.13 (d, *J* = 9.3 Hz, 1H), 3.49 (d, *J* = 9.3 Hz, 1H), 1.98 (t, *J* = 6.6 Hz, 1H), 1.87 – 1.70 (m, 1H), 1.65 – 1.54 (m, 1H), 1.44 (s, 9H), 1.25 (s, 3H), 1.05 (t, *J* = 7.5Hz, 3H) 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.5, 170.1, 135.8 (4C), 133.1, 132.7, 130.0, 129.9, 128.0 (2C), 127.9 (2C), 82.9, 78.8, 75.9, 66.6, 53.2, 28.0 (3C), 26.9 (3C), 20.8, 19.3, 16.7, 13.5; IR (neat, cm^{-1}) υ_{max} 3302, 2941, 2897, 1720, 1686, 1366, 1159, 1112, 1076; HRMS (FAB): calcd. for $C_{29}H_{42}NO_5Si$ $[M+H]^+$ 512.2832, found 512.2829.



Compound 35: To a solution of **34** (1.0 g, 2.0 mmol) in THF (9.8 mL), acetic acid (452 μL, 7.90 mmol) and 1.0M TBAF solution in THF (3.9 mL, 3.9 mmol) was added at 0 °C. The mixture was warmed up to room temperature and stirred for 12 h and quenched with saturated NH_4Cl aqueous solution. The mixture was extracted with EtOAc three times, and the combined organic fraction was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc = 1:2, *v*/*v*) to yield **35** (426 mg,

78%) as a white solid.

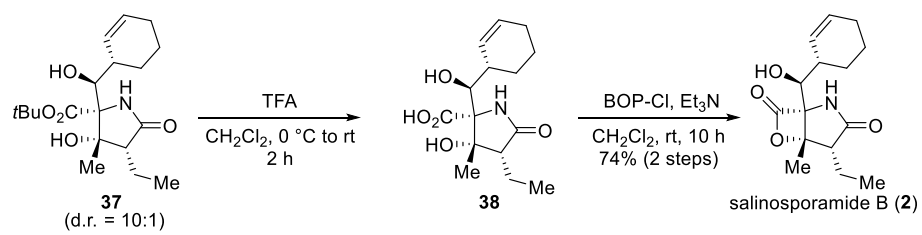
35: mp 163–166 °C; R_f = 0.28 (hexane/EtOAc = 1:3); $[\alpha]^{20}_D$ – 10.6 (*c* 0.5, MeOH); ^{1}H NMR (400MHz, CD_3OD) δ = 3.82 (d, *J* = 11.0 Hz, 1H), 3.73 (d, *J* = 11.0 Hz, 1H), 2.28 (t, *J* = 6.6 Hz, 1H), 1.78 – 1.63 (m, 1H), 1.61 – 1.52 (m, 1H), 1.50 (s, 9H), 1.48 (s, 3H), 1.11 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ = 179.7, 170.2, 83.3, 80.1, 75.8, 65.5, 54.7, 28.3 (3C), 21.2, 17.9, 13.9; IR (neat, cm^{-1}) υ_{max} 3334, 3000, 2456, 1716, 1685, 1654, 1369, 1153, 754; HRMS (FAB): calcd. for $C_{13}H_{24}NO_5$ $[M+H]^+$ 274.1651, found 274.1652.



Compound 37: To a stirred solution of **35** (150 mg, 0.547 mmol) in CH_2Cl_2 (5.5 mL), DMP (280 mg, 0.656 mmol) was added at room temperature and stirred for 2 h. In the meantime, to a solution of indium (315 mg, 2.74 mmol) in THF (5.5 mL), ammonium chloride (144 mg, 2.74 mmol) was added at room temperature. After 30 min, 3-bromocyclohexene (184 μL, 1.59 mmol) was slowly added at room temperature stirred for 30 min. After completion of DMP oxidation, the mixture was filtered through syringe filter for removing precipitate, and added to indium, ammonium chloride and 3-bromocyclohexane solution at room temperature. The reaction mixture was stirred for 6 h and filter through a pad of Celite, rinsed with

EtOAc and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc = 1:1, *v*/*v*) to yield **37** (135 mg, 70%, 10:1 d.r.) as a white solid.

37: mp 180–183 °C; R_f = 0.3 (hexane:EtOAc = 1:1); $[\alpha]^{20}_{D}$ – 174.4 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.46 (brs, 1H), 6.14 – 5.95 (m, 1H), 5.89 – 5.75 (m, 1H), 8.46 (brs, 1H), 4.06 (d, *J* = 10.3 Hz, 1H), 2.44 (dd, *J* = 7.6, 5.9 Hz, 1H), 2.27 (brs, 1H), 2.01 – 1.93 (m, 2H), 1.89 – 1.77 (m, 1H), 1.76 – 1.65 (m, 4H), 1.62 – 1.51 (m, 2H), 1.55 (s, 3H), 1.51 (s, 9H), 1.07 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 180.1, 171.5, 135.1, 123.7, 83.7, 81.7, 78.8, 75.8, 53.1, 38.5, 29.4, 28.2 (3C), 25.0, 20.8, 20.6, 16.7, 13.6; IR (neat, cm^{-1}) υ_{max} 3313, 2977, 2931, 2875, 1714, 1688, 1458, 1370, 1290, 1253, 1158, 1098, 1018, 950, 886, 845, 759, 691; HRMS (FAB): calcd. for $C_{19}H_{32}NO_5$ $[M+H]^+$ 354.2280, found 354.2290.

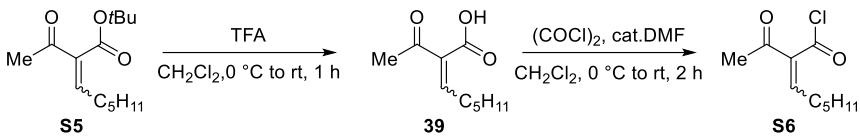


Compound 38: To a stirred solution of **37** (68 mg, 0.19 mmol) in CH_2Cl_2 (1.0 mL), TFA (0.5 mL) was added at 0 °C. The mixture was slowly warm up to room temperature and stirred for 2 h. The resulting mixture was concentrated under reduced pressure to provide carboxylic acid **38** (53 mg). The crude mixture was used in next step without further purification.

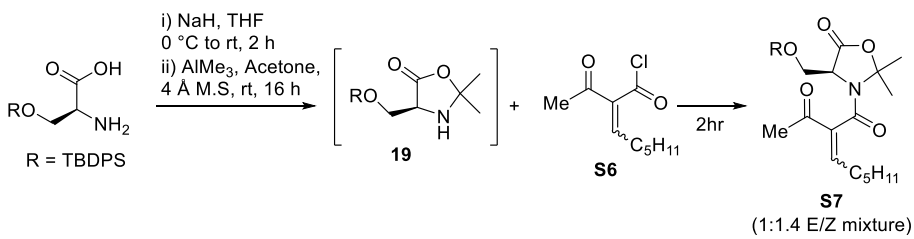
Salinosporamide B (**2**): To a solution of crude carboxylic acid prepared above (53 mg) in CH_2Cl_2 (1.0 mL), triethylamine (167 μL, 1.2 mmol) and BOP-Cl (147 mg, 0.579 mmol) was added at room temperature. The mixture was stirred at the same temperature for 10 h and quenched with saturated NH_4Cl aqueous solution. The mixture was extracted with EtOAc three times, and the combined organic fraction was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc = 3:1, *v*/*v*) to yield salinosporamide B (39.8 mg, 74% for 2 steps) as a white solid.

2: R_f = 0.5 (hexane/EtOAc = 1:1); $[\alpha]^{20}_{D}$ – 57 (*c* 0.286, MeOH); ^{1}H NMR (400MHz, DMSO-d_6) δ = 8.93 (s, 1H), 5.86 – 5.77 (m, 1H), 5.77 – 5.65 (m, 1H), 5.52 (d, *J* = 7.8 Hz, 1H), 3.66 (dd, *J* = 9.2, 7.9 Hz, 1H), 2.38 (dd, *J* = 8.5, 5.8 Hz, 1H), 2.33 – 2.23 (m, 1H), 1.95 – 1.87 (m, 2H), 1.83 – 1.77 (m, 1H), 1.75 (s, 3H), 1.75 – 1.62 (m, 2H), 1.62 – 1.47 (m, 1H), 1.48 – 1.32 (m, 1H), 1.28 – 1.16 (m, 1H), 1.07 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 175.9, 168.9, 128.6, 127.7, 86.2, 78.6, 69.1, 49.1, 37.7, 25.3, 24.6, 21.0, 20.2, 18.1, 12.4; IR (neat, cm^{-1}) υ_{max} 3355, 3341, 2960, 2925, 1821, 1697, 1681, 1445, 1309, 1029; HRMS (FAB): calcd. for $C_{15}H_{22}NO_4$ $[M+H]^+$ 280.1549, found 280.1557.

IV-2-3.Total synthesis of cinnabaramide A, E, F.



Compound S6: To a solution of E/Z mixture (~1.5:1) of **S5** (4.0 g, 17 mmol) in CH_2Cl_2 (24 mL), TFA (8 mL) was added at 0 °C and stirred at room temperature for 1 h. TFA was removed by co-evaporation with toluene in vacuo to provide carboxylic acid **39**. The crude carboxylic acid and DMF (20 μL) was dissolved in CH_2Cl_2 (25 mL), oxalyl chloride in CH_2Cl_2 (10 mL, 20 mmol) was added at 0 °C and stirred for 2 h at room temperature. The reaction mixture was concentrated under reduced pressure to provide acid chloride **S6**. The crude mixture was used in next step without further purification.



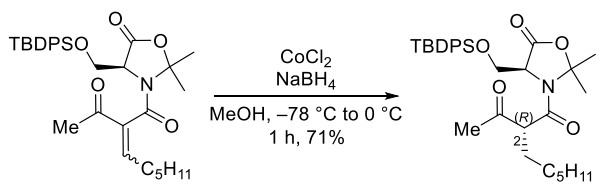
Compound S7: To a solution of L-serine-OTBDPS (4.0 g, 11.6 mmol) in THF, NaH (310 mg, 90 wt. %, dry, 11.6 mmol) was added at 0 °C and stirred at room temperature for 2 h. The solvents were evaporated under low pressure to obtain sodium salt form of L-serine-OTBDPS. To stirred mixture of sodium salt of L-serine-OTBDPS and oven activated 4Å molecular sieves in dry acetone under

nitrogen atmosphere was slowly added a solution of trimethylaluminium in hexane (5.8 mL, 12 mmol) at 0 °C. The mixture is slowly warmed to room temperature. After stirring for 12 h at the same temperature, acid chloride **S6** was slowly added at 0 °C and stirred for 2 h at room temperature. The mixture was filtered through a pad of celite and silica, rinsed with EtOAc and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to (hexane/EtOAc = 5:1, *v*/*v* to hexane/EtOAc, 3:1) to yield a 1:1.4 E/Z mixture of **S7** (3.6 g, 57 %) as yellowish oil. The minor form of **S7** was slowly transformed to major form of **S7** or decomposed.

S7 (major)**:** R_f = 0.33 (hexane/EtOAc, 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.63 – 7.55 (m, 4H), 7.46 – 7.34 (m, 6H), 6.57 (dd, *J* = 8.8, 6.7 Hz, 1H), 4.01 (t, *J* = 2.1 Hz, 1H), 3.96 (dd, *J* = 11.0, 2.0 Hz, 1H), 3.49 (dd, *J* = 11.0, 2.1 Hz, 1H), 2.21 – 2.09 (m, 2H), 2.15 (s, 3H), 2.00 (s, 3H), 1.91 (s, 3H), 1.39 – 1.29 (m, 2H), 1.28 – 1.16 (m, 4H), 1.04 (s, 9H), 0.85 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 195.5, 169.2, 164.7, 150.1, 140.0, 136.1 (2C), 135.8 (2C), 132.7, 131.7, 130.21, 130.15, 127.94 (2C), 127.92 (2C), 99.0, 63.9, 59.9, 31.5, 30.5, 28.0, 26.9, 26.8 (3C), 26.4, 25.9, 22.4, 19.2, 14.0; IR (neat, cm^{-1}) υ_{max} 2957, 2933, 2860, 1796, 1656, 1411, 1365, 1261, 1112, 968, 822; HRMS (FAB): calcd. for $C_{32}H_{44}NO_5Si$ $[M]^+$ 550.2989, found 550.2996.

S7 (minor)**:** R_f = 0.5 (hexane/EtOAc, 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.62 –

7.52 (m, 4H), 7.48 – 7.33 (m, 6H), 6.04 (t, *J* = 7.6 Hz, 1H), 4.24 – 4.13 (brs, 1H), 4.00 (dd, *J* = 11.2, 1.9 Hz, 1H), 3.86 – 3.72 (brs, 1H), 2.31 – 2.21 (m, 1H), 2.19 (s, 3H), 2.16 – 2.10 (m, 1H), 1.96 (s, 3H), 1.85 (s, 3H), 1.32 – 1.12 (m, 6H), 1.02 (s, 9H), 0.81 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.9, 169.0, 166.0, 147.0, 138.7, 136.0 (2C), 135.6 (2C), 132.6, 131.8, 130.3, 130.2, 128.1 (2C), 128.0 (2C), 98.7, 63.2, 60.3, 31.6, 30.5, 29.3, 28.4, 26.94 (3C), 26.88 (2C), 22.4, 19.3, 14.0; IR (neat, cm^{-1}) υ_{max} 2957, 2932, 2856, 1796, 1716, 1650, 1428, 1411, 1261, 1224, 1150, 967, 822; HRMS (FAB): calcd. for $C_{32}H_{44}NO_5Si$ $[M+H]^+$ 550.2989, found 550.2996.



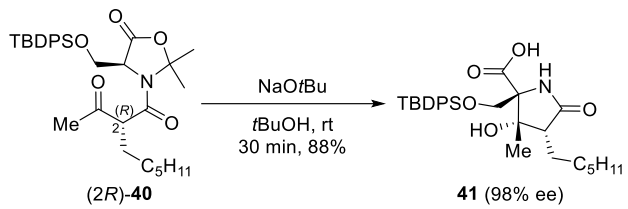
S7
(1:1.4 E/Z mixture)

(2*R*)-**40**
d.r. = 14:1

Compound (2*R*)-**40**: To a solution of **S7** (3.3 g, 6.0 mmol) in MeOH, $CoCl_2$-$6H_2O$ (7.1 g, 30 mmol) and $NaBH_4$ (1.1 g, 30 mmol) was added at –78 °C. The mixture was slowly warm up to 0 °C and stirred for 1 h. The reaction mixture was concentrated under reduced pressure to remove MeOH. The mixture was filtered through a pad of celite and silica, rinsed with EtOAc and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc = 8:1, *v*/*v*) to yield a 14:1 mixture of (2*R*)-**40** and (2*S*)-**40** (2.4 g, 71%) as a colorless oil.

(2*R*)-**40 :** R_f = 0.55 (hexane/EtOAc, 3:1); $[\alpha]^{20}_D$ – 30.5 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, two rotamers in a 25:1 ratio) δ = 7.68 – 7.54 (m, 4H), 7.50 – 7.30 (m, 6H), 4.56 – 4.46 (m, 1H), 4.10 (dd, *J* = 11.2, 2.3 Hz, 1H), 3.85 (dd, *J* = 11.2, 2.2 Hz, 1H), 3.19 (dd, *J* = 7.8, 6.7 Hz, 1H), 2.10 (s, 3H), 1.97 – 1.71 (m, 2H), 1.92 (s, 3H), 1.78 (s, 3H), 1.31 – 1.10 (m, 8H), 1.03 (s, 9H), 0.84 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 204.9, 168.9, 166.2, 135.89 (2C), 135.56 (2C), 132.4, 131.7, 130.4, 130.2, 128.13 (2C), 128.08 (2C), 99.0, 64.8, 61.2, 59.5, 31.5, 29.3, 28.8, 27.6, 26.9 (3C), 26.6, 26.3, 25.9, 22.7, 19.3, 14.2; IR (neat, cm^{-1}) υ_{max} 2954, 2930, 2858, 1794, 1709, 1655, 1402, 1262, 1105, 1044, 990; HRMS (FAB): calcd. for $C_{32}H_{46}NO_5Si$ $[M+H]^+$ 552.3145, found 552.3141.

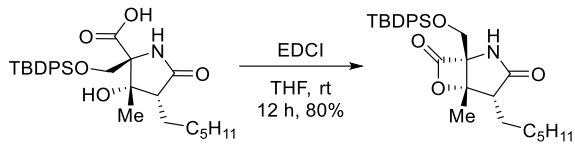
(2*S*)-**40 :** R_f = 0.68 (hexane/EtOAc, 3:1)ff; $[\alpha]^{20}_D$ + 33 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, two rotamers in a 7:1 ratio) δ = 7.66 – 7.53 (m, 4H), 7.46 – 7.34 (m, 6H), 4.34 (t, *J* = 2.1 Hz, 1H), 4.11 (dd, *J* = 11.3, 1.9 Hz, 1H), 4.01 (dd, *J* = 11.3, 2.1 Hz, 1H), 3.09 (dd, *J* = 8.5, 6.1 Hz, 1H), 2.09 (s, 3H), 2.01 – 1.72 (m, 2H), 1.95 (s, 3H), 1.82 (s, 3H), 1.36 – 1.11 (m, 8H), 1.03 (s, 9H), 0.83 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 203.9, 168.8, 167.7, 136.0 (2C), 135.7 (2C), 132.4, 131.8, 130.3, 130.2, 128.02 (2C), 127.96 (2C), 99.1, 64.8, 60.2, 60.1, 31.5, 31.2, 29.2, 27.5, 27.4, 27.0 (3C), 26.4, 26.0, 22.6, 19.3, 14.1; IR (neat, cm^{-1}) υ_{max} 2954, 2928, 2858, 1794, 1709, 1655, 1426, 1378, 1261, 1224, 1174, 968, 915; HRMS (FAB): calcd. for $C_{32}H_{46}NO_5Si$ $[M+H]^+$ 552.3145, found 552.3146.



Compound 41: To a stirred solution of (2*R*)-**40** (1.1 g, 2.0 mmol) in *t*BuOH (40 mL), Sodium *tert*-butoxide (961 mg, 10.0 mmol) was added at room temperature. The mixture was stirred at room temperature for 30 min and acidified with 1 n HCl aqueous solution at 0 °C and extracted with EtOAc three times. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH/acetic acid = 20:1:0.2, *v*/*v*/*v*) to give **41** (898 mg, 88%) as a white solid. The enantiomeric excess of **41** was determined to be 98%.

41: mp 150–154 °C; R_f = 0.4 (CH_2Cl_2/MeOH/acetic acid = 10:1:0.1); $[\alpha]^{20}_D$ + 47.5 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ = 7.71 – 7.61 (m, 4H), 7.49 – 7.35 (m, 6H), 3.89 (s, 2H), 2.45 (t, *J* = 6.1 Hz, 1H), 1.74 – 1.62 (m, 1H), 1.61 – 1.51 (m, 2H), 1.49 – 1.41 (m, 1H) 1.44 (s, 3H), 1.38 – 1.27 (m, 6H), 1.04 (s, 9H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ = 179.9, 172.6, 136.9 (2C), 136.7 (2C), 133.9, 133.5, 131.2, 131.1, 129.00 (2C), 128.96 (2C), 80.0, 75.7, 67.5, 53.0, 32.9, 30.7, 29.8, 27.3 (3C), 24.6, 23.7, 21.0, 20.1, 14.5; IR (neat, cm^{-1}) υ_{max} 2954, 2928, 2855, 1708, 1615, 1362, 1219, 1112, 1174, 825; HRMS (FAB): calcd. for $C_{29}H_{42}NO_5Si$ $[M+H]^+$ 512.2832, found 512.2827.

Procedure for the modification of 41 for determination of the enantiomeric excess of 41



41 **S8**

Compound S8: To a solution of **41** (17 mg, 0.033 mmol) in THF (1 mL), EDC·HCl (16 mg, 0.083 mmol) was added at room temperature and stirred for 12 h. The mixture was extracted with EtOAc three times. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc = 5:1, *v*/*v*) to yield **S8** (13 mg, 80%) as a colorless oil.

S8: R_f = 0.33 (hexane/EtOAc = 3:1, *v*/*v*); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.69 – 7.56 (m, 4H), 7.50 – 7.37 (m, 6H), 5.87 (s, 1H), 3.94 (d, *J* = 11.8 Hz, 1H), 3.83 (d, *J* = 11.8 Hz, 1H), 2.39 (dd, *J* = 9.6, 5.3 Hz, 1H), 1.89 – 1.78 (m, 1H), 1.77 (s, 3H), 1.75 – 1.65 (m, 1H), 1.59 – 1.46 (m, 2H), 1.41 – 1.21 (m, 6H), 1.03 (s, 9H), 0.86 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.2, 168.0, 135.8 (2C), 135.7 (2C), 132.0, 131.9, 130.5, 130.4, 128.3 (2C), 128.2 (2C), 85.3, 75.9, 59.0, 49.0, 31.6, 29.4, 27.9, 26.8 (3C), 25.7, 22.7, 20.4, 19.2, 14.2; HRMS (FAB): calcd. for $C_{29}H_{40}NO_4Si$ $[M+H]^+$ 429.2727, found 429.2720.

[Determination of the enantiomeric excess of **S8**]

The enantiomeric purity of I was analyzed by chiral HPLC. The chiral HPLC

chromatogram of **S8** was compared with that of *rac*-**S8**. Based on this comparison, the enantiomeric purity of **S8** was determined to be 99%.

HPLC conditions: CHIRALCEL AD-H (250 × 4.6 mm, 5 μm), hexane/2-propanol = 97:3 (*v*/*v*), flow rate = 0.7 mL/min, λ = 225 nm. The retention times are shown in Figure S11.

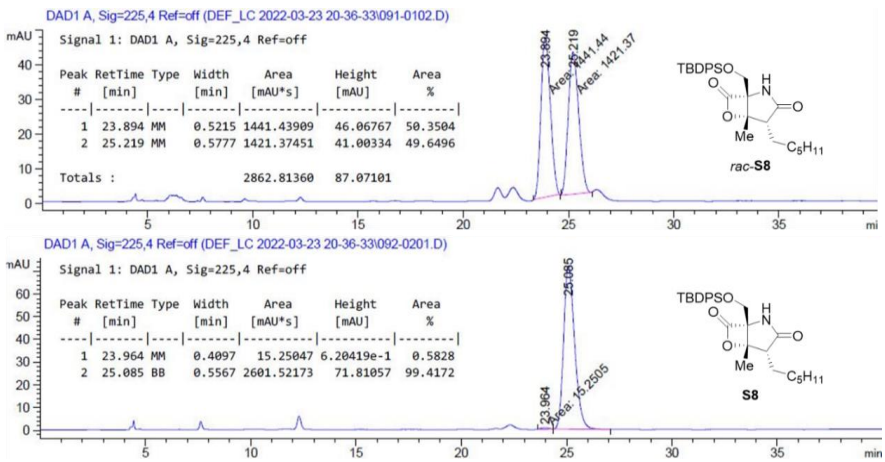
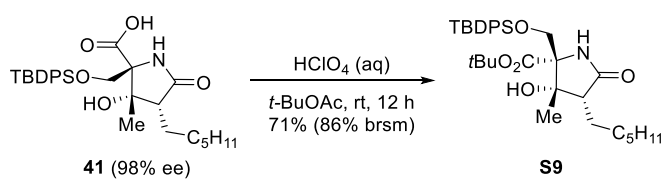


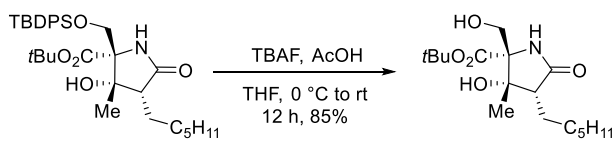
Figure S11. Chiral HPLC chromatograms of *rac*-**S8** and **S8**.



Compound S9: To a solution of **41** (721 mg, 1.41 mmol) in *tert*-Butyl acetate (14 mL), aqueous 50% $HClO_4$ (280 μL) was added at room temperature. The mixture was stirred at room temperature for 12 h and quenched with saturated $NaHCO_3$ aqueous solution at 0 °C. The mixture was extracted with EtOAc three times, and the combined organic fraction was dried over $MgSO_4$ and concentrated under

reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc = 6:1, *v*/*v*) to yield **S9** (568 mg, 71%) as a colorless oil, and **41** (107 mg, 15%) was recovered.

S9: R_f = 0.4 (hexane/EtOAc = 5:1, *v*/*v*); $[\alpha]^{20}_{D}$ – 29.9 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.68 (s, 1H), 7.68 (ddt, *J* = 26.7, 6.5, 1.8 Hz, 4H), 7.52 – 7.30 (m, 6H), 4.13 (d, *J* = 9.3 Hz, 1H), 3.49 (d, *J* = 9.3 Hz, 1H), 2.08 – 1.99 (m, 1H), 1.80 – 1.65 (m, 1H), 1.65 – 1.50 (m, 2H), 1.44 (s, 9H), 1.38 – 1.31 (m, 1H) 1.31 – 1.19 (m, 6H), 1.23 (s, 3H), 1.05 (s, 9H), 0.89 – 0.79 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.7, 170.2, 135.80 (2C), 135.79 (2C), 133.1, 132.7, 130.0, 129.9, 128.0 (2C), 127.9 (2C), 82.8, 78.7, 76.0, 66.6, 51.6, 31.9, 29.9, 28.8, 28.0 (3C), 26.9 (3C), 23.6, 22.8, 20.7, 19.3, 14.2; IR (neat, cm^{-1}) υ_{max} 3315, 2954, 2928, 2856, 1722, 1690, 1368, 1315, 1252, 1163, 1077; HRMS (FAB): calcd. for $C_{33}H_{50}NO_5Si$ $[M+H]^+$ 568.3458, found 568.3460.

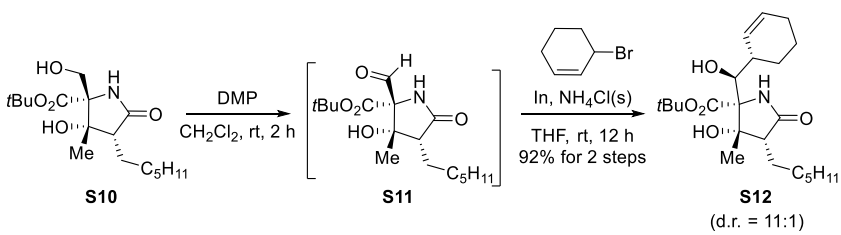


S9 **S10**

Compound S10: To a solution of **S9** (533 mg, 0.939 mmol) in THF (4.7 mL), acetic acid (215 μL, 3.76 mmol) and 1.0M TBAF solution in THF (1.9 mL, 1.9 mmol) was added at 0 °C. The mixture was warm up to room temperature and stirred for 12 h and quenched with saturated NH_4Cl aqueous solution. The mixture was extracted with EtOAc three times, and the combined organic fraction was dried

over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc = 1:2, *v*/*v*) to yield **S10** (263 mg, 85%) as a white solid.

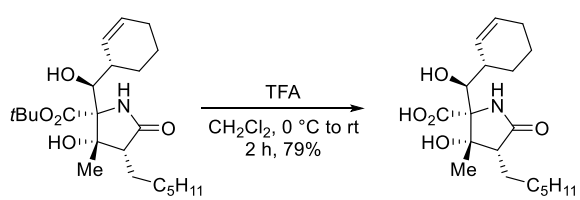
S10: mp 113–118 °C; R_f = 0.5 (EtOAc); $[\alpha]^{20}_D$ + 44.3 (*c* 0.5, MeOH); ^{1}H NMR (400MHz, $CDCl_3$) δ = 3.81 (d, *J* = 11.1 Hz, 1H), 3.73 (d, *J* = 11.0 Hz, 1H), 2.35 (t, *J* = 6.2 Hz, 1H), 1.71 – 1.52 (m, 3H), 1.52 – 1.41 (m, 1H), 1.50 (s, 9H), 1.47 (s, 3H), 1.39 – 1.27 (m, 6H), 0.96 – 0.86 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 179.8, 170.2, 83.3, 80.1, 75.8, 65.5, 53.0, 32.9, 30.8, 29.8, 28.3 (3C), 24.7, 23.7, 21.1, 14.4; IR (neat, cm^{-1}) υ_{max} 3337, 2954, 2926, 2856, 1719, 1685, 1677, 1655, 1368, 1319, 1249, 1158, 1020; HRMS (FAB): calcd. for $C_{17}H_{32}NO_5$ $[M+H]^+$ 330.2280, found 330.2285.



Compound S12: To a stirred solution of **S10** (200 mg, 0.607 mmol) in CH_2Cl_2 (6.1 mL), DMP (309 mg, 0.728 mmol) was added at room temperature and stirred for 2 h. In the meantime, to a solution of indium (356 mg, 3.10 mmol) in THF (6.1 mL), ammonium chloride (166 mg, 3.10 mmol) was added at room temperature. After 30 min, 3-bromo cyclohexene (209 μL, 1.82 mmol) was slowly added at room temperature stirred for 30 min. After completion of DMP oxidation, the crude

mixture of **S11** was filtered through syringe filter for removing precipitate, and added to indium, ammonium chloride and 3-bromo cyclohexane solution at room temperature. The reaction mixture was stirred for 12 h and filter through a pad of Celite, rinsed with EtOAc and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc = 3:1, *v*/*v*) to yield **S12** (229 mg, 92%, 11:1 d.r.) as a white solid.

S12: mp 165–170 °C; R_f = 0.3 (hexane/EtOAc = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.35 (brs, 1H), 6.06 – 5.96 (m, 1H), 5.83 – 5.75 (m, 1H), 4.05 (s, 1H), 2.57 – 2.46 (m, 1H), 2.27 (brs, 1H), 2.08 – 1.90 (m, 2H), 1.87 – 1.75 (m, 2H), 1.75 – 1.57 (m, 5H), 1.57 – 1.37 (m, 2H), 1.54 (s, 3H), 1.50 (s, 9H), 1.40 – 1.16 (m, 6H), 0.93 – 0.75 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 180.2, 171.4, 135.2, 123.7, 83.7, 81.7, 78.7, 75.8, 51.4, 38.5, 31.9, 29.9, 29.4, 28.8, 28.2 (3C), 25.0, 23.6, 22.8, 20.7, 20.6, 14.3; IR (neat, cm^{-1}) υ_{max} 3580, 3337, 3330, 2928, 2866, 1789, 1673, 1370, 1294, 1155, 1016; HRMS (FAB): calcd. for $C_{23}H_{40}NO_5$ $[M+H]^+$ 410.2906, found 410.2911.

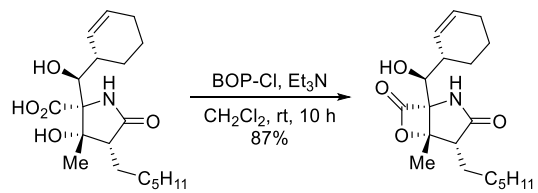


S12 cinnabaramide E (**10**)

Cinnabaramide E (**10**): To a stirred solution of **S12** (117 mg, 0.286 mmol) in CH_2Cl_2 (1.4 mL), TFA (0.7 mL) was added at 0 °C. The mixture was slowly warm

up to room temperature and stirred for 2 h. The resulting mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH/acetic acid = 15:1:0.1, *v*/*v*/*v*) to yield cinnabaramide E (**10**) (80 mg, 79%) as a white solid.

10: R_f = 0.2 (CH_2Cl_2/MeOH/acetic acid = 15:1:0.1, *v*/*v*/*v*); $[\alpha]^{20}_D$ – 23.4 (*c* 0.12, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.43 (s, 1H), 5.81 (dq, *J* = 10.5, 2.2 Hz, 1H), 5.63 (dq, *J* = 10.0, 3.3 Hz, 1H), 4.74 (brs, 2H), 3.72 (d, *J* = 5.4 Hz, 1H), 2.40 (t, *J* = 6.2 Hz, 1H), 2.17 (d, *J* = 7.2 Hz, 1H), 1.87 (dq, *J* = 9.4, 5.4, 4.0 Hz, 2H), 1.65 (td, *J* = 10.8, 5.8 Hz, 2H), 1.54 – 1.29 (m, 6H), 1.44 (s, 3H), 1.29 – 1.21 (m, 6H), 0.85 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 177.7, 172.5, 129.3, 127.2, 80.1, 75.1, 74.9, 50.7, 38.5, 31.2, 29.1, 28.3, 26.9, 24.5, 23.6, 22.1, 21.6, 21.1, 14.0; IR (neat, cm^{-1}) υ_{max} 2928, 1711, 1683, 1360, 1254, 1219, 1080, 948; HRMS (FAB): calcd. for $C_{19}H_{32}NO_5$ $[M+H]^+$ 354.2280, found 354.2278.

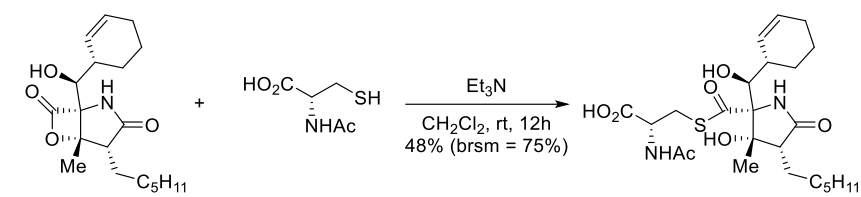


cinnabaramide E (**10**) cinnabaramide A (**7**)

Cinnabaramide A (**7**): To a solution of **10** (60 mg, 0.17 mmol) in CH_2Cl_2 (1.7 mL), Et_3N (142 μL, 1.02 mmol) and BOP-Cl (130 mg, 0.51 mmol) was added at room temperature. The mixture was stirred at the same temperature for 10 h and quenched with saturated NH_4Cl aqueous solution. The mixture was extracted with

EtOAc three times, and the combined organic fraction was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc = 3:1, *v*/*v*) to yield cinnabaramide A (**7**) (50 mg, 87%) as a white solid.

7: R_f = 0.45 (hexane/EtOAc = 1:1); $[\alpha]^{20}_D$ – 94.9 (*c* 0.5, MeOH);); ^{1}H NMR (400MHz, DMSO-d_6) δ = 8.93 (s, 1H), 5.81 (dd, *J* = 10.4, 2.3 Hz, 1H), 5.72 (dq, *J* = 10.1, 3.2 Hz, 1H), 5.51 (d, *J* = 7.9 Hz, 1H), 3.66 (dd, *J* = 9.1, 7.5 Hz, 1H), 2.42 (dd, *J* = 7.6, 5.6 Hz, 1H), 2.35 – 2.22 (m, 1H), 1.95 – 1.88 (m, 2H), 1.86 – 1.77 (m, 1H), 1.76 – 1.65 (m, 1H), 1.73 (s, 3H), 1.63 – 1.35 (m, 5H), 1.33 – 1.18 (m, 7H), 0.87 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 176.0, 168.9, 128.6, 127.7, 86.1, 78.6, 69.1, 47.7, 37.7, 31.0, 28.8, 27.1, 25.3, 24.7, 24.6, 22.0, 21.0, 20.1, 14.0; IR (neat, cm^{-1}) υ_{max} 3350, 2922, 2855, 1819, 1696, 1677, 1431, 1381, 1355, 1307, 1227, 1043, 826; HRMS (FAB): calcd. for $C_{19}H_{30}NO_4$ $[M+H]^+$ 336.2175, found 336.2184.



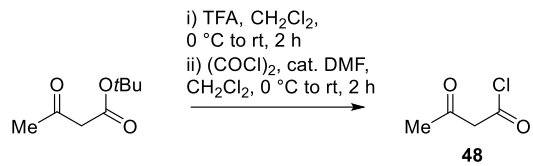
cinnabaramide A (**7**) cinnabaramide F (**11**)

Cinnabaramide F (**11**): To a stirred solution of **7** (32 mg, 0.095 mmol) in CH_2Cl_2 (1.0 mL), Et_3N (27 μL, 0.19 mmol) and *N*-acetyl l-cysteine (16 mg, 0.095 mmol) was added at room temperature. The mixture was stirred at the same temperature

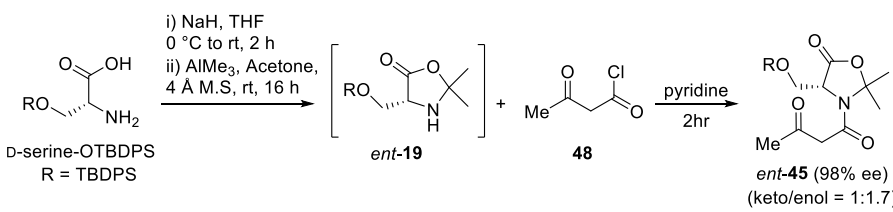
for 12 h and concentrated under reduced pressure. The residue was purified via recycling preparative HPLC (HPLC conditions: JAIGEL-ODS-AP-L (20 mm (i.d.) x 500 mm (l), 10 μm), H_2O/MeOH = 20:80, flow rate = 10 mL/min, λ = 202nm and 234 nm) to yield cinnabaramide F (**11**) (23 mg, 48%) as a white solid and cinnabarmide A (**7**) (9 mg, 27%) was recovered.

11: R_f = 0.13 (CH_2Cl_2/MeOH/acetic acid = 10:1:0.1, *v*/*v*/*v*); $[\alpha]^{20}_D$ + 38.2 (*c* 0.5, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.14 (s, 1H), 7.98 (d, *J* = 7.7 Hz, 1H), 5.78 (dd, *J* = 10.5, 2.3 Hz, 1H), 5.63 (dt, *J* = 10.3, 3.1 Hz, 1H), 5.00 (d, *J* = 7.5 Hz, 1H), 4.76 (brs, 1H), 4.21 – 4.12 (m, 1H), 3.77 (t, *J* = 6.8 Hz, 1H), 3.29 (dd, *J* = 13.0, 4.1 Hz, 1H), 2.92 (dd, 1H), 2.44 (t, *J* = 6.1 Hz, 1H), 2.12 (brs, 1H), 1.88 – 1.82 (m, 2H), 1.81 (s, 3H), 1.67 – 1.55 (m, 2H), 1.53 – 1.40 (m, 2H), 1.44 (s, 3H), 1.40 – 1.28 (m, 3H), 1.28 – 1.18 (m, 6H), 1.14 – 0.99 (m, 1H), 0.85 (t, *J* = 7.0, 3H); ^{13}C NMR (214 MHz, , DMSO-d_6) δ = 201.9, 179.1, 172.2, 169.2, 129.4, 127.3, 80.7, 80.0, 75.6, 51.7, 50.6, 38.2, 31.2, 30.1, 29.1, 28.1, 27.1, 24.6, 23.5, 22.5, 22.2, 21.4, 21.1, 14.0; IR (neat, cm^{-1}) υ_{max} 3362, 2927, 2858, 1657, 1650, 1420, 1375, 1222, 1129, 1040, 885, 792; HRMS (FAB): calcd. for $C_{24}H_{39}N_2O_7S$ $[M+H]^+$ 499.2478, found 499.2490.

IV-2-4.Total synthesis of salinosporamide A (1).



Compound 48: To a solution of *t*butyl acetoacetate (4.0 g, 25 mmol) in CH_2Cl_2 (50 mL), TFA (17 mL) was added at 0 °C and stirred at room temperature for 1 h. TFA was removed by co-evaporation with toluene in vacuo to provide carboxylic acid. The crude carboxylic acid and DMF (20 μL) was dissolved in CH_2Cl_2 (40 mL), oxalyl chloride in CH_2Cl_2 (15 mL, 30 mmol) was added at 0 °C and stirred for 2 h at room temperature. The reaction mixture was concentrated under reduced pressure to provide acid chloride **48**. The crude mixture was used in next step without further purification.



Compound *ent*-45: To a solution of D-serine-OTBPDS (4.0 g, 11.6 mmol) in THF, NaH (311 mg, 90 wt. %, dry, 11.6 mmol) was added at 0 °C and stirred at room temperature for 2 h. The solvents were evaporated under low pressure to obtain sodium salt form of D-serine-OTBPDS. To stirred mixture of sodium salt of D-

serine-OTBDPS and oven activated 4Å molecular sieves in dry acetone under nitrogen atmosphere was slowly added a solution of trimethylaluminium in hexane (5.8 mL, 11.6 mmol) at 0 °C. The mixture was slowly warmed to room temperature. After stirring for 16 h at the same temperature, anhydrous pyridine (2.3 mL, 29 mmol) and acid chloride **48** was slowly added at 0 °C. The mixture was stirred for 2 h at room temperature and filtered through a pad of celite and silica, rinsed with EtOAc and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to (hexane/EtOAc = 4:1, *v*/*v*) to yield a 1:1.7 mixture of keto and enol form of *ent*-**45** (3.1 g, 58%) as a yellowish oil.

ent-**45**: R_f = 0.25 (hexane/EtOAc = 3:1, *v*/*v*); $[\alpha]^{20}_{D}$ – 77.2 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.73 – 7.53 (m, 4H), 7.52 – 7.30 (m, 6H), 4.64 (brs, 1H, enol), 4.36 (t, *J* = 2.8 Hz, 1H, keto), 4.27 (brs, 1H, enol), 4.05 (dd, *J* = 11.2, 2.5 Hz, 1H, keto), 4.05 – 4.00 (m, 2H, enol) 3.86 (dd, *J* = 11.2, 2.5 Hz, 1H, keto), 3.38 (d, *J* = 15.3 Hz, 1H, keto), 3.27 (d, *J* = 15.3 Hz, 1H, keto), 2.18 (s, 3H, keto), 1.91 (brs, 3H. enol), 1.86 (s, 3H, enol), 1.84 (brs, 3H, enol), 1.82 (s, 6H, keto), 1.04 (s, 9H, keto), 1.01 (s, 9H, enol); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 201.4 (keto), 177.0 (keto), 169.3 (enol), 168.8 (enol), 164.3 (enol), 135.84 (2C, keto), 135.81 (2C, enol), 135.6 (2C, keto), 135.5 (2C, enol), 132.4 (enol), 132.3 (keto), 131.9 (enol), 131.7 (keto), 130.4 (keto), 130.3 (keto), 130.2 (enol), 130.1 (enol), 128.19 (2C, keto), 128.16 (2C, keto), 128.1 (2C, enol), 127.9 (2C, enol), 99.1 (enol), 98.7 (keto),

89.0 (enol), 64.2 (keto), 62.8 (keto), 60.5 (enol), 59.8 (keto), 59.2 (enol), 51.1 (keto), 30.9 (keto), 26.91 (3C, keto), 26.88 (3C, enol), 26.63 (enol), 26.59 (enol), 26.57 (enol), 26.3 (keto), 26.1 (keto), 22.1 (enol), 19.3 (keto); IR (neat, cm^{-1}) υ_{max} 2933, 2859, 1794, 1631, 1459, 1351, 1262, 1221, 1103, 965, 821; HRMS (FAB): calcd. for $C_{26}H_{34}O_5Si$ $[M+H]^+$ 468.2206, found 468.2216.

[Determination of the enantiomeric excess of **45**]

The enantiomeric purity of **45** was analyzed by chiral HPLC. The chiral HPLC chromatogram of **45** was compared with that of *rac*-**45**. Based on this comparison, the enantiomeric purity of *ent*-**45** was determined to be 98%.

HPLC conditions: CHIRALCEL AD-H (250 × 4.6 mm, 5 μm), hexane/2-propanol = 93:7 (*v*/*v*), flow rate = 0.5 mL/min, λ = 225 nm. The retention times are shown in Figure S12.

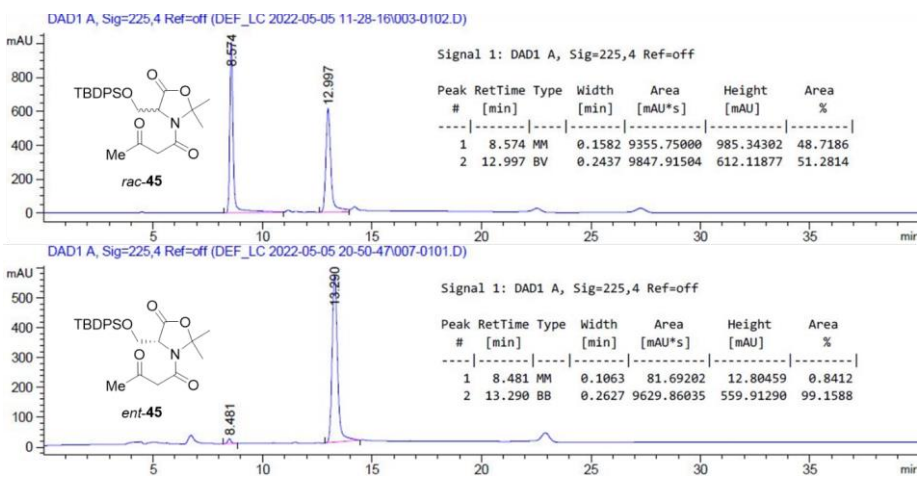
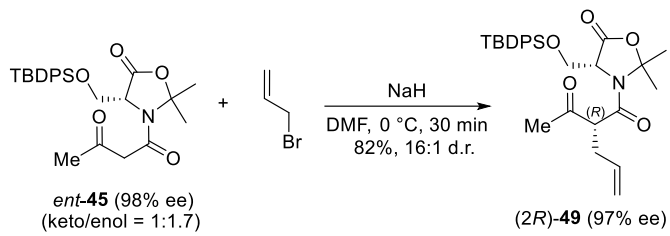


Figure S12. Chiral HPLC chromatograms of *rac*-**45** and *ent*-**45**.



ent-**45** (98% ee)
(keto/enol = 1:1.7)

(2*R*)-**49** (97% ee)

Compound (2*R*)-**49**: To a solution of *ent*-**45** (2.2 g, 4.7 mmol) in anhydrous THF (24 mL), allyl bromide (2.07 mL, 23.5 mmol) and NaH (138 mg, 90 wt. %, dry, 5.17 mmol) were added at 0 °C and stirred for 30 min. The mixture was quenched with 1 n HCl aqueous solution and extracted with EtOAc three times. The combined organic fraction was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc = 6:1, *v*/*v*) to yield (2*R*)-**49** (1.8 g, 77%) as a white solid and (2*S*)-**49** (119 mg, 5%) as a colorless oil.

(2*R*)-**49:** mp 125–130 °C; R_f = 0.4 (hexane/EtOAc = 3:1, *v*/*v*); $[\alpha]^{20}_D$ + 27.4 (*c* 0.1, $CHCl_3$ two rotamers in a 12:1 ratio); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.65 – 7.56 (m, 4H), 7.46 – 7.33 (m, 6H), 5.62 (ddt, *J* = 17.2, 10.1, 7.2 Hz, 1H), 5.09 (dd, *J* = 17.1, 1.4 Hz, 1H), 5.04 (ddt, *J* = 10.1, 1.7, 0.9 Hz, 1H), 4.34 (t, *J* = 2.2 Hz, 1H), 4.13 (dd, *J* = 11.3, 2.1 Hz, 1H), 4.01 (dd, *J* = 11.3, 2.3 Hz, 1H), 3.18 (dd, *J* = 9.4, 5.4 Hz, 1H), 2.69 – 2.57 (m, 1H), 2.57 – 2.48 (m, 1H), 2.06 (s, 3H), 1.94 (s, 3H), 1.79 (s, 3H), 1.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 202.7, 168.7, 167.3, 136.0 (2C), 135.7 (2C), 133.2, 132.4, 131.8, 130.33, 130.28, 128.1 (4C), 119.1, 99.2, 64.9, 60.1, 59.1, 34.9, 27.4, 27.0 (3C), 26.4, 26.1, 19.3; IR (neat, cm^{-1}) υ_{max}

2940, 2932, 2859, 1793, 1710, 1655, 1404, 1367, 1263, 1110, 969, 918, 702; HRMS (FAB): calcd. for $C_{29}H_{38}NO_5Si$ $[M+H]^+$ 508.2519, found 508.2526.

(2*S*)-**49:** R_f = 0.33 (hexane/EtOAc = 3:1, *v*/*v*); $[\alpha]^{20}_D$ – 27 (*c* 0.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$ two rotamers in a 14:1 ratio) δ = 7.60 (ddt, *J* = 11.7, 6.6, 1.6 Hz, 4H), 7.45 – 7.33 (m, 6H), 5.62 – 5.38 (m, 1H), 4.96 (d, *J* = 17.1 Hz, 1H), 4.88 (d, *J* = 10.2 Hz, 1H), 4.52 (t, *J* = 2.4 Hz, 1H), 4.10 (dd, *J* = 11.2, 2.4 Hz, 1H), 3.85 (dd, *J* = 11.2, 2.2 Hz, 1H), 3.30 (t, *J* = 7.4 Hz, 1H), 2.63 – 2.49 (m, 2H), 2.11 (s, 3H), 1.91 (s, 3H), 1.79 (s, 3H), 1.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 203.9, 168.8, 165.7, 135.93 (2C), 135.61 (2C), 133.7, 132.5, 131.7, 130.4, 130.3, 128.15 (2C), 128.09 (2C), 118.3, 99.0, 64.8, 60.2, 59.6, 32.7, 27.0, 26.9 (3C), 26.3, 25.9, 19.3; IR (neat, cm^{-1}) υ_{max} 2940, 2934, 2855, 1794, 1712, 1655, 1402, 1380, 1262, 1112, 968, 918, 703; HRMS (FAB): calcd. for $C_{29}H_{38}NO_5Si$ $[M+H]^+$ 508.2519, found 508.2518.

[Determination of the enantiomeric excess of **49**]

The enantiomeric purity of (2*R*)-**49** was analyzed by chiral HPLC. The chiral HPLC chromatogram of (2*R*)-**49** was compared with that of *rac*-(2*R*)-**49**. Based on this comparison, the enantiomeric purity of (2*R*)-**49** was determined to be 98%.

HPLC conditions: CHIRALCEL OD-H (250 × 4.6 mm, 5 μm), hexane/2-propanol = 93:7 (*v*/*v*), flow rate = 0.5 mL/min, λ = 290 nm. The retention times are

shown in Figure S13.

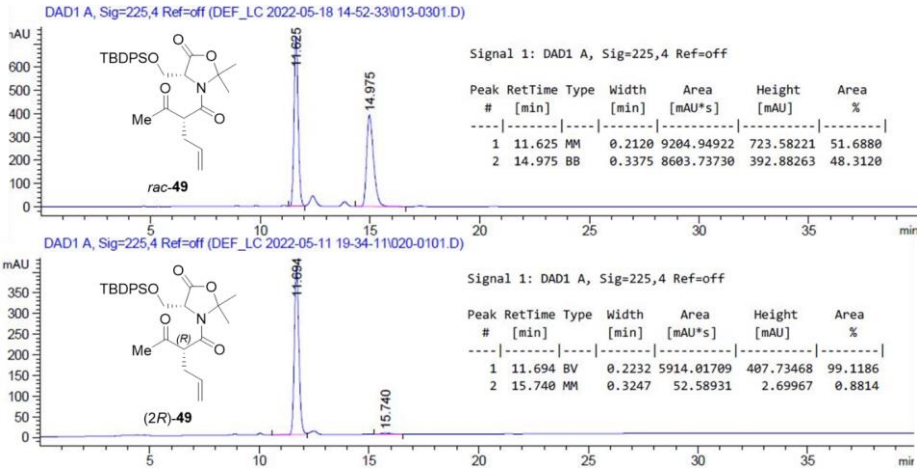
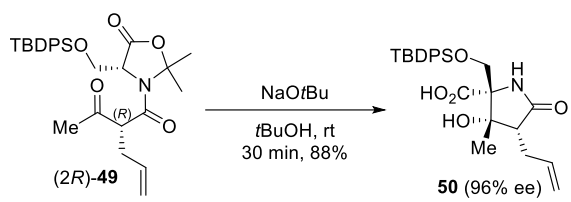


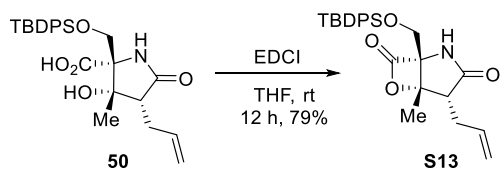
Figure S13. Chiral HPLC chromatograms of *rac*-**49** and **49**.



Compound 50: To a stirred solution of (2*R*)-**49** (2.2 g, 4.3 mmol) in *t*BuOH (86 mL), Sodium *tert*-butoxide (2.06 g, 21.5 mmol) was added at room temperature. The mixture was stirred at room temperature for 30 min and quenched with 1 n HCl aqueous solution and extracted with EtOAc three times. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH/acetic acid = 20:1:0.2, *v*/*v*/*v*) to give **50** (1.8 g, 88%) as a white solid. The enantiomeric excess of **50** was determined to be 96%.

50: mp 180–184 °C; R_f = 0.3 (CH_2Cl_2/MeOH/acetic acid = 10:1:0.1, *v*/*v*); $[\alpha]^{20}_D$ + 41.2 (*c* 0.1, $CHCl_3$); ^{1}H NMR (400 MHz, MeOD) δ = 7.66 (dt, *J* = 7.9, 1.7 Hz, 4H), 7.59 – 7.33 (m, 6H), 6.03 – 5.89 (m, 1H), 5.10 (dtd, *J* = 17.1, 2.0, 1.2 Hz, 1H), 4.99 (dtd, *J* = 10.1, 1.8, 0.8 Hz, 1H), 3.95 – 3.83 (m, 2H), 2.60 (dd, *J* = 8.1, 5.4 Hz, 1H), 2.55 – 2.42 (m, 1H), 2.42 – 2.28 (m, 1H), 1.45 (s, 3H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, MeOD) δ = 178.9, 172.5, 138.9, 136.8 (2C), 136.7 (2C), 133.9, 133.6, 131.2, 131.1, 129.0 (2C), 128.9 (2C), 116.3, 79.9, 75.8, 67.5, 53.3, 29.0, 27.3 (3C), 21.2, 20.0; IR (neat, cm^{-1}) υ_{max} 3370, 2934, 2929, 2857, 1687, 1589, 1427, 1376, 1112, 1039, 824, 701; HRMS (FAB): calcd. for $C_{26}H_{34}NO_5Si$ $[M+H]^+$ 468.2206, found 468.2205.

Procedure for the modification of 50 for determination of the enantiomeric excess of 50



Compound S13: To a solution of **50** (18 mg, 0.038 mmol) in THF (1 mL), EDC·HCl (19 mg, 0.099 mmol) was added at room temperature and stirred for 12 h. The mixture was extracted with EtOAc three times. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc = 4:1, *v*/*v*) to yield

S13 (13.5 mg, 79%) as a white solid.

S13 : R_f = 0.33 (hexane/EtOAc = 3:1, *v*/*v*); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.68 – 7.56 (m, 4H), 7.51 – 7.34 (m, 6H), 5.97 – 5.80 (m, 1H), 5.22 (d, *J* = 17.0 Hz, 1H), 5.13 (d, *J* = 10.1 Hz, 1H), 3.95 (d, *J* = 11.9 Hz, 1H), 3.84 (d, *J* = 11.8 Hz, 1H), 2.73 – 2.60 (m, 1H), 2.52 – 2.42 (m, 2H), 1.74 (s, 3H), 1.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.3, 168.0, 135.8 (2C), 135.7 (2C), 135.0, 132.03, 131.93, 130.5, 130.4, 128.3 (2C), 128.2 (2C), 118.4, 85.1, 76.2, 58.9, 49.1, 29.6, 26.9 (3C), 20.3, 19.3; IR (neat, cm^{-1}) υ_{max} 3228, 2933, 2860, 1828, 1710, 1472, 1428, 1335, 1104, 1033, 919, 821; HRMS (FAB): calcd. for $C_{26}H_{32}O_4Si$ $[M+H]^+$ 450.2101, found 450.2103.

[Determination of the enantiomeric excess of **S13**]

The enantiomeric purity of **S13** was analyzed by chiral HPLC. The chiral HPLC chromatogram of I was compared with that of *rac*-**S13**. Based on this comparison, the enantiomeric purity of **S13** was determined to be 96%.

HPLC conditions: CHIRALCEL AD-H (250 × 4.6 mm, 5 μm), hexane/2-propanol = 97:3 (*v*/*v*), flow rate = 0.7 mL/min, λ = 225 nm. The retention times are shown in Figure S14.

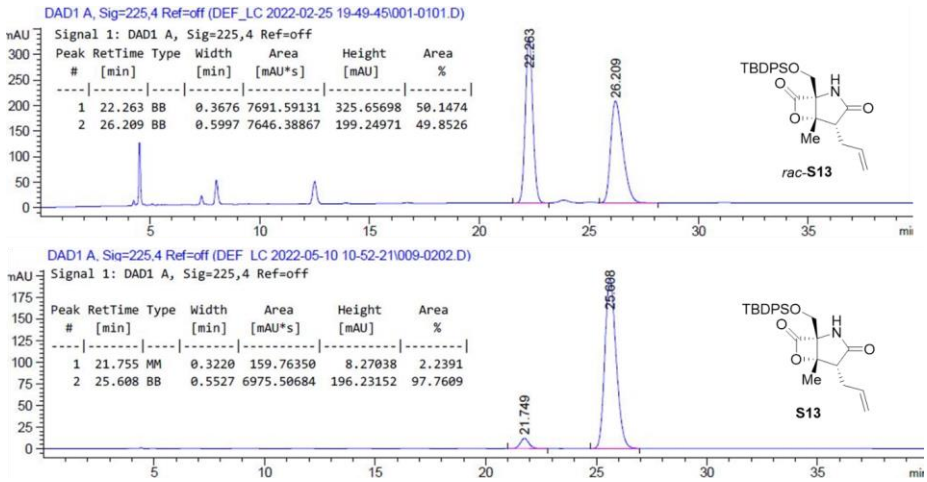
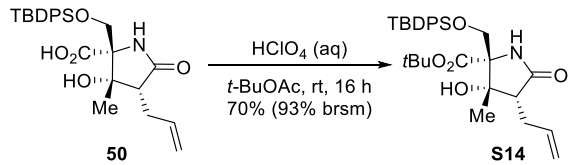


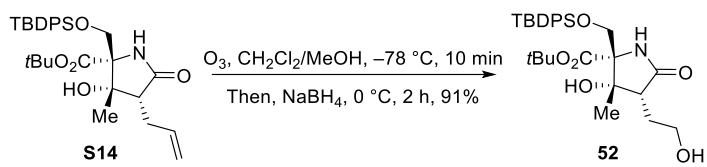
Figure S14. Chiral HPLC chromatograms of *rac*-**S13** and **S13**.



Compound S14: To a solution of **50** (1.6 g, 3.4 mmol) in *tert*-Butyl acetate (34 mL), aqueous 50% $HClO_4$ (680 μL) was added at room temperature. The mixture was stirred at room temperature for 16 h and quenched with saturated $NaHCO_3$ aqueous solution at 0 °C. The mixture was extracted with EtOAc three times, and the combined organic fraction was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc = 3:1, *v*/*v*) to yield **S14** (1.25 g, 70%) as a colorless oil, and **50** (370 mg, 23%) was recovered.

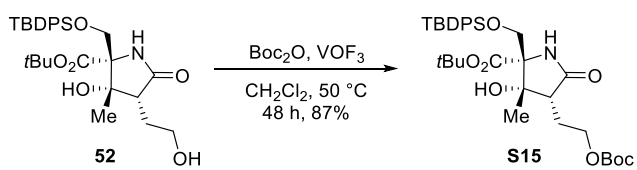
S14: R_f = 0.31 (hexane/EtOAc = 3:1, *v*/*v*); $[\alpha]^{20}_D$ – 36.2 (*c* 0.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ = 8.77 (brs, 1H), 7.74 – 7.60 (m, 4H), 7.45 – 7.34 (m, 6H),

5.97 – 5.84 (m, 1H), 5.10 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.96 (dt, *J* = 10.0, 1.7 Hz, 1H), 4.14 (d, *J* = 9.3 Hz, 1H), 3.49 (d, *J* = 9.3 Hz, 1H), 2.60 – 2.49 (m, 1H), 2.44 – 2.33 (m, 1H), 2.20 (t, *J* = 6.8 Hz, 1H), 1.44 (s, 9H), 1.24 (s, 3H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.7, 170.1, 137.8, 135.8 (4C), 133.0, 132.6, 130.02, 129.97, 128.0 (2C), 127.9 (2C), 116.1, 83.0, 78.7, 76.0, 66.6, 51.6, 28.03 (3C), 27.98, 26.9 (3C), 20.9, 19.3; IR (neat, cm^{-1}) υ_{max} 3309, 2941, 2932, 2958, 1722, 1691, 1473, 1428, 1368, 1253, 1163, 1113, 1077, 938. 702; HRMS (FAB): calcd. for $C_{30}H_{42}NO_5Si$ $[M+H]^+$ 524.2832, found 524.2825.



Compound 52: To a solution of **S14** (1.1 g, 2.1 mmol) in CH_2Cl_2 (21 mL) and MeOH (21 mL) was cooled to –78 °C and bubbled with O_3 for 10 min. The mixture was slowly warm up to 0 °C, $NaBH_4$ (794 mg, 21 mmol) was added to the reaction mixture and stirring for 2 h at the same temperature and quenched with saturated NH_4Cl aqueous solution. The mixture was concentrated under reduced pressure to remove MeOH and extracted with EtOAc three times and the combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo.* The residue was purified by flash chromatography on silica gel (hexane/EtOAc = 1:1, *v*/*v*) to give **52** (1.0 g, 91%) as a colorless oil. The relative configuration was determined by NOESY experiments.

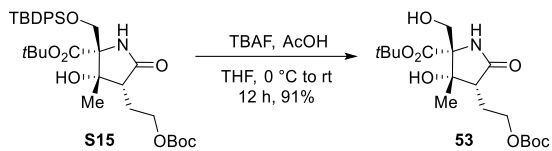
52: R_f = 0.45 (EtOAc only); $[\alpha]^{20}_D$ -12.4 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ = 8.91 (brs, 1H), 7.75 – 7.58 (m, 4H), 7.48 – 7.33 (m, 6H), 4.14 (d, *J* = 9.5 Hz, 1H), 3.83 (dt, *J* = 9.8, 4.6 Hz, 1H), 3.65 (td, *J* = 10.7, 10.3, 3.6 Hz, 1H), 3.54 (d, *J* = 9.5 Hz, 1H), 2.32 (dd, *J* = 10.0, 2.7 Hz, 1H), 2.10 – 1.95 (m, 1H), 1.79 – 1.65 (m, 1H), 1.43 (s, 9H), 1.21 (s, 3H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 178.5, 169.9, 135.8 (2C), 135.7 (2C), 132.8, 132.4, 130.14, 130.07, 128.1 (2C), 128.0 (2C), 83.5, 78.8, 77.4, 66.4, 62.4, 52.2, 28.0 (3C), 26.9 (3C), 26.4, 19.8, 19.3; IR (neat, cm^{-1}) υ_{max} 3315, 2962, 2935, 2861, 1723, 1690, 1682, 1675, 1428, 1370, 1255, 1162, 1113, 1077, 941, 702; HRMS (FAB): calcd. for $C_{29}H_{42}NO_6Si$ $[M+H]^+$ 528.2781, found 528.2771.



Compound S15: To a solution of **52** (890 mg, 1.69 mmol) in CH_2Cl_2 (8.4 mL), Boc_2O (1.9 mL, 8.4 mmol) and VOF_3 (209 mg, 0.169 mmol) were added at room temperature. The mixture was stirred at 50 °C for 48 h and filtered through a short silica plug and rinsed with EtOAc. The filtrate was concentrated in vacuo and the residue was purified by flash chromatography on silica gel (hexane/EtOAc = 5:1, *v*/*v*) to yield **S15** (921 mg, 87%) as a colorless oil.

S15: R_f = 0.4 (hexane/EtOAc = 5:1, *v*/*v*); $[\alpha]^{20}_D$ –12.2 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ = 8.67 (brs, 1H), 7.85 – 7.55 (m, 4H), 7.55 – 7.31 (m, 6H),

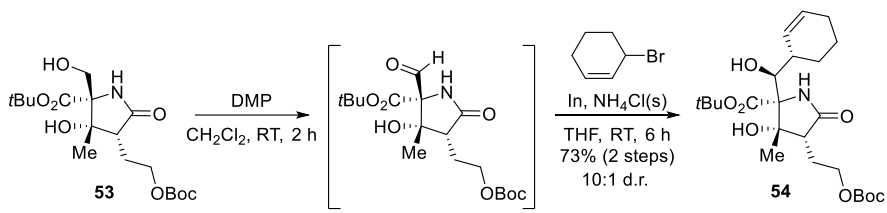
5.60 (brs, 1H), 4.26 (dd, *J* = 7.0, 5.6 Hz, 2H), 4.12 (d, *J* = 9.4 Hz, 1H), 3.53 (d, *J* = 9.4 Hz, 1H), 2.30 (dd, *J* = 8.2, 4.9 Hz, 1H), 2.14 – 1.99 (m, 1H), 1.95 – 1.81 (m, 1H), 1.43 (s, 9H), 1.42 (s, 9H), 1.22 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.1, 170.1, 153.6, 135.8 (4C), 133.0, 132.6, 130.05, 129.98, 128.1 (2C), 127.9 (2C), 83.2, 81.8, 78.6, 76.1, 66.6, 65.4, 47.6, 28.0 (3C), 27.9 (3C), 26.9 (3C), 23.1, 20.3, 19.3; IR (neat, cm^{-1}) υ_{max} 3360, 2956, 2929, 2868, 1724, 1692, 1459, 1369, 1279, 1255, 1163, 1114, 1079, 846, 768, 703; HRMS (FAB): calcd. for $C_{34}H_{50}NO_8Si$ $[M+H]^+$ 628.3306, found 628.3315.



Compound 53: To a solution of **S15** (820 mg, 1.3 mmol) in THF (13mL), AcOH (302 μL, 5.2 mmol) and 1.0M TBAF solution in THF (2.6 mL, 2.6 mmol) were added at 0 °C. The mixture was warmed to room temperature and stirred at the same time for 12 h. The reaction mixture was added to a saturated NH_4Cl aqueous solution and extracted with EtOAc twice. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc = 1:1, *v*/*v*) to yield **53** (461 mg, 91%) as a white solid.

53: mp 56–60 °C; R_f = 0.33 (hexane/EtOAc, 1:2); $[\alpha]^{20}_D$ – 15.6 (*c* 0.5, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) 8.16 (s, 1H), 5.09 (brs, 1H), 4.27 (ddd, *J* = 7.1, 5.8, 2.1

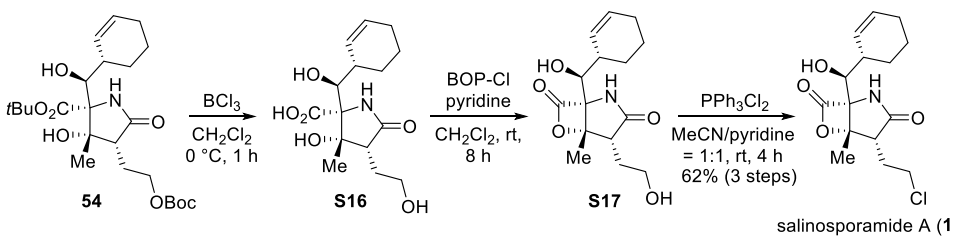
Hz, 2H), 3.93 (d, *J* = 11.4 Hz, 1H), 3.78 (d, *J* = 11.4 Hz, 1H), 2.49 (dd, *J* = 8.1, 5.0 Hz, 1H), 2.09 – 1.96 (m, 1H), 1.95 – 1.82 (m, 1H), 1.49 (s, 9H), 1.44 (s, 9H), 1.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 178.2, 169.8, 153.6, 83.8, 82.0, 79.3, 75.6, 65.4, 65.0, 48.1, 28.2 (3C), 27.9 (3C), 23.1, 20.4; IR (neat, cm^{-1}) υ_{max} 3360, 2979, 2956, 1719, 1689, 1458, 1395, 1369, 1278, 1253, 1166, 1095, 947, 845, 754; HRMS (FAB): calcd. for $C_{18}H_{32}NO_8$ $[M+H]^+$ 390.2128, found 390.2122.



Compound 54: To a stirred solution of **53** (160 mg, 0.411 mmol) in CH_2Cl_2 (4.1 mL), DMP (209 mg, 0.493 mmol) was added at room temperature and stirred for 2 h. In the meantime, to a solution of indium (282 mg, 2.46 mmol) in THF (4.1 mL), ammonium chloride (132 mg, 2.46 mmol) was added at room temperature. After 30 min, 3-bromocyclohexene (141 μL, 1.23 mmol) was slowly added at room temperature stirred for 30 min. After completion of DMP oxidation, the mixture was filtered through syringe filter for removing precipitate, and added to indium, ammonium chloride and 3-bromo cyclohexane solution at room temperature. The reaction mixture was stirred for 6 h and filter through a pad of Celite, rinsed with EtOAc and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc = 2:1, *v*/*v*) to yield **54** (141 mg, 73%,

10:1 d.r.) as a colorless oil.

54: R_f = 0.2 (hexane:EtOAc = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.44 (brs, 1H), 6.07 – 5.98 (m, 1H), 5.84 – 5.74 (m, 1H), 5.37 (brs, 1H), 4.38 – 4.20 (m, 2H), 4.07 (d, J = 9.2 Hz, 1H), 2.75 (dd, J = 8.8, 4.6 Hz, 1H), 2.31 – 2.22 (m, 1H), 2.06 – 1.93 (m, 3H), 1.92 – 1.77 (m, 2H), 1.77 – 1.64 (m, 3H), 1.59 – 1.48 (m, 1H), 1.53 (s, 3H), 1.50 (s, 9H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 179.5, 171.3, 153.7, 135.3, 123.6, 84.0, 81.7, 81.5, 79.0, 75.8, 65.6, 47.6, 38.5, 29.4, 28.2 (3C), 27.9 (3C), 25.0, 23.1, 20.6, 20.4; IR (neat, cm^{-1}) υ_{max} 3360, 2980, 2931, 1741, 1713, 1686, 1458, 1369, 1280, 1254, 1157, 1099, 841, 797; HRMS (FAB): calcd. for $C_{24}H_{40}NO_8$ $[M+H]^+$ 470.2754, found 470.2755.



Compound S16: To a stirred solution of **54** (67 mg, 0.14 mmol) in CH_2Cl_2 (2.8 mL) at 0 °C, BCl_3 (1.0 M in CH_2Cl_2, 0.42 mL, 0.42 mmol) was slowly added and stirred for 1 h at the same temperature. The mixture was quenched with MeOH (1 mL) and stirred for 5 min. The resulting mixture was filtered through silica and celite pad (eluting with CH_2Cl_2/MeOH = 20:1, *v*/*v* to CH_2Cl_2/MeOH = 4:1). The mixture was concentrated under reduced pressure to provide crude carboxylic acid **S16** (42 mg). The crude mixture was used in next step without further purification.

Compound S17: To a stirred solution of crude carboxylic acid (42 mg) in CH_2Cl_2 (1.0 mL), pyridine (0.5 mL) and BOP-Cl (107 mg, 0.42 mmol) was added at room temperature. The mixture was stirred at the same temperature for 8 h and quenched with saturated NH_4Cl aqueous solution. The mixture was extracted with EtOAc three times, and the combined organic fraction was dried over $MgSO_4$ and concentrated under reduced pressure to provide crude β-lactone **S17** (35 mg). The crude mixture was used in next step without further purification.

Salinosporamide A (**1**): To a stirred solution of **S17** (35 mg) in MeCN (0.5 mL) and pyridine (0.5 mL), Ph_3PCl_2 (93 mg, 0.28 mmol) was added at room temperature. The mixture was stirred for 4 h and quenched with H_2O (5 mL) and extracted with EtOAc three times, and the combined organic fraction was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc = 1:1, *v*/*v*) to yield salinosporamide A (**1**) (28 mg, 62% for 2 steps) as a white solid.

1: R_f = 0.5 (hexane/EtOAc = 1:1); $[\alpha]^{20}_D$ – 74.5 (*c* 0.5, MeOH); ^{1}H NMR (400 MHz, pyridine-d_5) δ = 10.67 (s, 1H), 7.61 (d, *J* = 9.0 Hz, 1H), 6.48 – 6.40 (m, 1H), 5.91 (ddt, *J* = 10.1, 5.0, 2.6 Hz, 1H), 4.29 (t, *J* = 9.1 Hz, 1H), 4.16 (dt, *J* = 10.7, 6.9 Hz, 1H), 4.05 (dt, *J* = 10.8, 6.7 Hz, 1H), 3.21 (dd, *J* = 7.7, 6.6 Hz, 1H), 2.94 – 2.82 (m, 1H), 2.52 (ddt, *J* = 14.4, 7.8, 6.7 Hz, 1H), 2.41 – 2.28 (m, 2H), 2.10 (s, 3H), 1.98 – 1.89 (m, 2H), 1.78 – 1.64 (m, 2H), 1.44 – 1.32 (m, 1H); ^{13}C NMR (214 MHz,

pyridine-d_5) δ = 176.8, 169.3, 128.9, 128.6, 86.2, 80.2, 70.8, 46.0, 43.2, 39.2, 28.9, 26.3, 25.2, 21.6, 19.9; IR (neat, cm^{-1}) υ_{max} 2929, 2865, 1821, 1690, 1474, 1384, 1354, 1145, 1028, 829; HRMS (FAB): calcd. for $C_{15}H_{21}ClNO_4$ $[M+H]^+$ 314.1159, found 314.1150.

IV-3. Computational studies

IV-3-1. General procedure for molecular energy calculations

Density functional theory (DFT) calculations were carried out using wB97XD functionals with the 6-31+G(d) basis set in Gaussian 16. Transition-state optimizations were performed with the Berny geometry optimization algorithm. Frequency calculations were carried out to ensure that minima structures had no negative frequency and the transition structures had only one imaginary frequency as well as to calculate contributions to the Gibbs free energy (reported at 298.15 K and 1 atm). The connectivity of reactants and products was confirmed by intrinsic reaction coordination (IRC) calculations. All molecules were modeled in the solvent phase (THF/H2O (1:1), solvation model based on density (SMD)).

IV-3-2. Energy profiles for intramolecular aldol cyclization of (2R)-29.

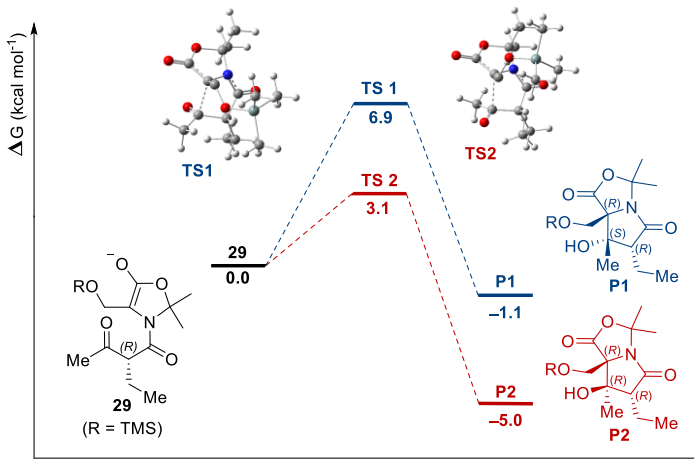


Table S7. Electronic energies (E), zero-point energies (ZPE), enthalpies (H), and Gibbs free energies (G) (in Hartree, Ha) of the compound calculated at the B3LYP, 6-31+G(d) level of theory. The relative Gibbs free energy is shown in kcal/mol, and the imaginary frequency is shown in cm^{-1}.

Compound	E	ZPE	H	G	$\Delta G^{a,b}$	imaginary frequency
29	-1307.5582	-1307.1598	-1307.1317	-1307.2189	0.0	-
TS 1	-1307.5529	-1307.1540	-1307.1274	-1307.2080	6.9	-142.82
TS 2	-1307.5597	-1307.1600	-1307.1336	-1307.2140	3.1	-118.82
P1	-1307.5658	-1307.1659	-1307.1390	-1307.2206	-1.1	
P2	-1307.5734	-1307.1726	-1307.1460	-1307.2268	-5.0	

[a]1 Ha = 627.509391 kcal/mol. [b]Relative energy Gibbs free energy between compound and **29**

IV-4. X-ray Crystallographic data for (2*S*)-18 (CCDC 2179295)

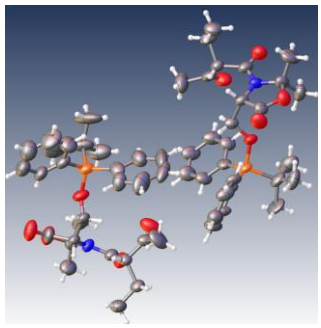


Figure S15. X-ray crystallographic structure of (2*S*)-**18** (dimer form)

Identification code	exp_1774
Empirical formula	$C_{28}H_{37}NO_5Si$
Formula weight	495.67
Temperature/K	293.5(6)
Crystal system	monoclinic
Space group	P21
a/Å	12.288(2)
b/Å	10.6855(17)
c/Å	22.791(5)
α/°	90
β/°	105.19(2)
γ/°	90
Volume/Å3	2888.1(10)
Z	4
ρcalcg/cm3	1.140
μ/mm-1	0.998
F(000)	1064.0
Crystal size/mm3	0.25 × 0.2 × 0.1
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	7.454 to 149.288
Index ranges	$-14 \leq h \leq 15$, $-7 \leq k \leq 13$, $-27 \leq l \leq 25$
Reflections collected	10877
Independent reflections	7900 [Rint = 0.1605, Rsigma = 0.1058]
Data/restraints/parameters	7900/1/645
Goodness-of-fit on F2	1.090
Final R indexes [I>=2σ (I)]	R1 = 0.1265, wR2 = 0.3721
Final R indexes [all data]	R1 = 0.1683, wR2 = 0.3965
Largest diff. peak/hole / e Å-3	0.42/-0.62
Flack parameter	0.02(12)

V. References

[1] R. H. Feling, G. O. Buchanan, T. J. Mincer, C. A. Kauff-man, P. R. Jensen, W. Fenical, *Angew. Chem. Int. Ed*. **2003**, *42*, 355–357; *Angew. Chem.* **2003**, *115*, 369–371.

[2] a) W. Fenical, P. R. Jensen, M. A. Palladino, K. S. Lam, G. K. Lloyd, B. C. Potts, *Bioorg. Med. Chem.* **2009**, *17*, 2175–2180; b) M. Nett, T. A. Gulder, A. J. Kale, C. C. Hughes, B. S. Moore, *J. Med. Chem.* **2009**, *52*, 6163–6167.

[3] T. A. M. Gulder, B. S. Moore, *Angew. Chem., Int. Ed.* **2010**, *49*, 9346–9367; *Angew. Chem*. **2010**, *122*, 9534 – 9556.

[4] a) P. G. Williams, G. O. Buchanan, R. H. Feling, C. A. Kauffman, P. R. Jensen, W. Fenical, *J. Org. Chem.* **2005**, *70*, 6196–6203; b) K. A. Reed, R. R. Manam, S. S. Mitchell, J. Xu, S. Teisan, T.-H. Chao, G. Deyanat-Yazdi, S. T. C. Neuteboom, K. S. Lam, B. C. M. Potts, *J. Nat. Prod.* **2007**, *70*, 269–276.

[5] M. Stadler, J. Bitzer, A. Mayer-Bartschmid, H. Müller, J. Benet-Buchholz, F. Gantner, H.-V. Tichy, P. Reinemer, K. B. Bacon, *J. Nat. Prod.* **2007**, *70*, 246–252.

[6] Enantioselective total synthesis: a) L. R. Reddy, P. Saravanan, E. J. Corey, *J. Am. Chem. Soc.* **2004**, *126*, 6230–6231; b) A. Endo, S. J. Danishefsky, *J. Am. Chem. Soc.* **2005**, *127*, 8298–8299; c) e) T. T. Ling, V. R. Macherla, R. R.

Manam, K. A. McArthur, B. C. M. Potts, *Org. Lett.* **2007**, *9*, 2289–2292; d) K. Takahashi, M. Midori, K. Kawano, J. Ishihara, S. Hatakeyama, *Angew. Chem. Int. Ed.* **2008**, *47*, 6244–6246; *Angew. Chem.* **2008**, *120*, 6340–6342; (e) H. Nguyen, G. Ma, D. Romo, *Chem. Commun.* **2010**, *46*, 4803–4805; (g) Sato, H. Fukuda, M. Tomizawa, T. Masaki, M. Shibuya, N. Kanoh, Y. Iwabuchi, *Heterocycles* **2010**, *81*, 2239–2246; h) H. Nguyen, G. Ma, T. Gladysheva, T. Fremgen, D. Romo, *J. Org. Chem.* **2011**, *76*, 2–12; i) Y. Kaiya, J. Hasegawa, T. Momose, T. Sato, N. Chida, *Chem. Asian J.* **2011**, *6*, 209–219; j) N. Satoh, S. Yokoshima, T. Fukuyama, *Org. Lett*. **2011**, *13*, 3028–3031; k) L. B. Marx, J. W. Burton, *Chem. Eur. J*. **2018**, *24*, 6747–6754; l) H. Gholami, A. Kulshrestha, O. K. Favor, R. J. Staples, B. Borhan, *Angew. Chem. Int. Ed.* **2019**, *58*, 10110–10113; *Angew. Chem.* **2019**, *131*, 10216–10219; For racemic total synthesis: m) N. P. Mulholland, G. Pattenden, L. A. S. Walters, *Org. Biomol. Chem.* **2006**, *4*, 2845–2846; n) G. Ma, H. Nguyen, D. Romo, *Org. Lett.* **2007**, *9*, 2143–2146; (o) N. P. Mulholland, G. Pattenden, I. A. S. Walters, *Org. Biomol. Chem.* **2008**, *6*, 2782–2789.

[7] For formal synthesis: a) V. Caubert, J. Masse, P. Retailleau, N. Langlois, *Tetrahedron Lett*. **2007**, *48*, 381–384; b) I. V. Margalef, L. Rupnicki, H. W. Lam, *Tetrahedron* **2008**, *64*, 7896–7901; c) T. Momose, Y. Kaiya, J. Hasegawa, T. Sato, N. Chida, *Synthesis* **2009**, *17*, 2983–2991; d) J. R. Struble, J. W. Bode,

Tetrahedron **2009**, *65*, 4957–4967; e) R. A. Mosey, J. J. Tepe, *Tetrahedron Lett.* **2009**, *50*, 295–297; f) T. T. Ling, B. C. Potts, V. R. Macherla, *J. Org. Chem.* **2010**, *75*, 3882–3885; g) A. W. J. Logan, S. J. Sprague, R. W. Foster, L. B. Marx, V. Garzya, M. S. Hallside, A. L. Thompson, J. W. Burton, *Org. Lett.* **2014**, *16*, 4078–4081.

[8] a) J. H. Kim, S. Lee, S. Kim, *Angew. Chem. Int. Ed.* **2015**, *54*, 10875–10878; *Angew. Chem.* **2015**, *127*, 11025–11028; b) J. H. Kim, I. Kim, Y. Song, M. J. Kim, S. Kim, *Angew. Chem. Int. Ed.* **2019**, *58*, 11018–11022; *Angew. Chem.* **2019**, *131*, 11134–11138; c) Y. Song, J. H. Kim, Y. C. Kim, S. Kim, *Chem. Eur. J*. **2021**, *27*, 10731–10736.

[9] J. H. Kim, H. Jeon, C. Park, S. Park, S. Kim, *Angew. Chem. Int. Ed.* **2021**, *60*, 12060–12065; *Angew. Chem.* **2021**, *133*, 12167–12172.

[10] For reviews, see: a) H. W. Zhao, D. C. Hsu, P. R. Carlier, *Synthesis* **2005**, 1–16; b) D. Campolo, S. Gastaldi, C. Roussel, M. P. Bertrand, M. Nechab, *Chem. Soc. Rev.* **2013**, *42*, 8434–8466; c) V. Alezra, T. Kawabata, *Synthesis* **2016**, *48*, 2997–3016.

[11] For reviews, see: a) J. Steinreiber, K. Faber, H. Griengl, *Chem. Eur. J.* **2008**, *14*, 8060–8072; b) H. Pellissier, *Tetrahedron* **2011**, *67*, 3769–3802; c) H. Pellissier, *Tetrahedron* **2016**, *72*, 3133–3150.

[12] a) M. Branca, S. Pena, R. Guillot, D. Gori, V. Alezra, C. Kouslovsky, *J. Am.*

Chem. Soc. **2009**, *131*, 10711– 10718; b) B. Viswambharan, D. Gori, R. Guillot, C. Kouklovsky, V. Alezra, *Org. Lett.* **2014**, *16*, 788–791.

[13] D. A. Evans, M. D. Ennis, T. Le, N. Mandel, G. Mandel, *J. Am. Chem. Soc.* **1984**, *106*, 1154–1156.

[14] O. Popik, B. Zambroń, J. Mlynarski, *Eur. J. Org. Chem.* **2013**, 7484-7487.

[15] The compound *ent*-**21** was rapidly converted to **27** through the oxazolidinone ring opening reaction with NaOEt in EtOH, while **25** was unreactive under the same conditions.

[16] The absolute stereochemistry of *ent*-**21** was determined by the synthesis of salinosporamide B (**2**) from *ent*-**21**. The sign of the optical rotation ($[\alpha]^{20}_{D}$= +49.4 (*c* 0.3, MeOH)) for the obtained **2** was opposite that of the optical rotation reported for the natural product ($[\alpha]^{25}_{D}$= –54.5(*c* 0.286, MeOH)).

[17] The stereochemistry of (2*S*)-**18** was determined by X-ray crystallographic analysis. See the supporting information for details.

[18] As the reaction time was prolonged, **28** was formed, albeit in small amounts, presumably due to the presence of inadvertent moisture.

[19] For examples of aldol/retro-aldol equilibrium in bicyclic pyroglutamates, see: a) M. G. Moloney, M. Yaqoob, *Tetrahedron Lett.* **2008**, *49*, 6202–6204; b) L. Josa-Culleré, C. Towers, F. Willenbrock, V. M. Macaulay, K. E. Christensen, M. G. Moloney, *Org. Biomol. Chem.* **2017**, *15*, 5373–5379.

[20] a) T. C. Bruice, T. H. Fife, *J. Am. Chem. Soc.* **1962**, *84*, 1973–1979; b) Fife, T. H.; T. H. Fife, B. M. Benjamin, *J. Am. Chem. Soc.* **1973**, *95*, 2059–2061; c) J. E. Hutchins, T. H. Fife, *J. Am. Chem. Soc.* **1973**, *95*, 3786–3790; d) F. Cuminet, S. Caillol, É. Dantras, É. Leclerc, V. Ladmiral, *Macromolecules* **2021**, *54*, 3927–3961.

[21] For examples of enzymatic or catalytic hydrolytic dynamic kinetic resolution (DKR), see: a) M. M. Jones, J. M. J. Williams, *Chem. Commun.* **1998**, 2519–2520; b) B. Xia, J. Xu, Z. Xiang, Y. Cen, Y. Hu, X. Lin, Q. Wu, *ACS Catal.* **2017**, *7*, 4542–4549; c) E. Yama-moto, K. Wakafuji, Y. Furutachi, K. Kobayashi, T. Kamachi, M. Tokunaga, *ACS Catal.* **2018**, *8*, 5708–5713.

[22] Y. Li, Z. Wang, X. Huang, Preparation Method of Palbociclib. CN112920182A, 2021.

[23] The replacement of $CoCl_2$ with $NiCl_2$ resulted in lower diastereoselectivity (d.r. = 8:1). When the reaction was performed with Adam's catalyst under hydrogen gas, the d.r. was only 2.7:1.

[24] (a) M. Moreno-Mañas, R. M. Sebastiàn, A. Vallribera, E. Molins, *Tetrahedron* **1995**, *51*, 10795–10800; b) J. Clariana, N. Galvez, C. Marchi, M. Moreno-Mañas, A. Vallribera, E. Molins, *Tetrahedron* **1999**, *55*, 7331–7344; c) N. Galvez, E. Molins, M. Moreno-Mañas, R. M. Sebastiàn, N. Serra, E. Trepat, A. Vallribera, *J. Heterocycl. Chem.*, **2000**, *37*, 895–905; (d) M. De Rosa, L.

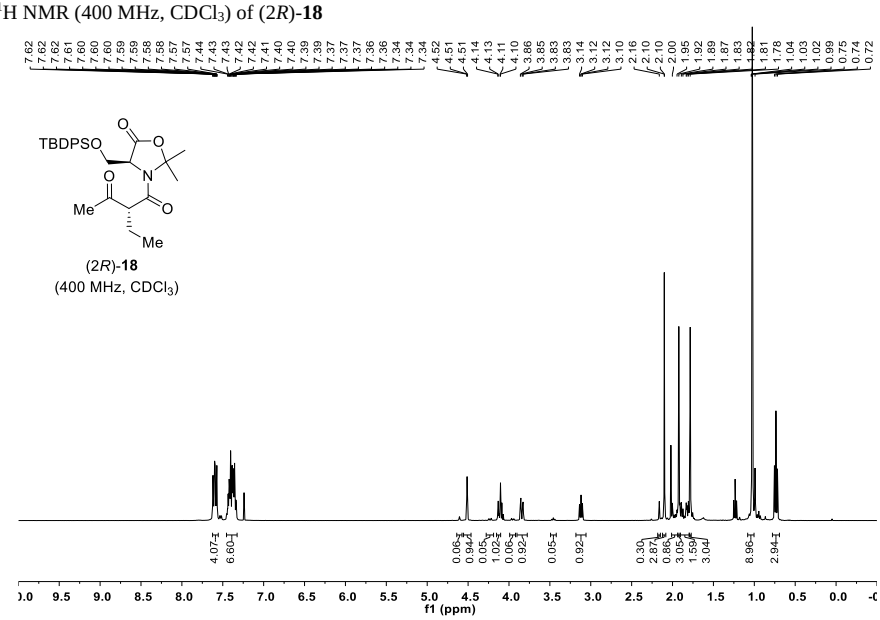
Palombi, M. R. Acocella, M. Fruilo, R. Villano, A. Soriente, A. Scettri, *Chirality* **2003**, *15*, 579–583; (e) O. S. Shneider, E. Pisarevsky, P. Fristrup, A. M. Szpilman, *Org. Lett.* **2015**, *17*, 282–285.

[25] K. Bell, D. V. Sadasivam, I. R. Gudipati, H. Ji, D. Birney, *Tetrahedron Lett.* **2009**, *50*, 1295−1297.

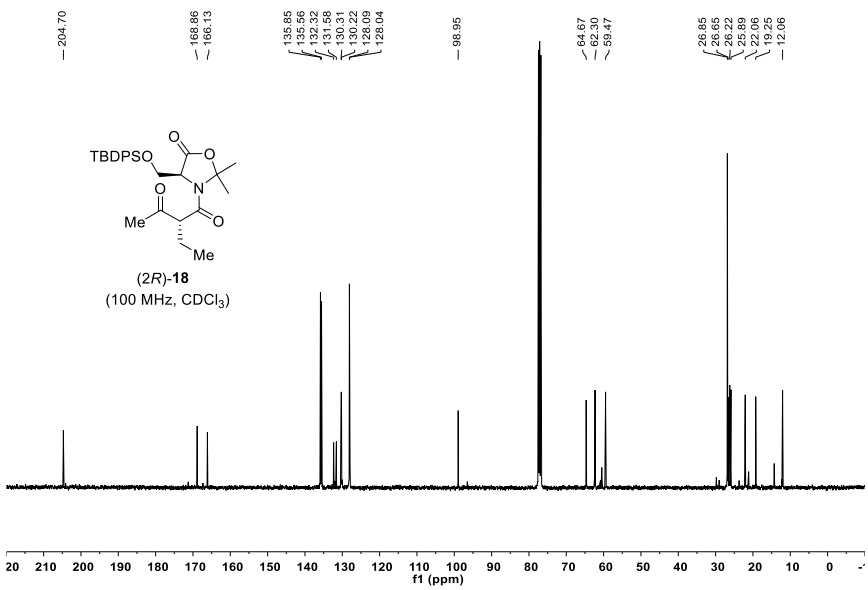
Appendix I

Spectral Analysis

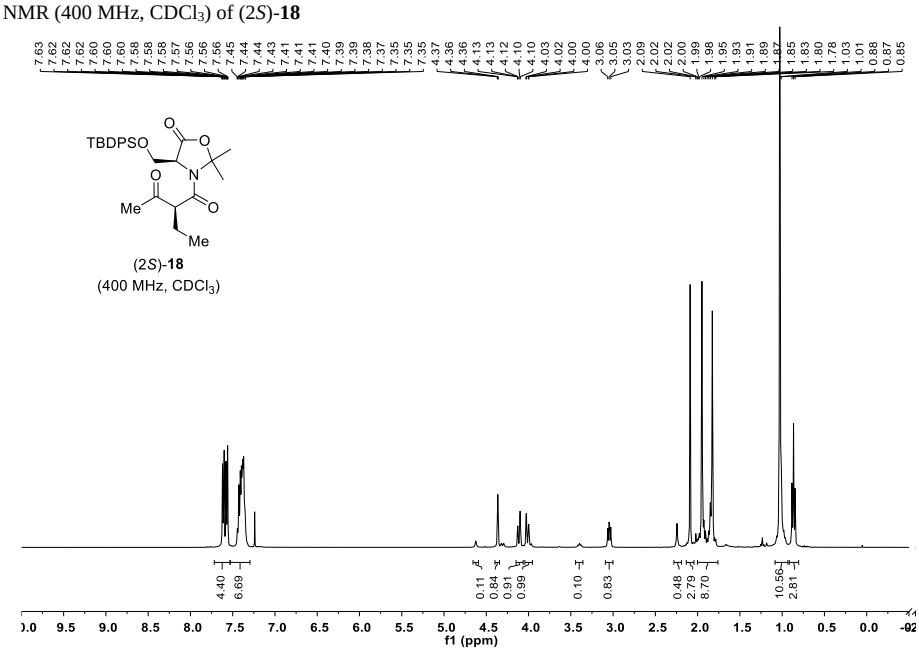
^{1}H NMR (400 MHz, $CDCl_3$) of (2*R*)-**18**



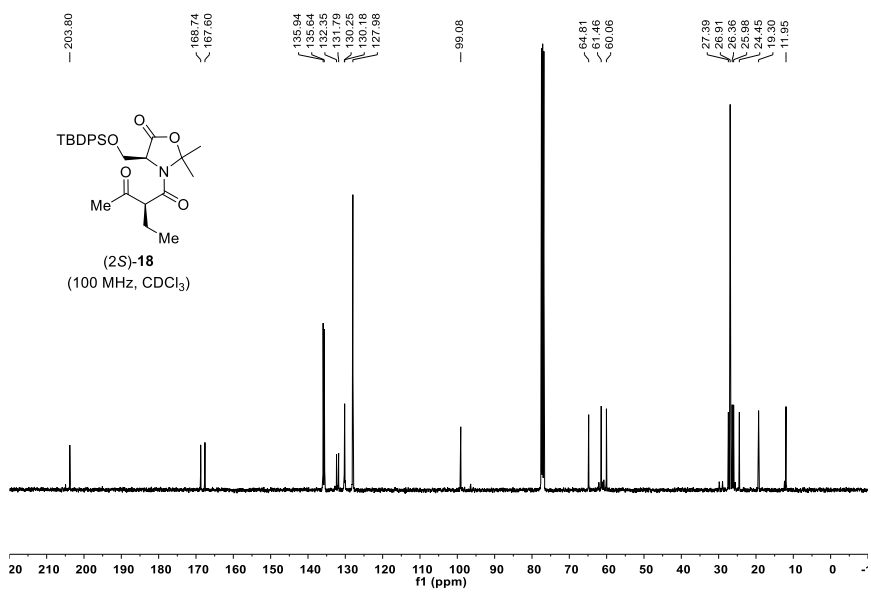
^{13}C NMR (100 MHz, $CDCl_3$) of (2*R*)-**18**



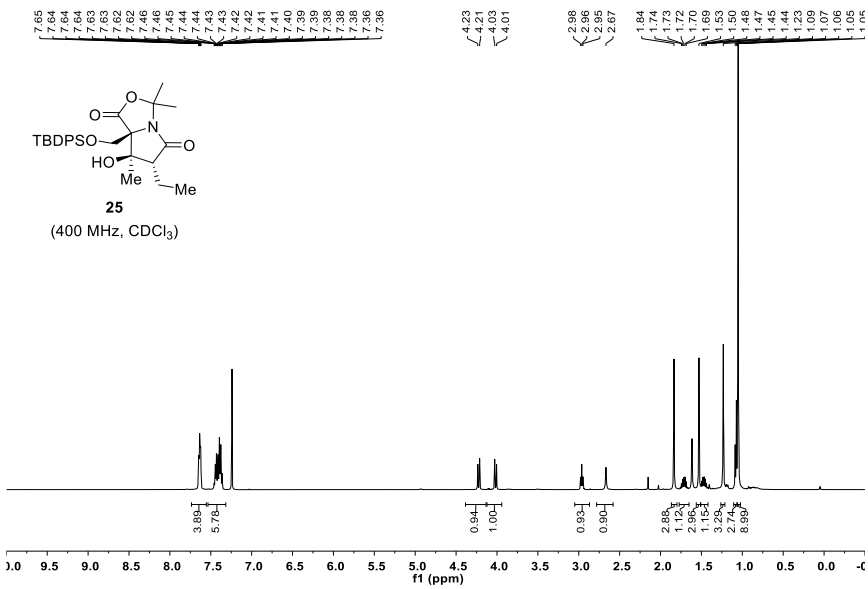
^{1}H NMR (400 MHz, $CDCl_3$) of (2*S*)-**18**



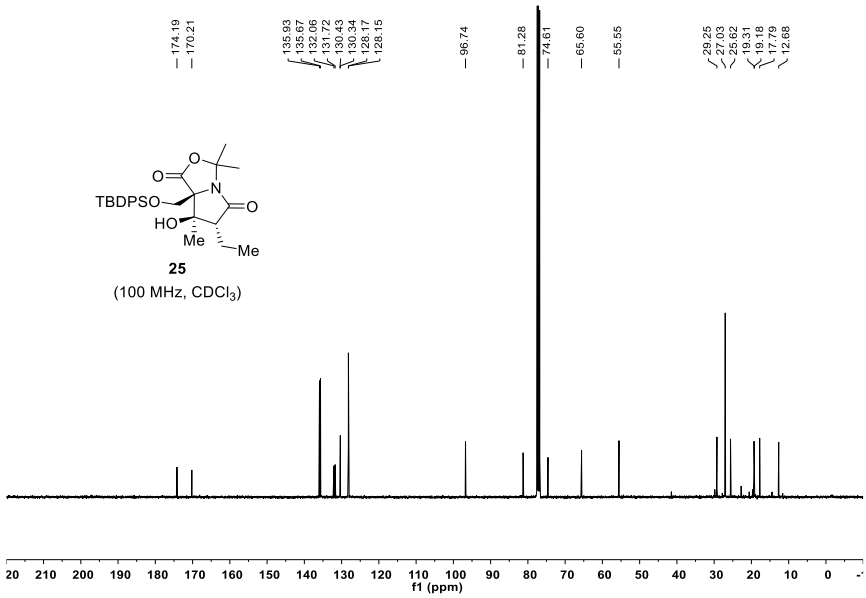
^{13}C NMR (100 MHz, $CDCl_3$) of (2*S*)-**18**

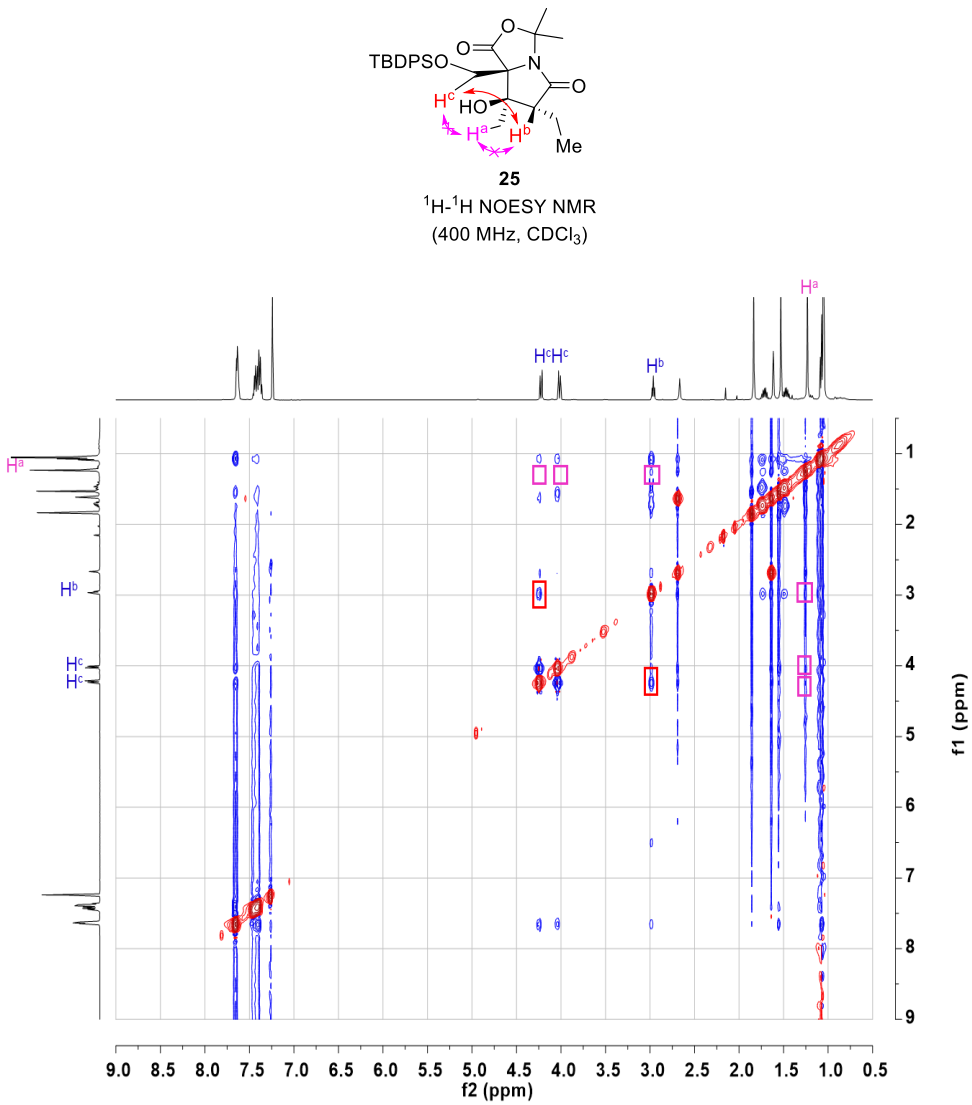


^{1}H NMR (400 MHz, $CDCl_3$) of **25**

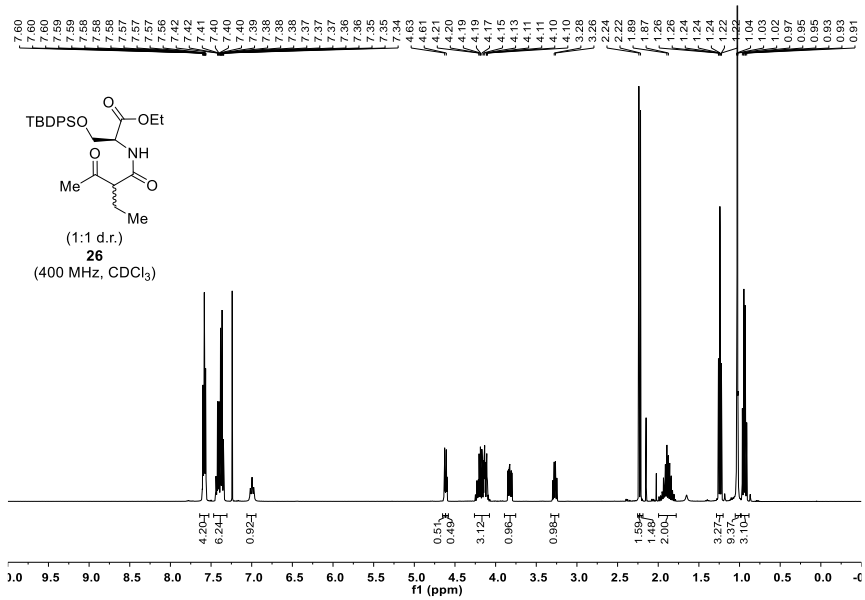


^{13}C NMR (100 MHz, $CDCl_3$) of **25**

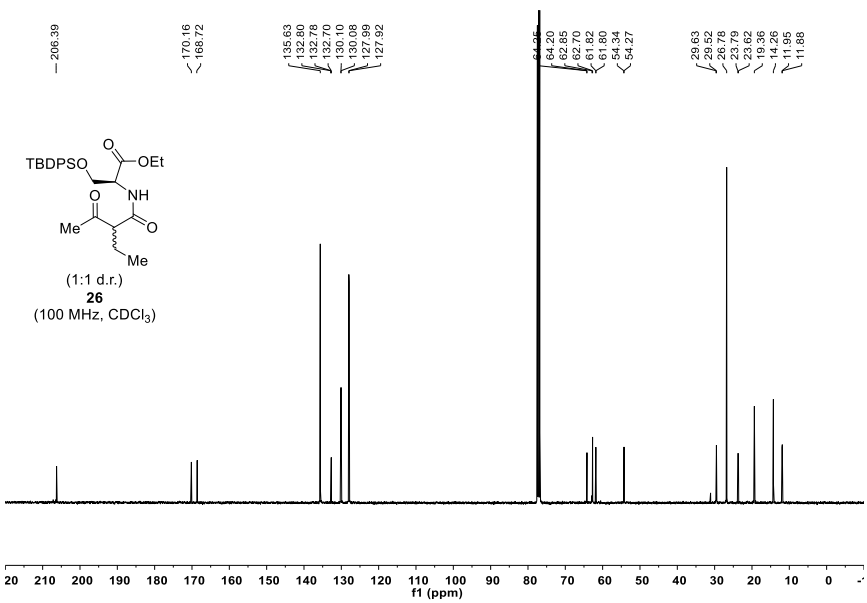



TBDPSO
O
O
N
O
Me
HO
Hc
Ha
Hb
25
1H-1H NOESY NMR
(400 MHz, CDCl3)
Ha
HcHc
Hb
f1 (ppm)
f2 (ppm)
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
1 2 3 4 5 6 7 8 9

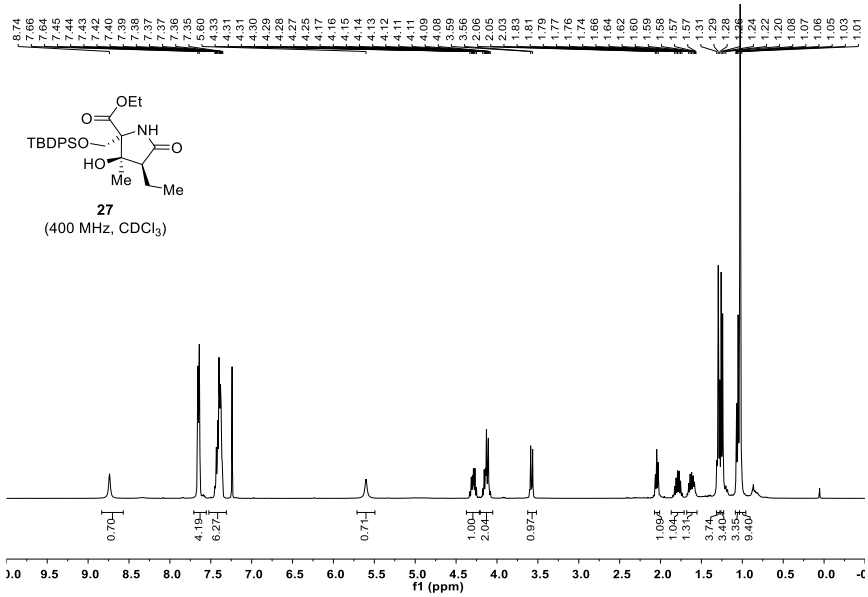
^{1}H NMR (400 MHz, $CDCl_3$) of **26**



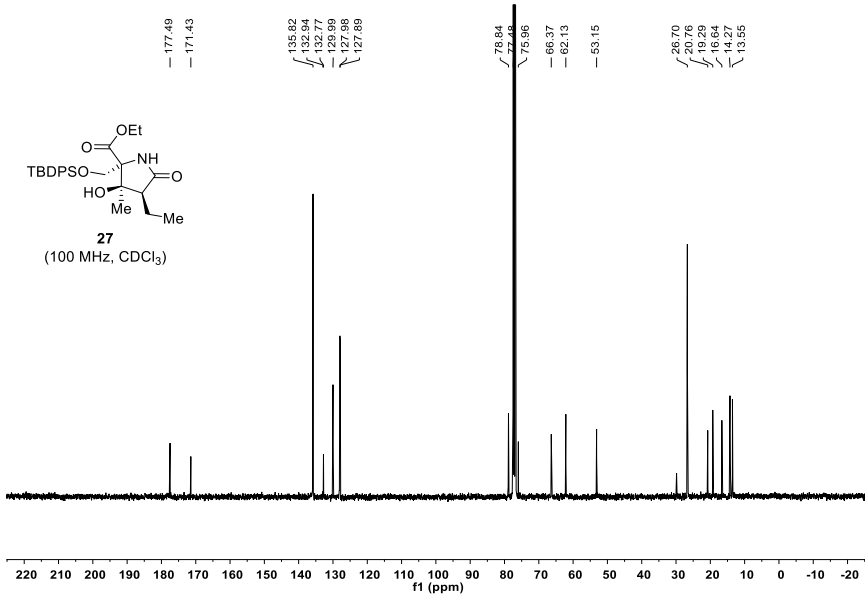
^{13}C NMR (100 MHz, $CDCl_3$) of **26**

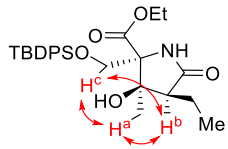


^{1}H NMR (400 MHz, $CDCl_3$) of **27**



^{13}C NMR (100 MHz, $CDCl_3$) of **27**

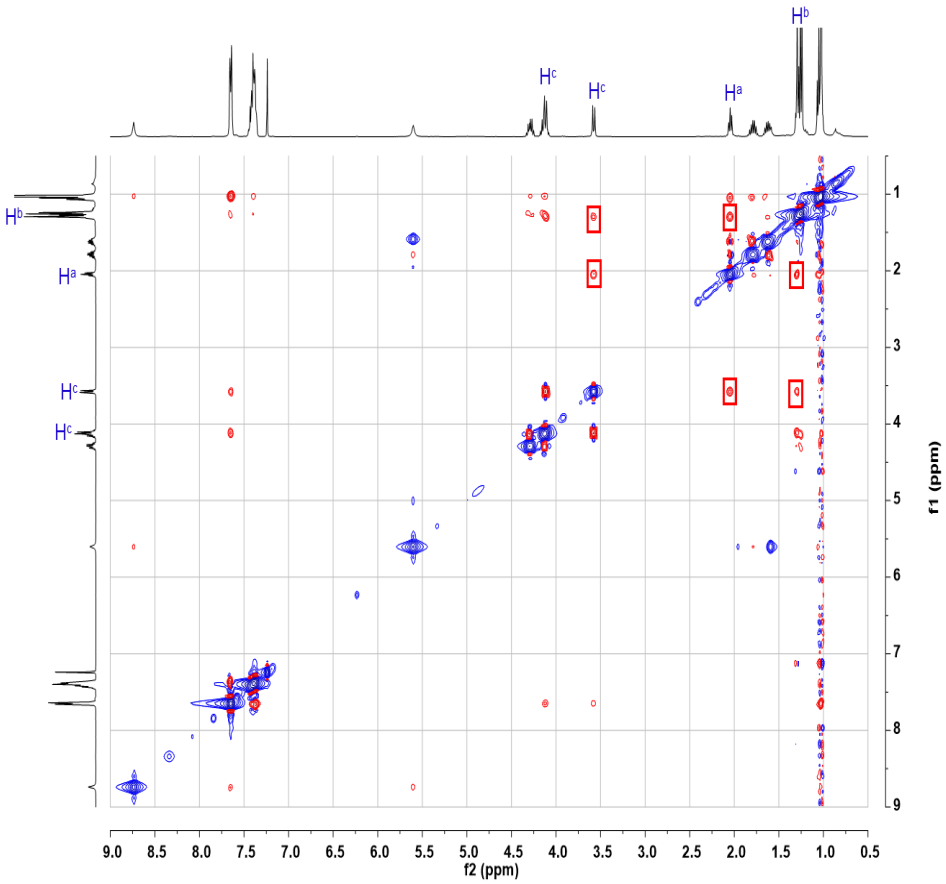




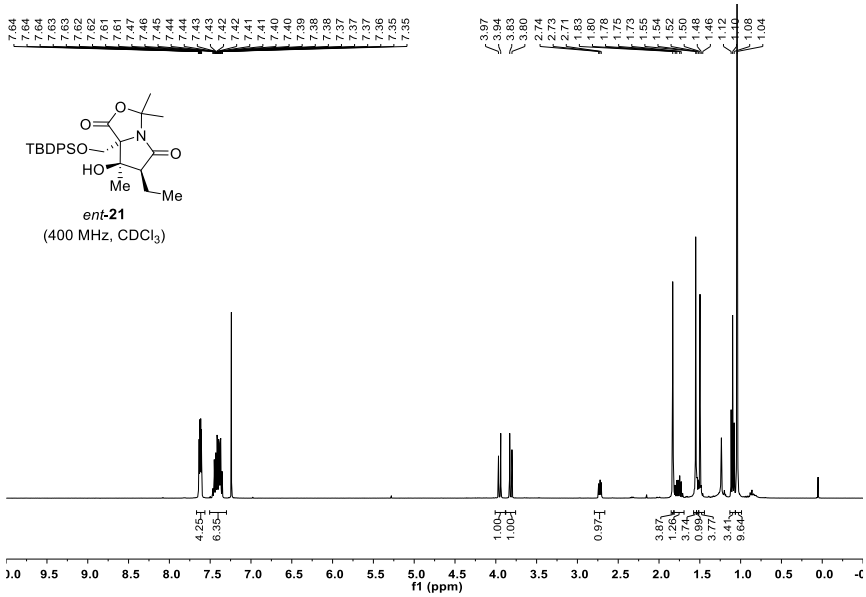
27

^{1}H-^{1}H NOESY NMR

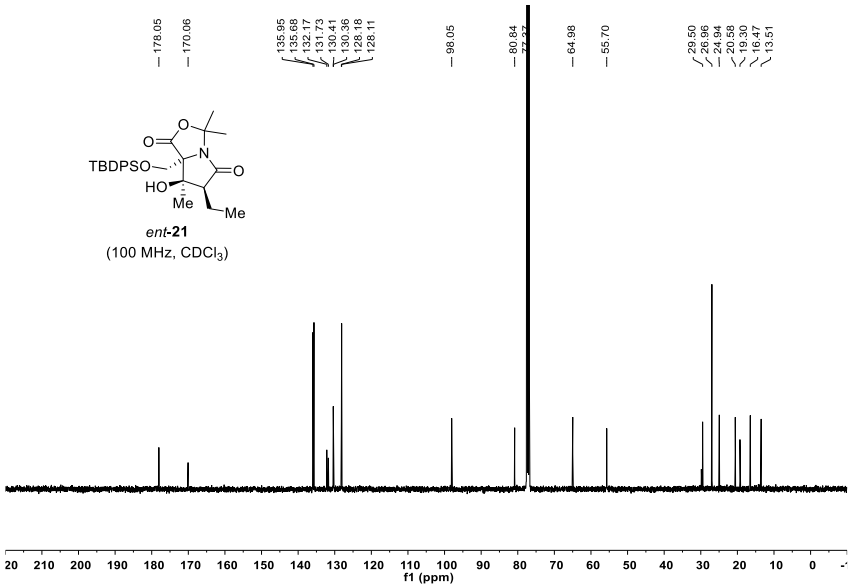
(400 MHz, $CDCl_3$)

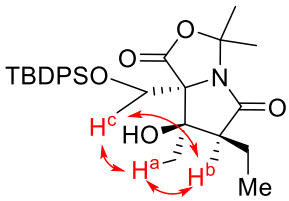


^{1}H NMR (400 MHz, $CDCl_3$) of *ent*-**21**



^{13}C NMR (100 MHz, $CDCl_3$) of *ent*-**21**

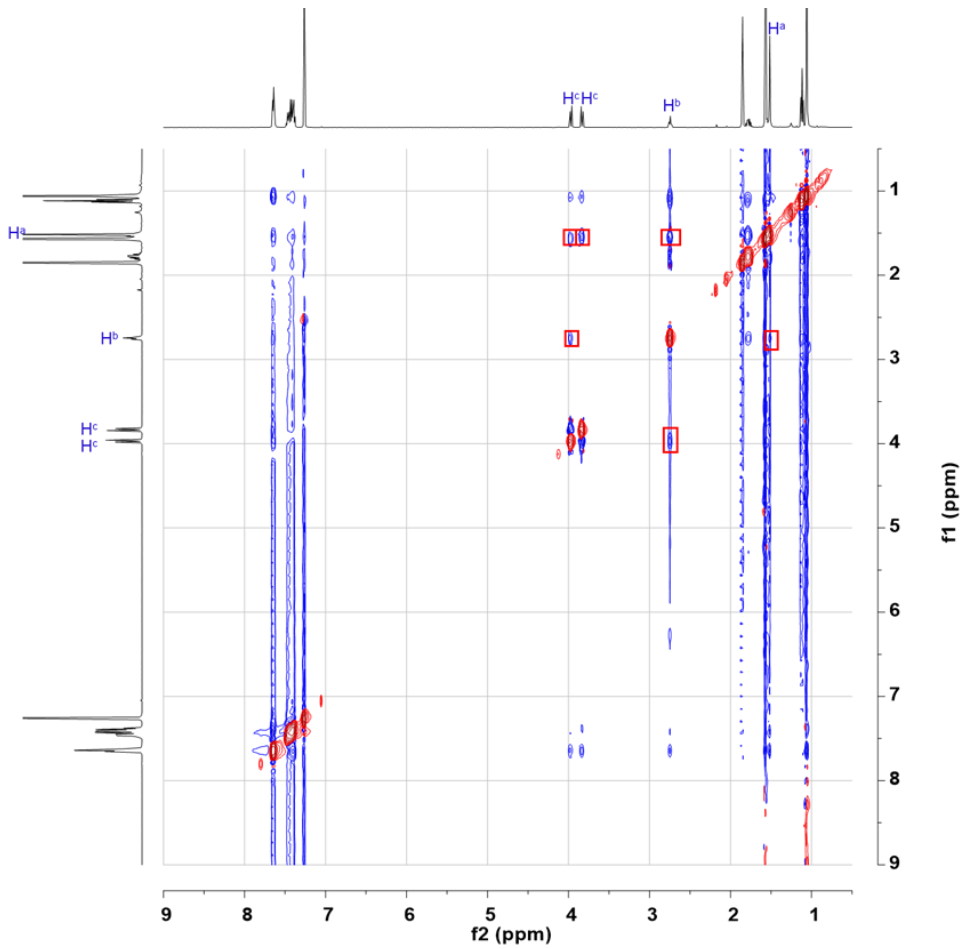




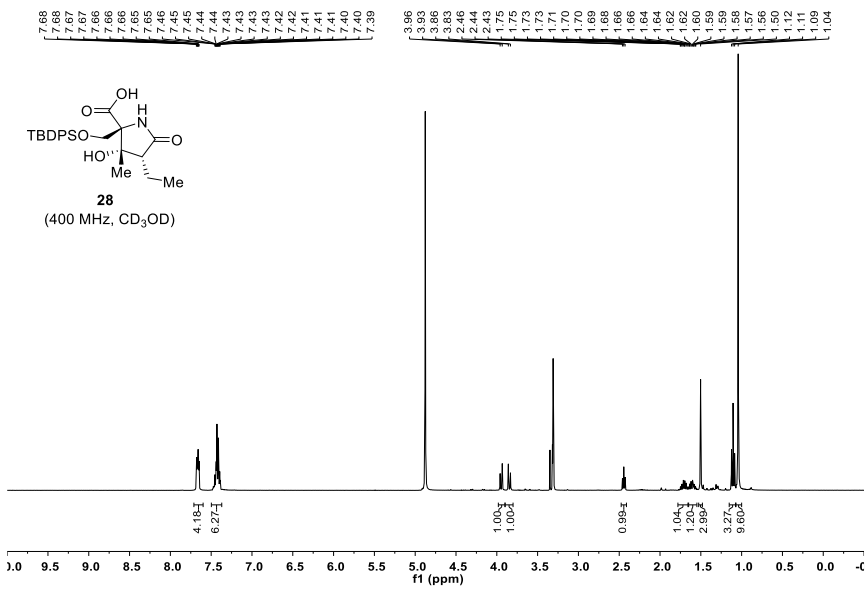
ent-**21**

^{1}H-^{1}H NOESY NMR

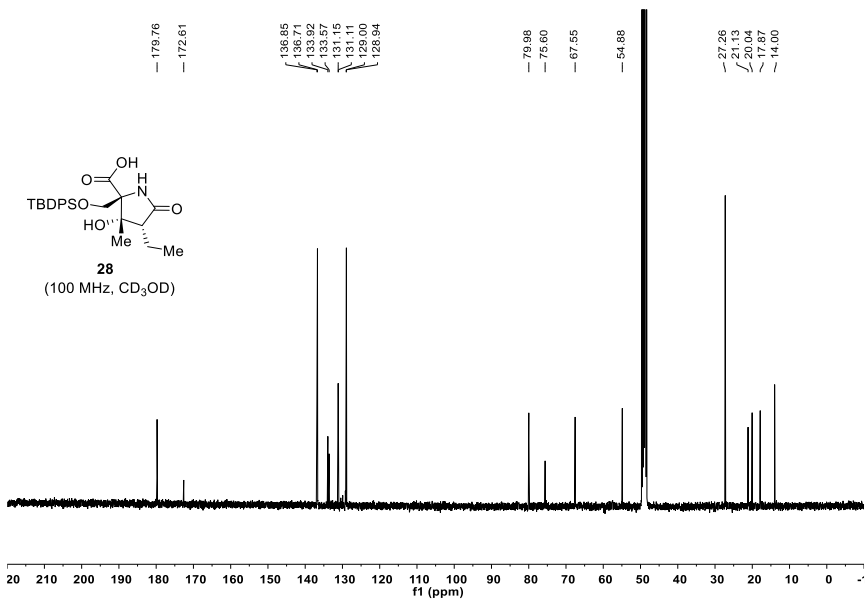
(400 MHz, $CDCl_3$)



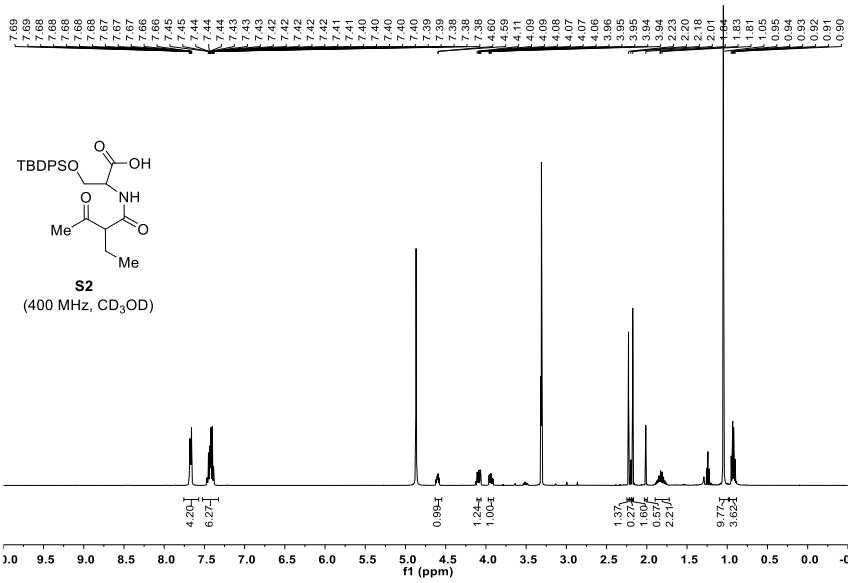
^{1}H NMR (400 MHz, CD_3OD) of **28**



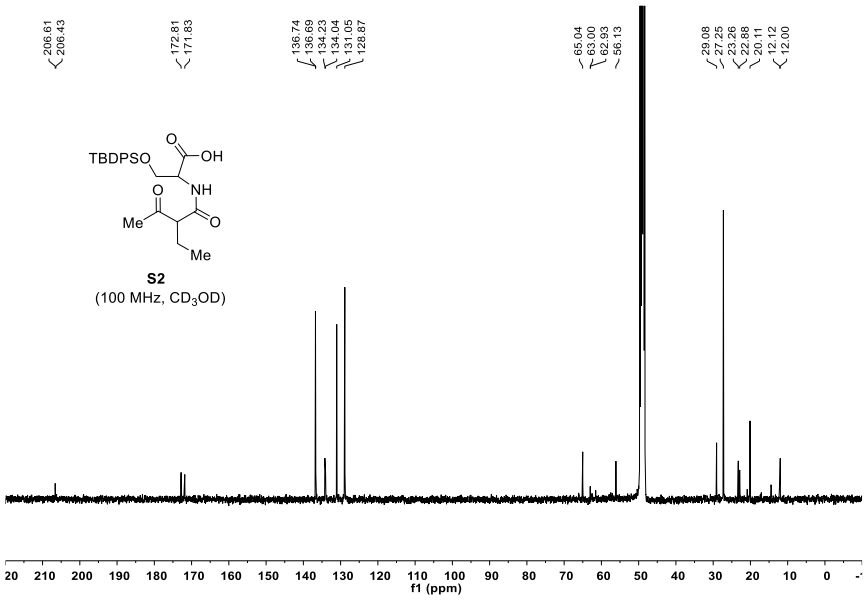
^{13}C NMR (100 MHz, CD_3OD) of **28**



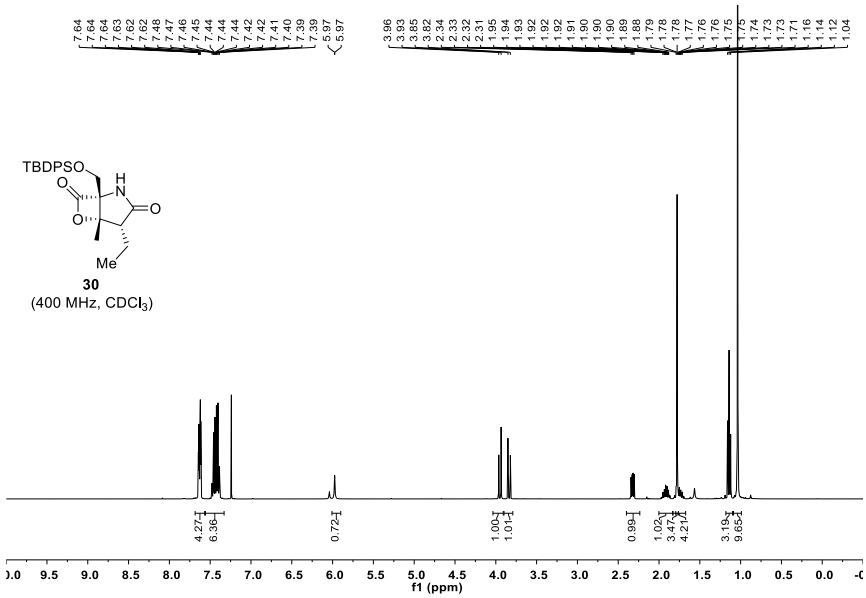
^{1}H NMR (400 MHz, CD_3OD) of **S2**



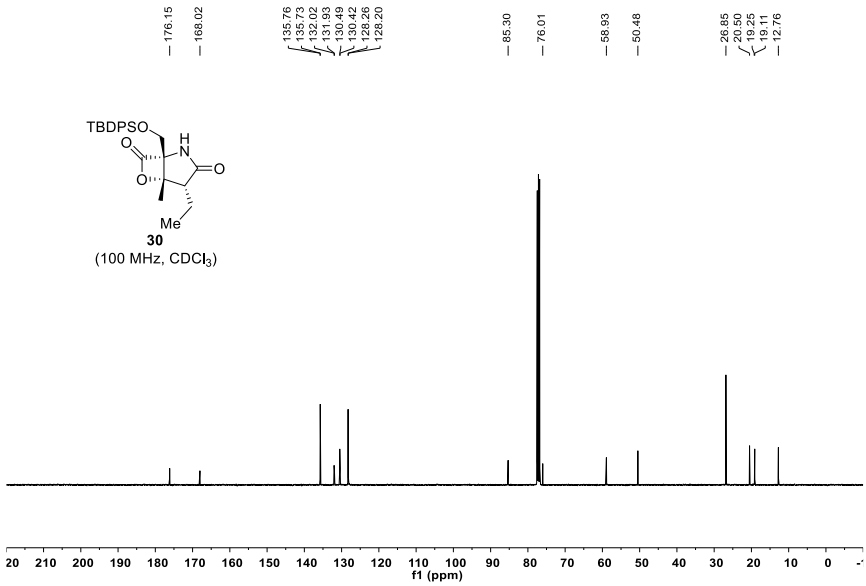
^{13}C NMR (100 MHz, CD_3OD) of **S2**



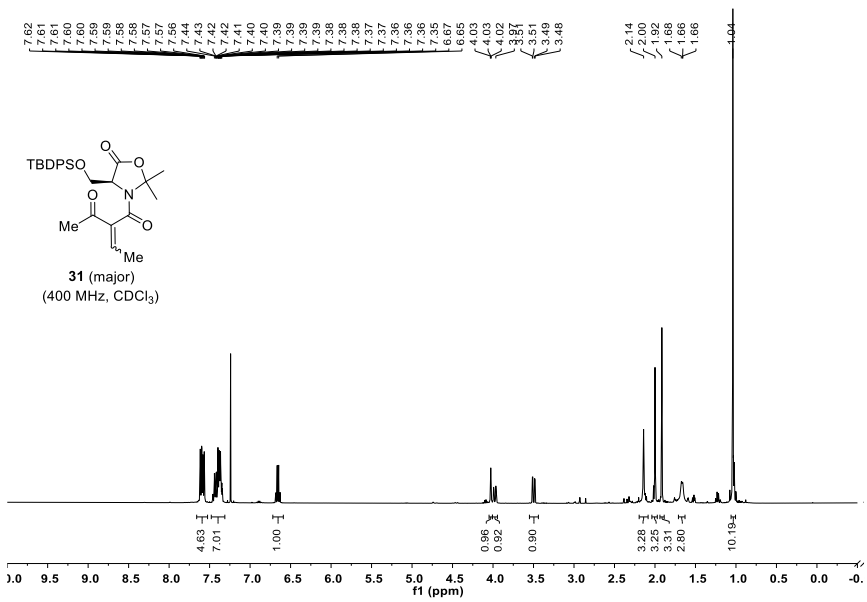
^{1}H NMR (400 MHz, $CDCl_3$) of **30**



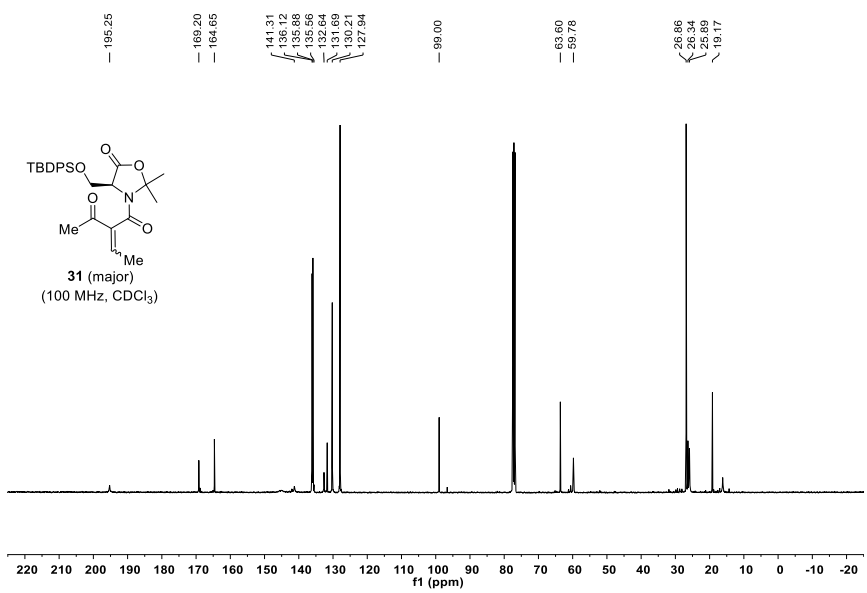
^{13}C NMR (100 MHz, $CDCl_3$) of **30**



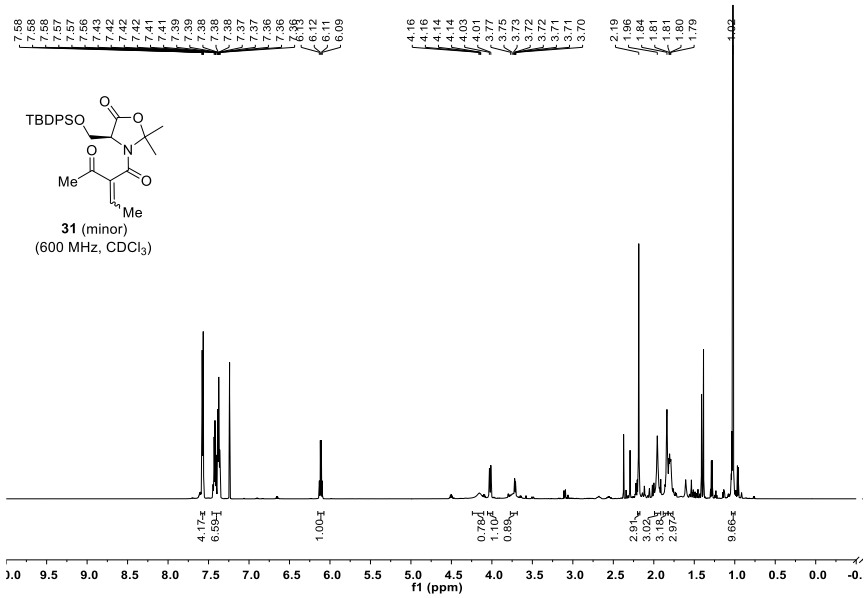
^{1}H NMR (400 MHz, $CDCl_3$) of **31** (major)



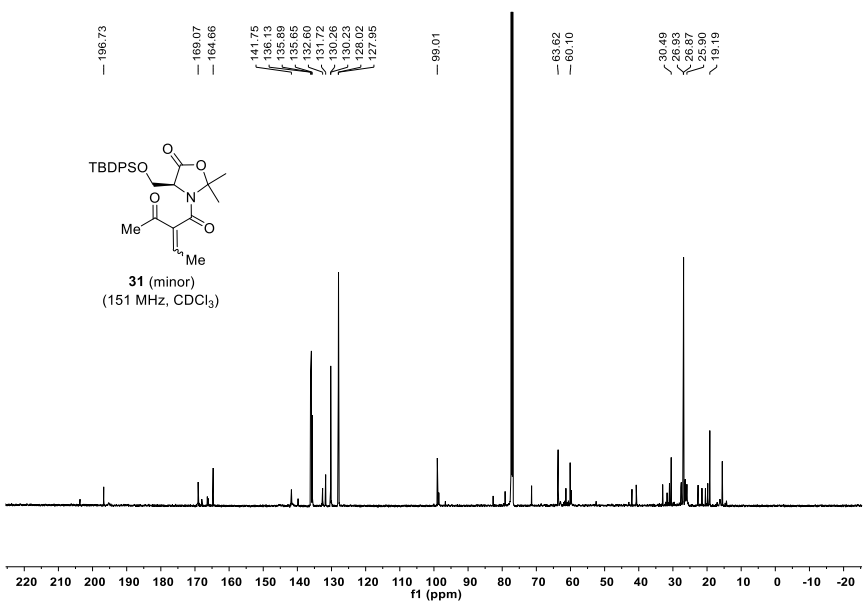
^{13}C NMR (100 MHz, $CDCl_3$) of **31** (major)



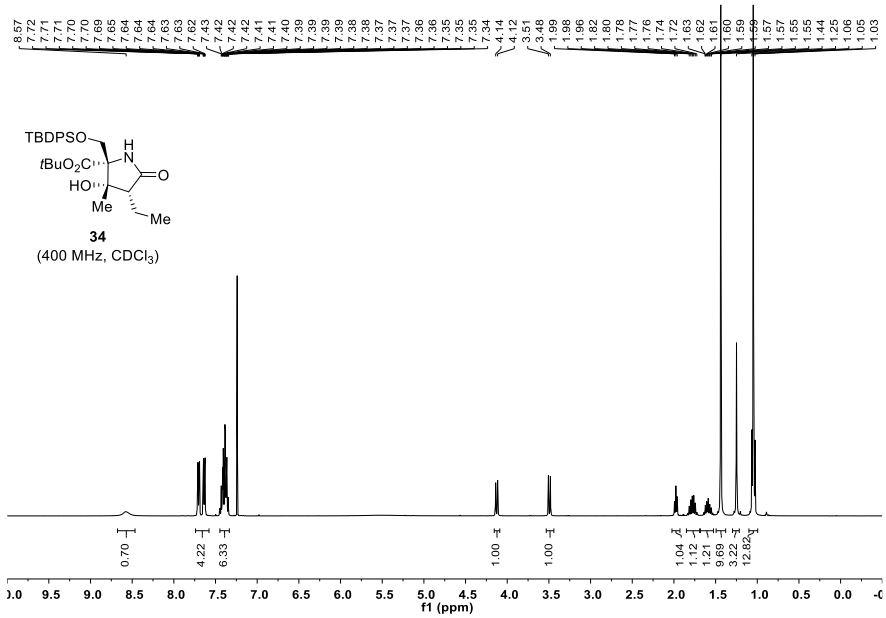
^{1}H NMR (600 MHz, $CDCl_3$) of **31** (minor)



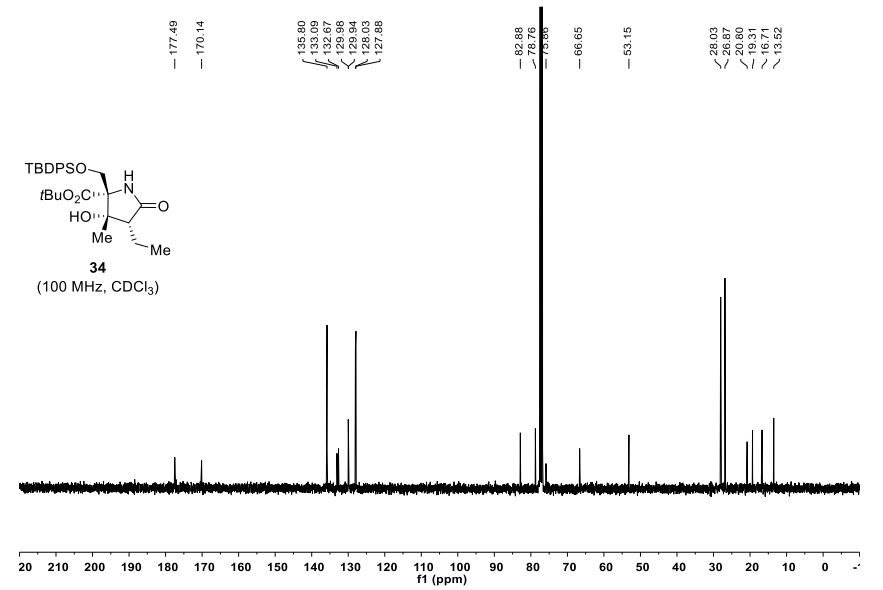
^{13}C NMR (151 MHz, $CDCl_3$) of **31** (minor)



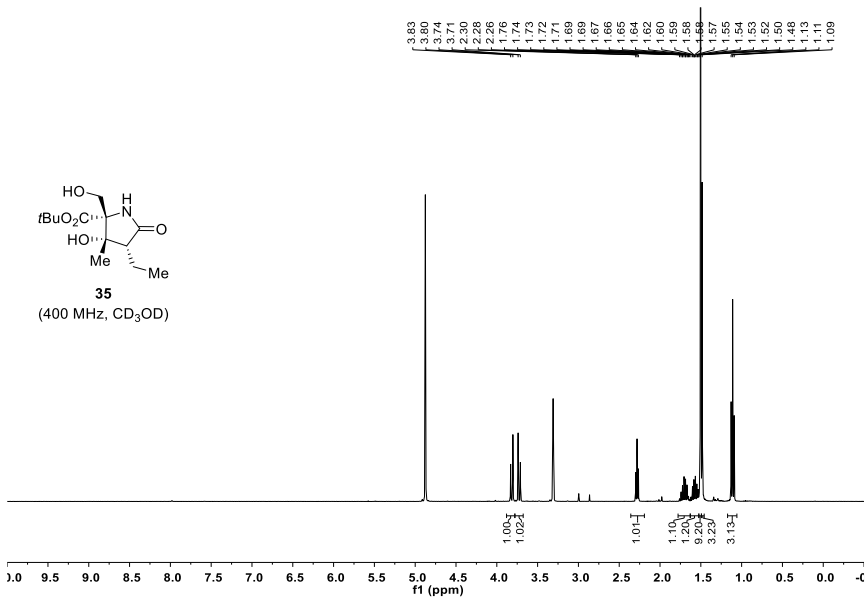
^{1}H NMR (400 MHz, $CDCl_3$) of **34**



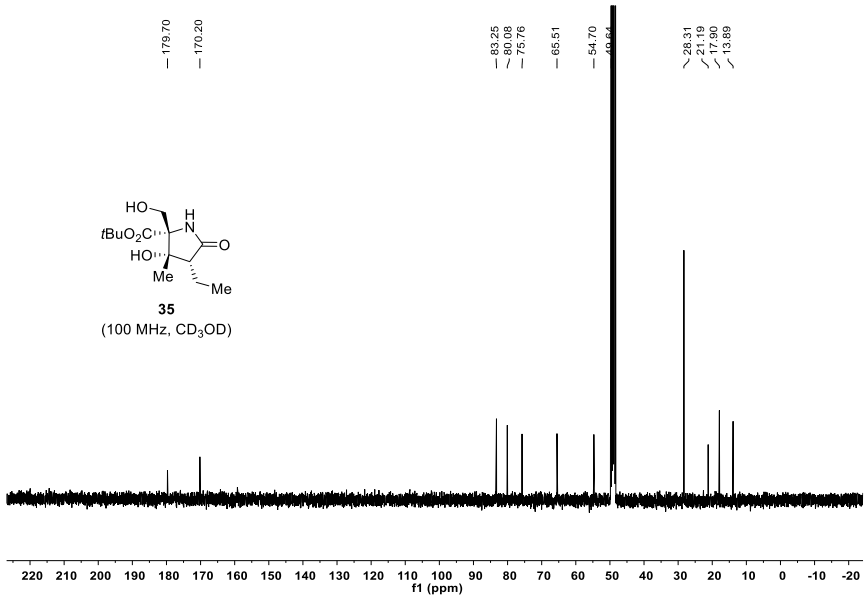
^{13}C NMR (100 MHz, $CDCl_3$) of **34**



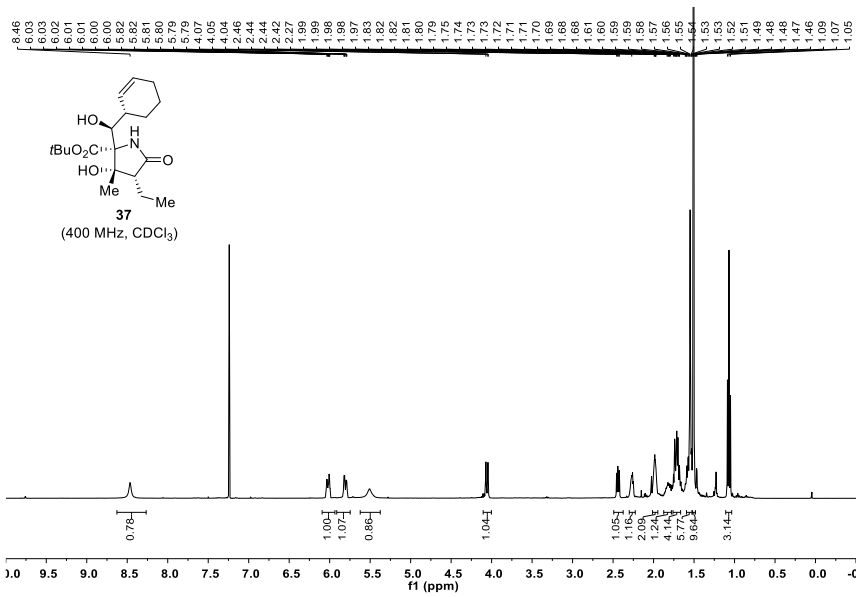
^{1}H NMR (400 MHz, CD_3OD) of **35**



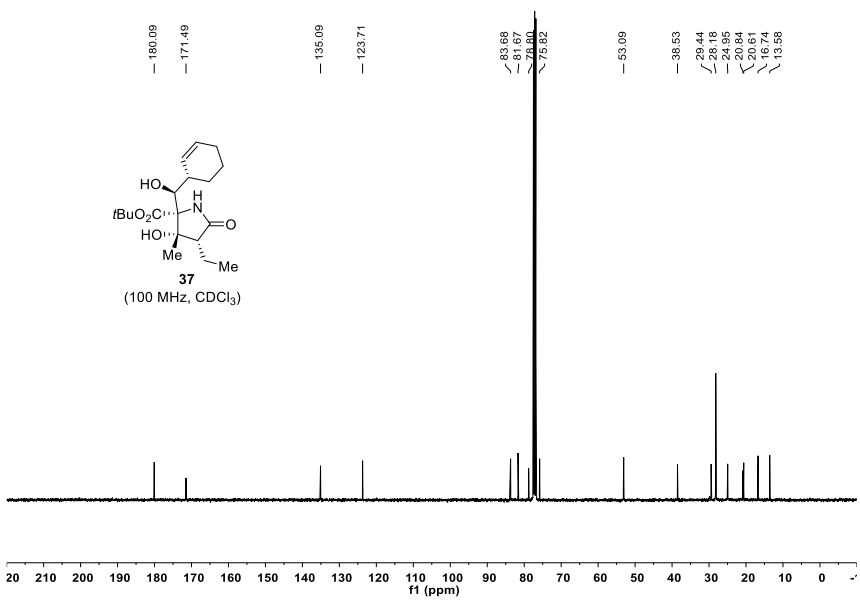
^{13}C NMR (100 MHz, CD_3OD) of **35**



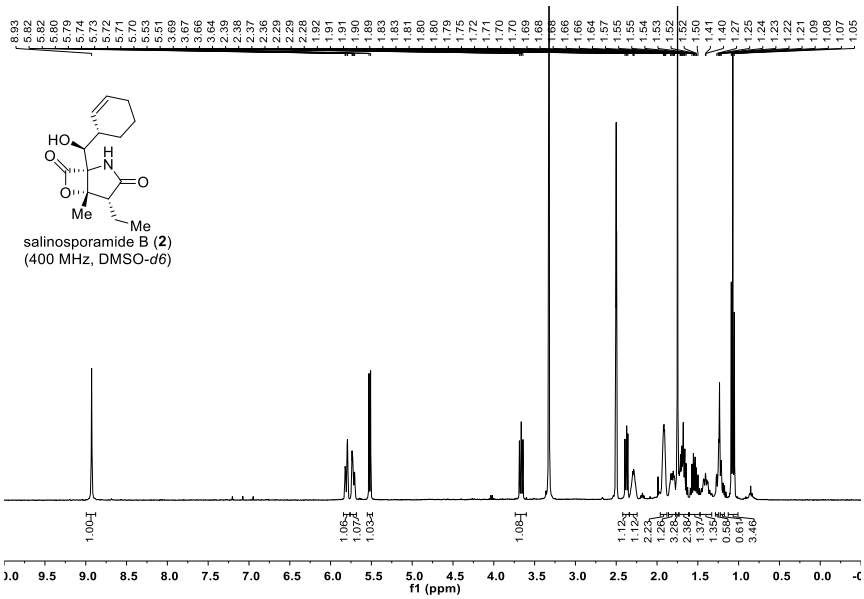
^{1}H NMR (400 MHz, $CDCl_3$) of **37**



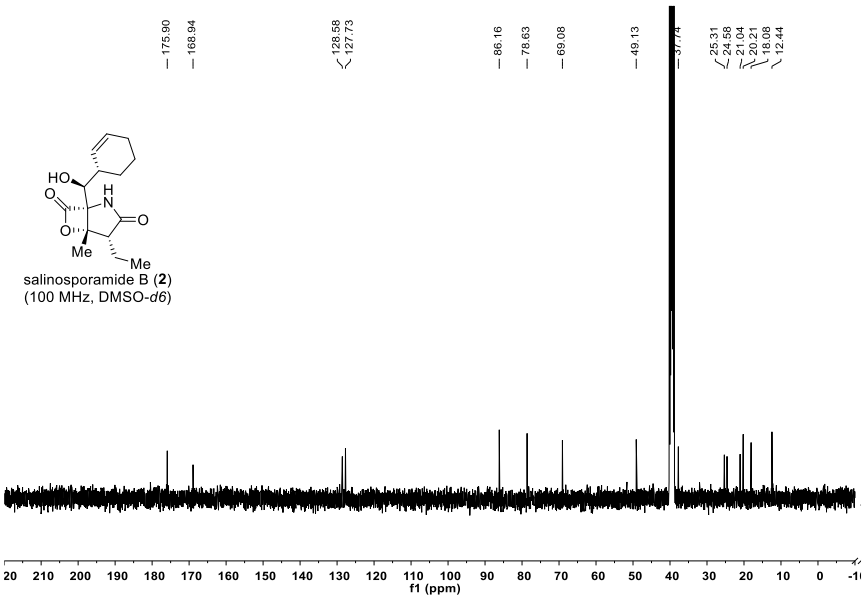
^{13}C NMR (100 MHz, $CDCl_3$) of **37**



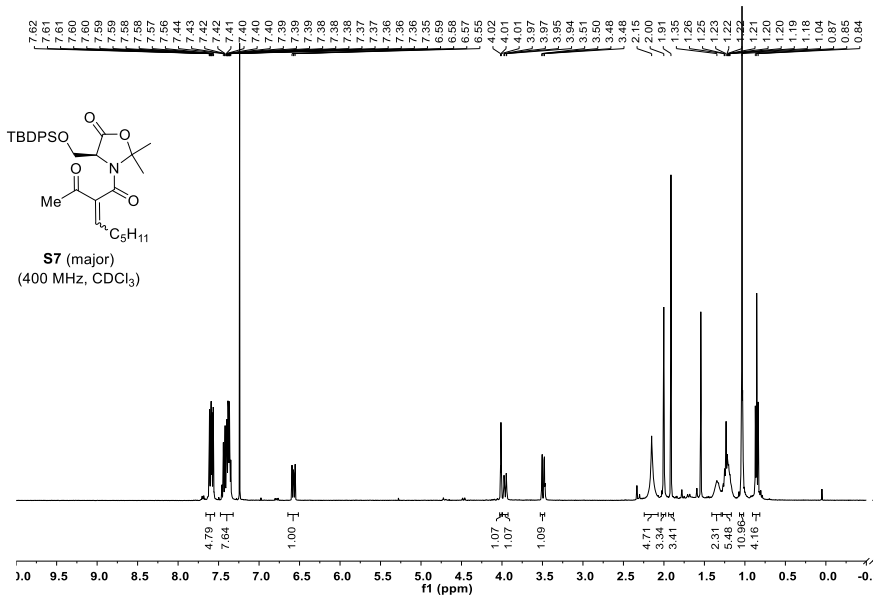
^{1}H NMR (400 MHz, DMSO-d_6) of salinosporamide B (**2**)



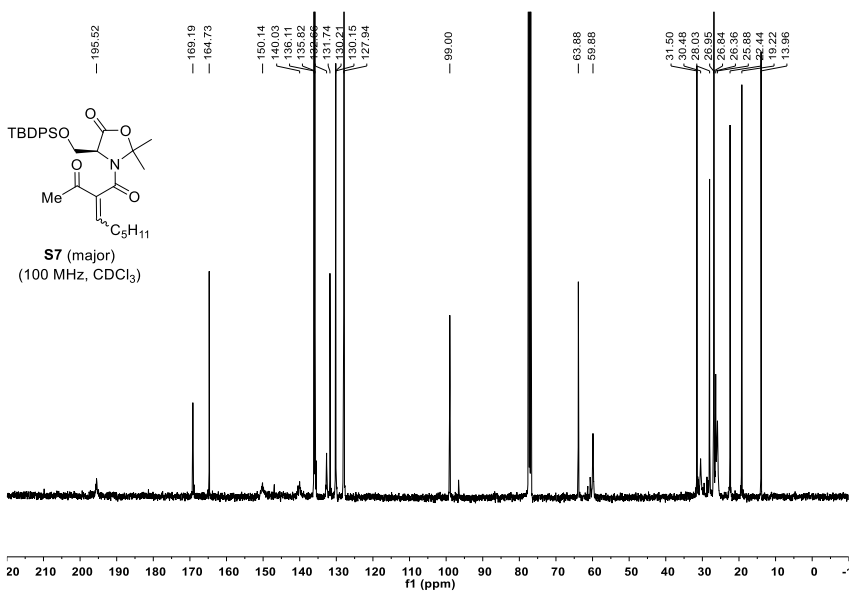
^{13}C NMR (400 MHz, DMSO-d_6) of salinosporamide B (**2**)



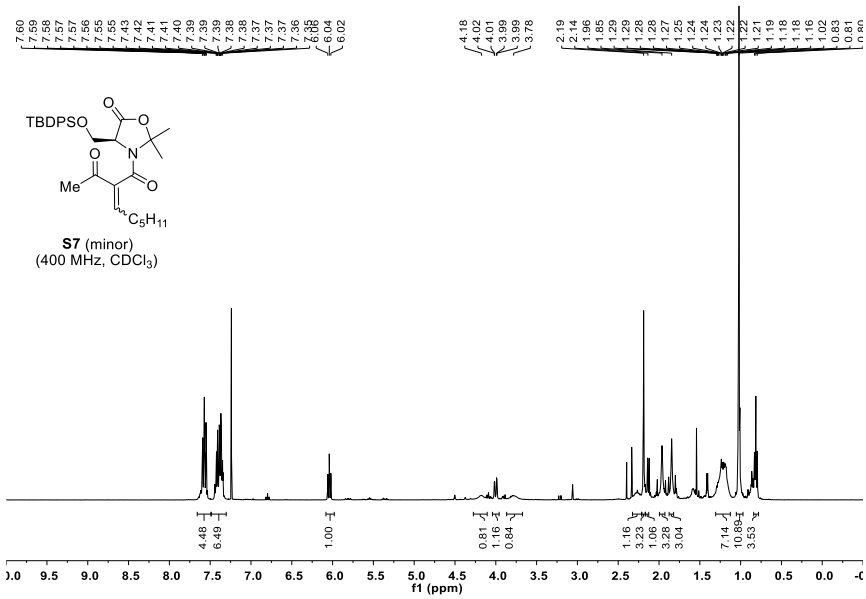
^{1}H NMR (400 MHz, $CDCl_3$) of **S7** (major)



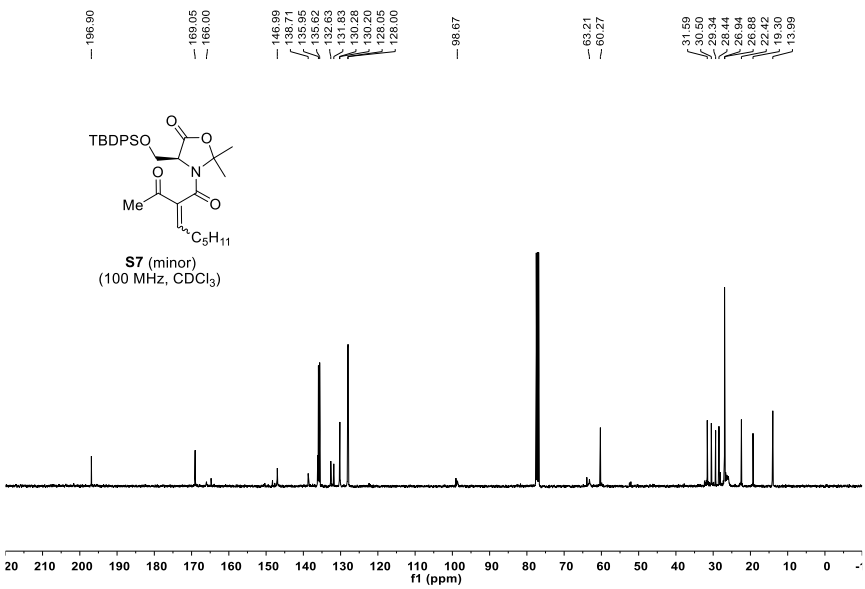
^{13}C NMR (100 MHz, $CDCl_3$) of **S7** (major)



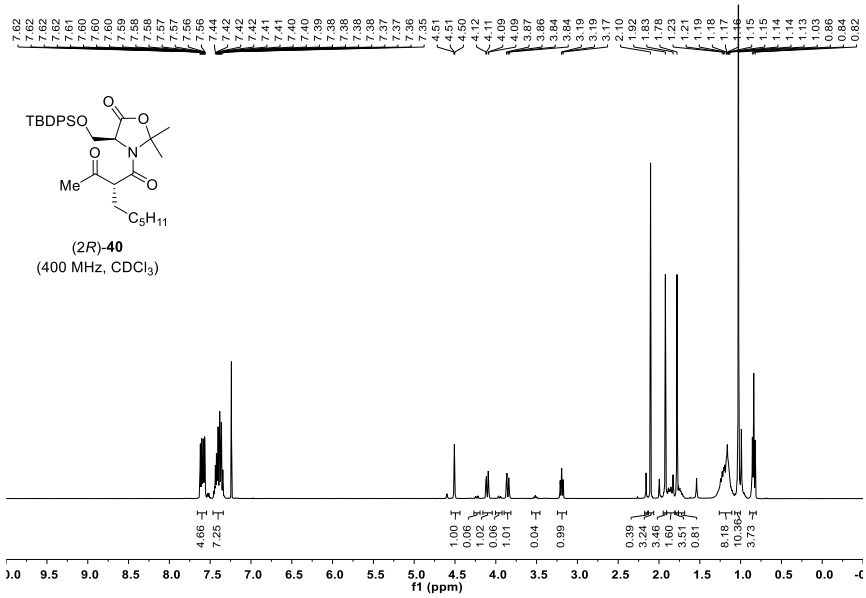
^{1}H NMR (400 MHz, $CDCl_3$) of **S7** (minor)



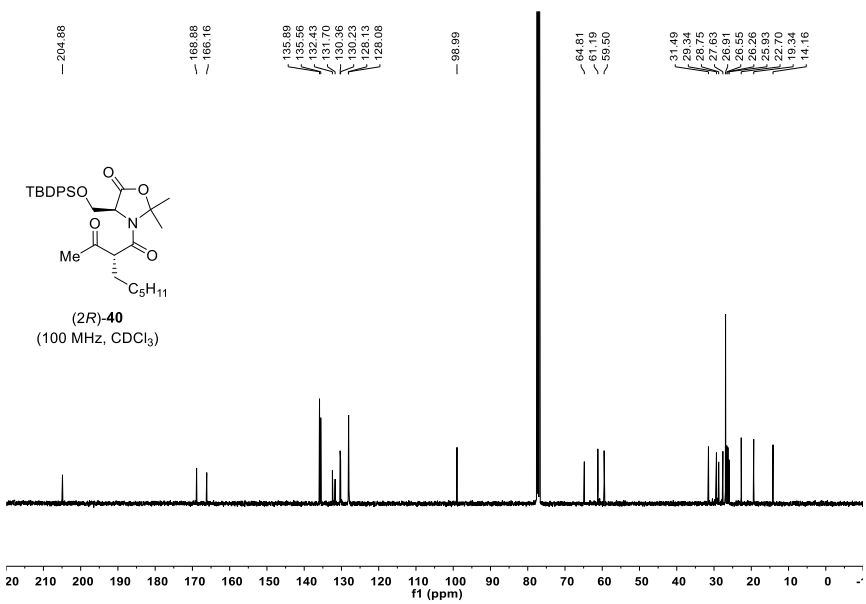
^{13}C NMR (100 MHz, $CDCl_3$) of **S7** (minor)



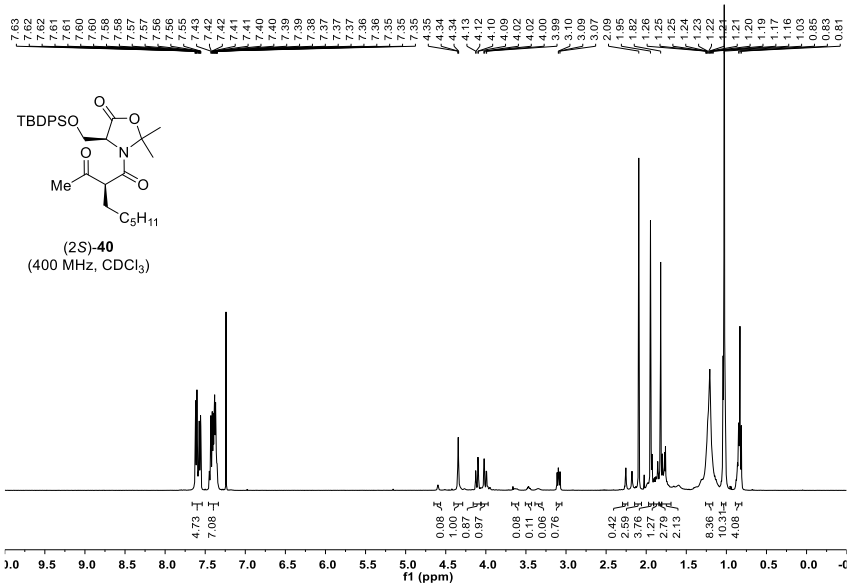
^{1}H NMR (400 MHz, $CDCl_3$) of (2*R*)-**40**



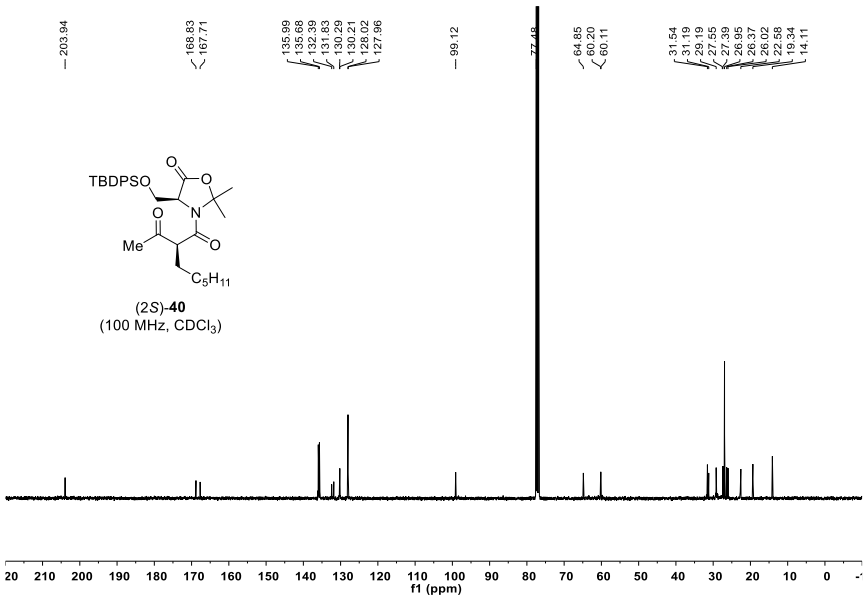
^{13}C NMR (100 MHz, $CDCl_3$) of (2*R*)-**40**



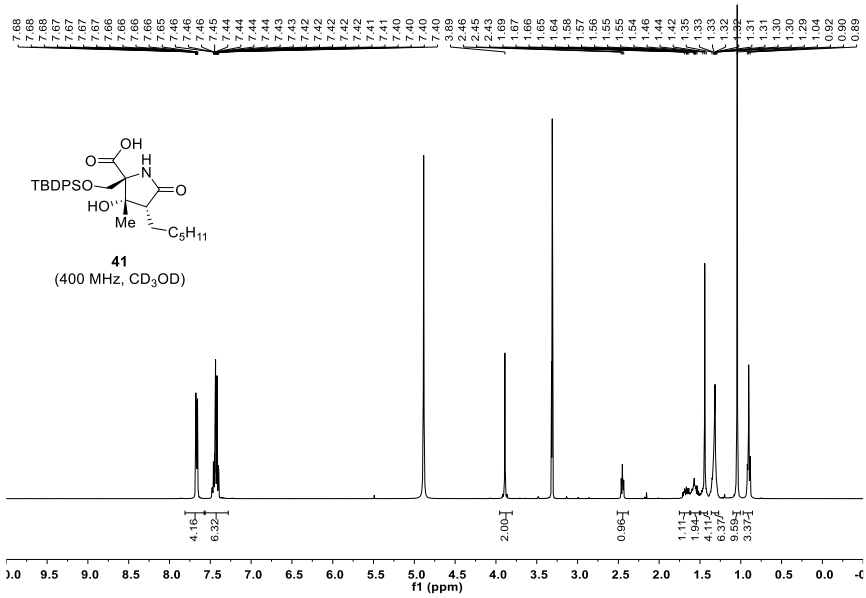
^{1}H NMR (400 MHz, $CDCl_3$) of (2*S*)-**40**



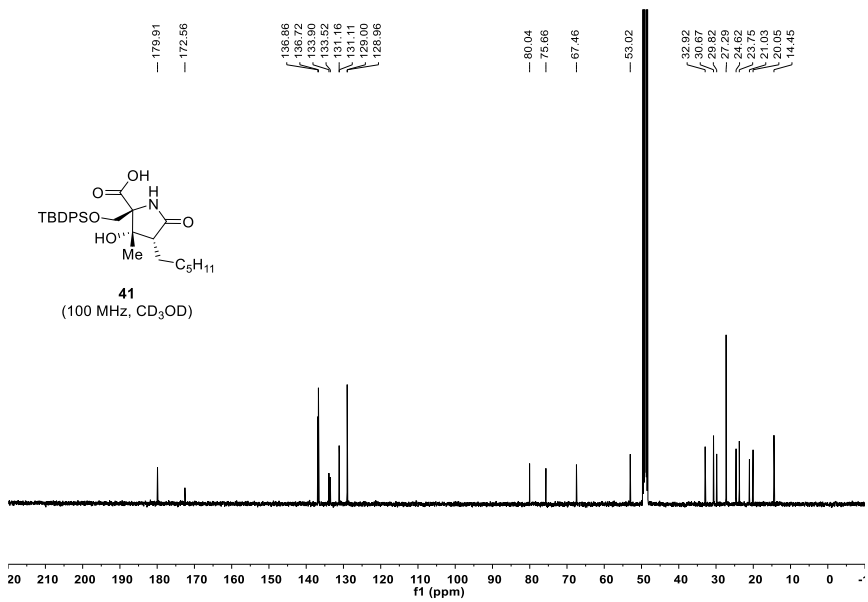
^{13}C NMR (100 MHz, $CDCl_3$) of (2*S*)-**40**



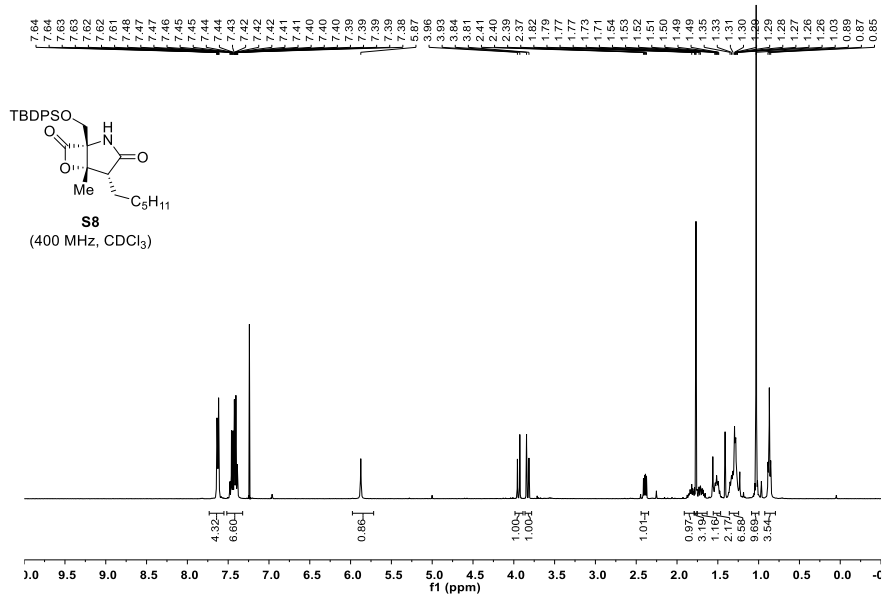
^{1}H NMR (400 MHz, CD_3OD) of **41**



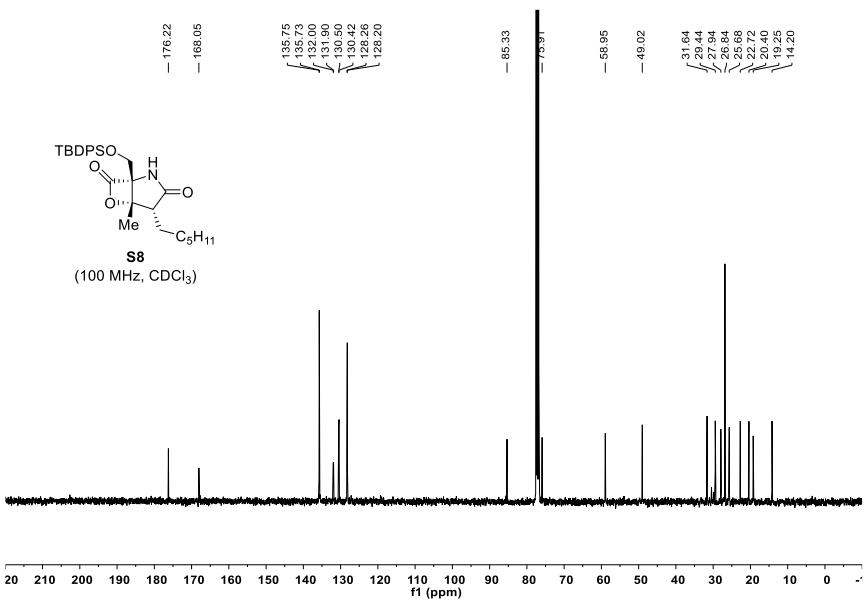
^{13}C NMR (100 MHz, CD_3OD) of **41**



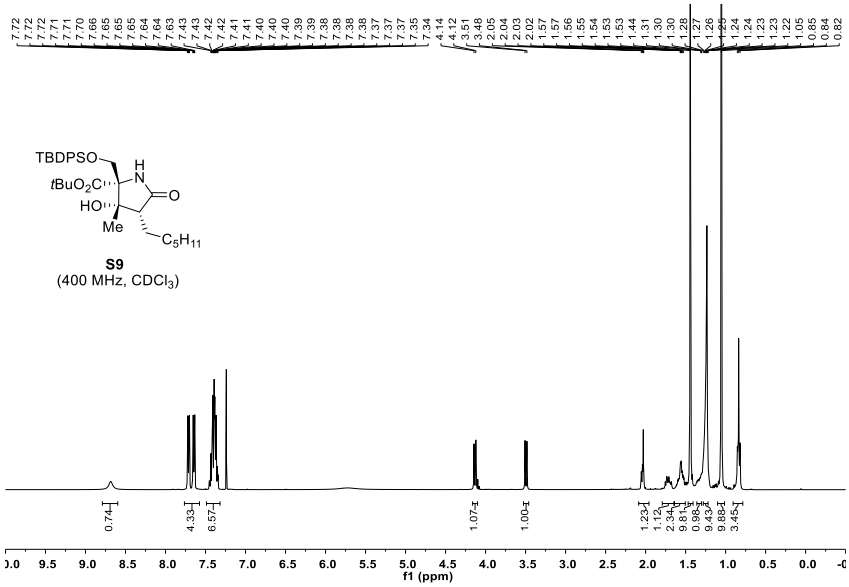
^{1}H NMR (400 MHz, $CDCl_3$) of **S8**



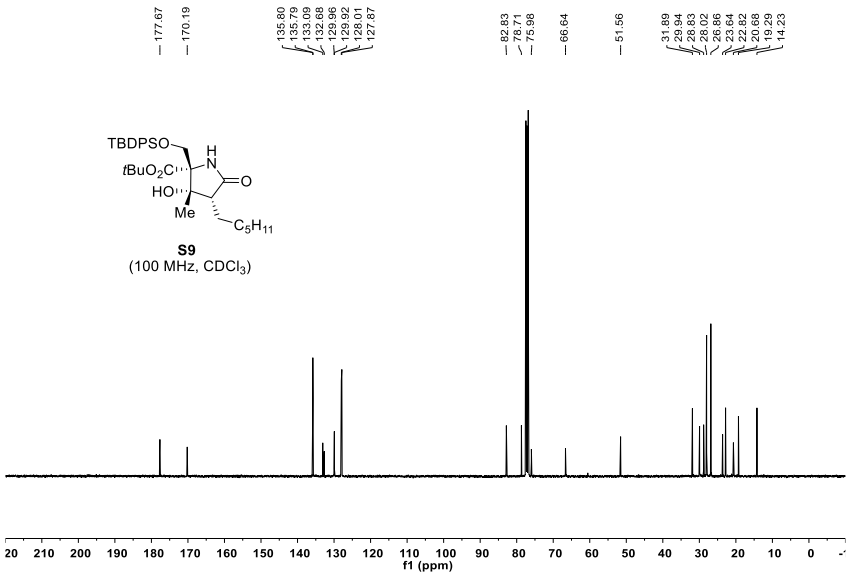
^{13}C NMR (100 MHz, $CDCl_3$) of **S8**



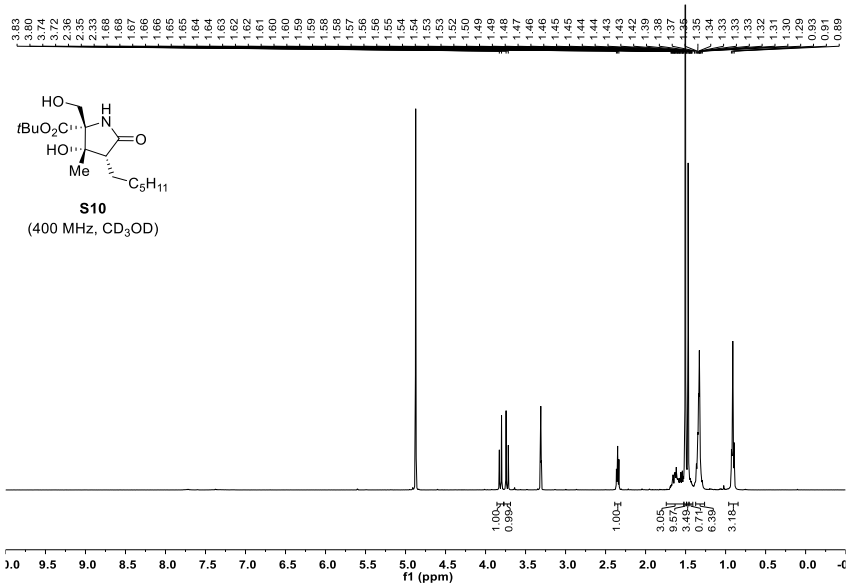
^{1}H NMR (400 MHz, $CDCl_3$) of **S9**



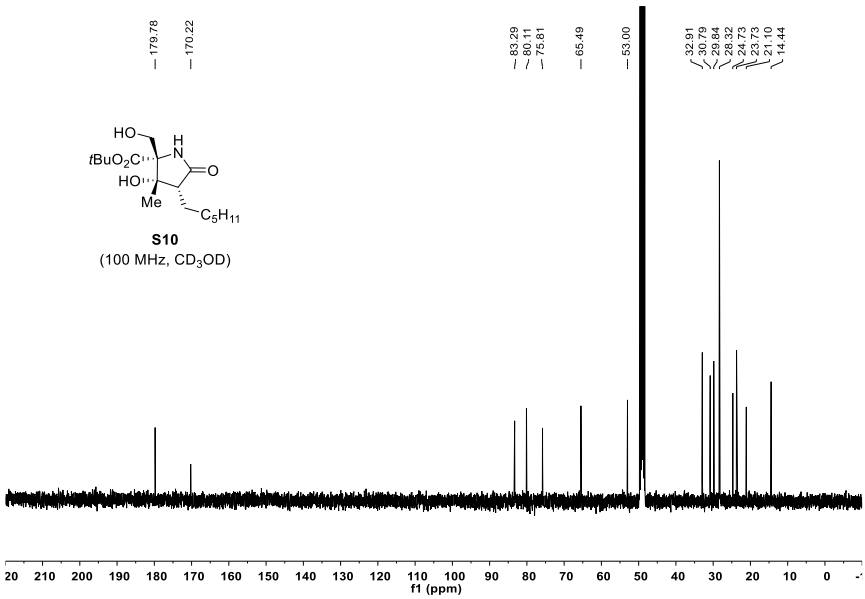
^{13}C NMR (100 MHz, $CDCl_3$) of **S9**



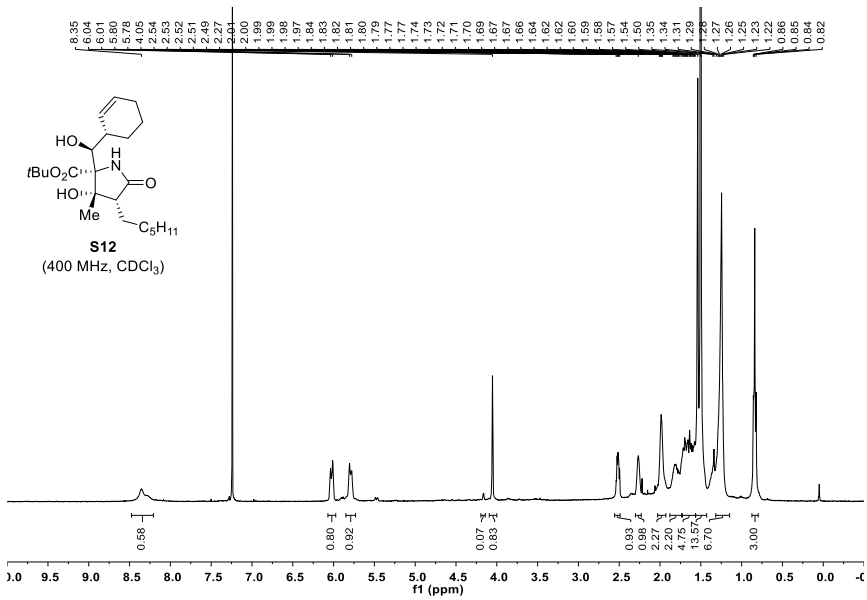
^{1}H NMR (400 MHz, CD_3OD) of **S10**



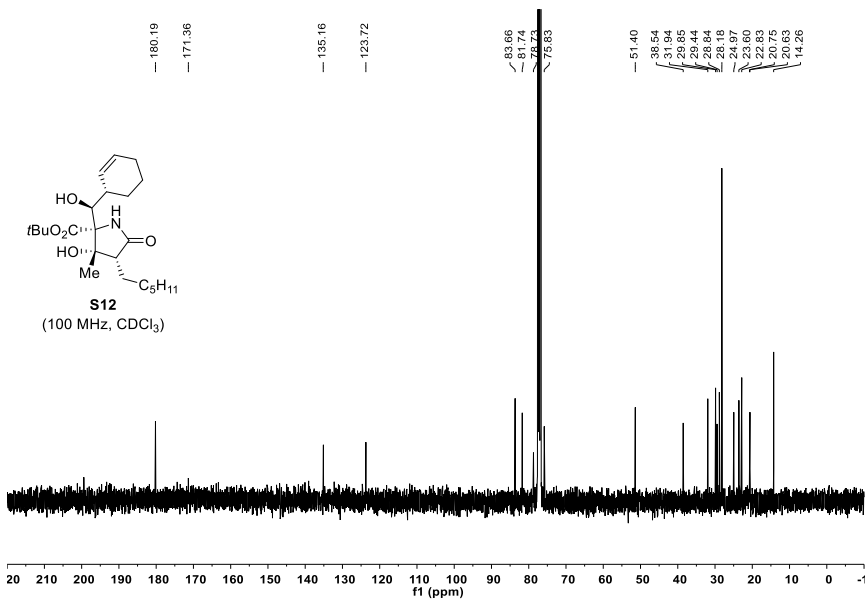
^{13}C NMR (100 MHz, CD_3OD) of **S10**



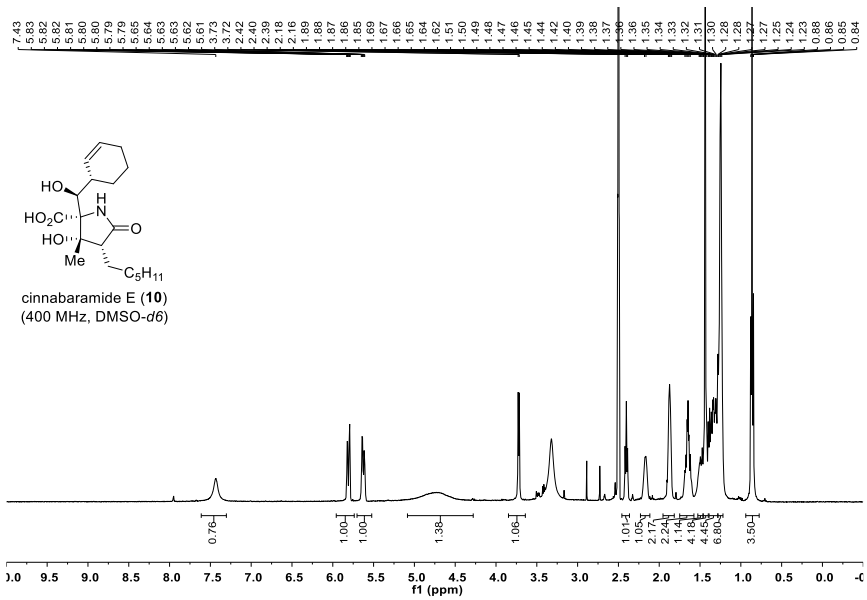
^{1}H NMR (400 MHz, $CDCl_3$) of **S12**



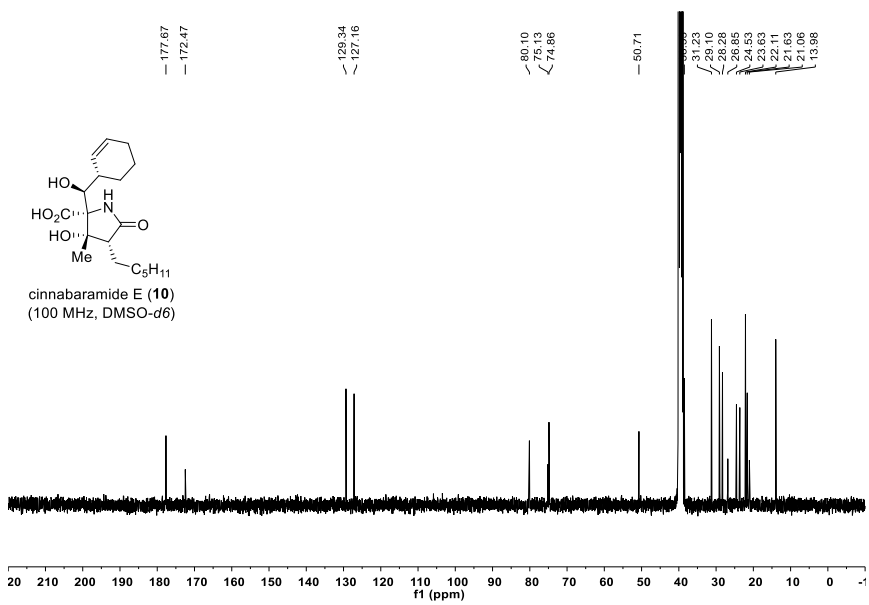
^{13}C NMR (100 MHz, $CDCl_3$) of **S12**



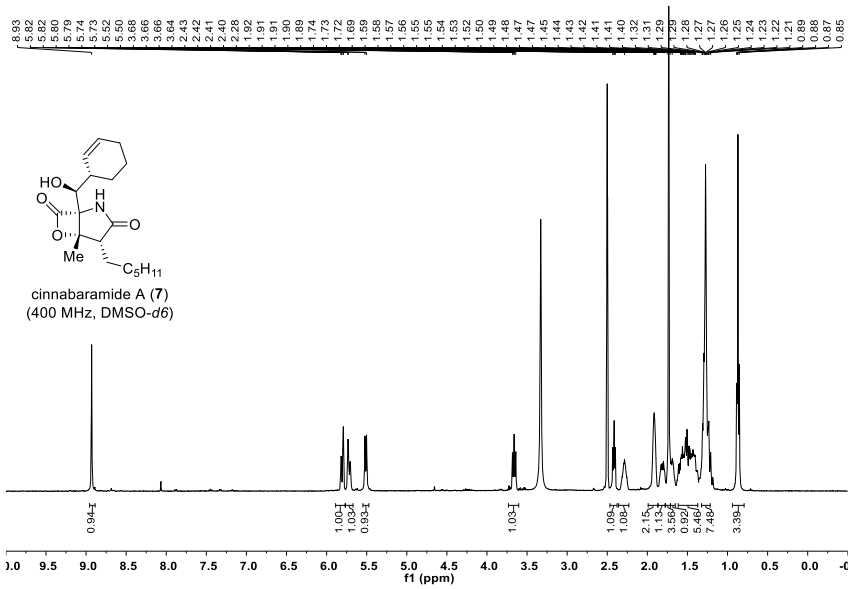
^{1}H NMR (400 MHz, DMSO-*d6*) of cinnabaramide E (**10**)



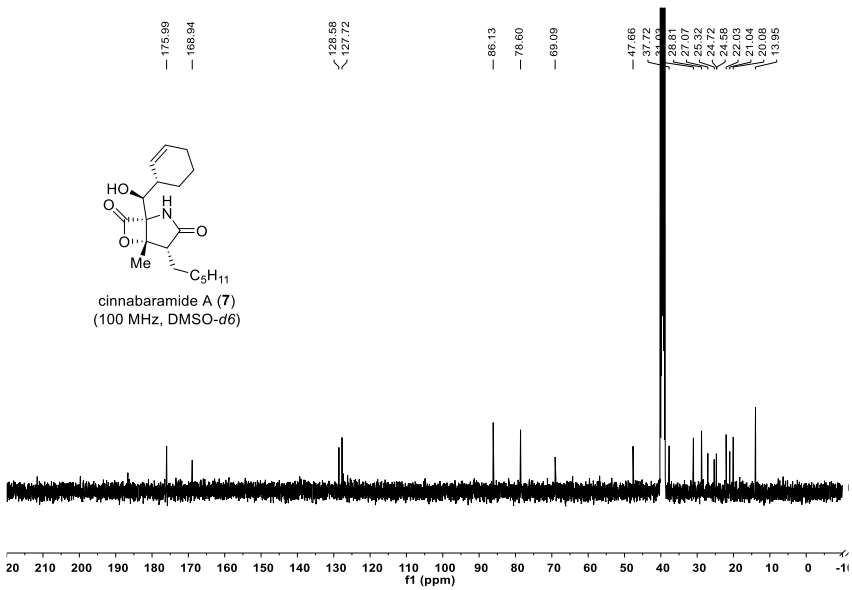
^{13}C NMR (100 MHz, DMSO-*d6*) of cinnabaramide E (**10**)



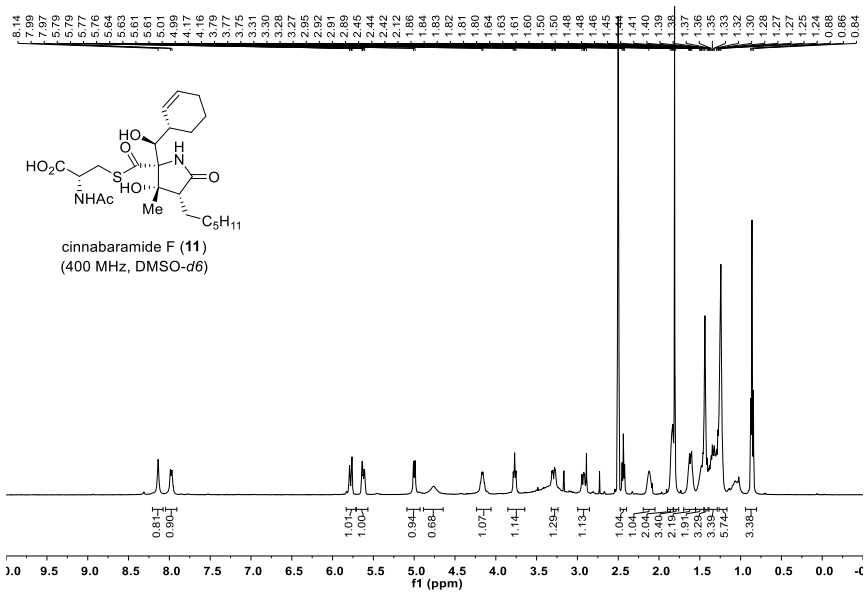
^{1}H NMR (400 MHz, DMSO-*d6*) of cinnabaramide A (**7**)



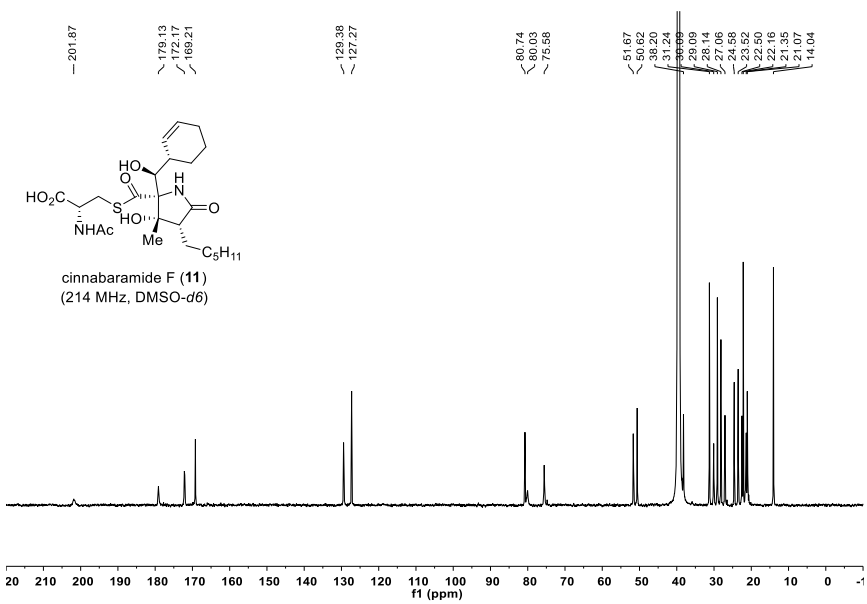
^{13}C NMR (100 MHz, DMSO-*d6*) of cinnabaramide A (**7**)



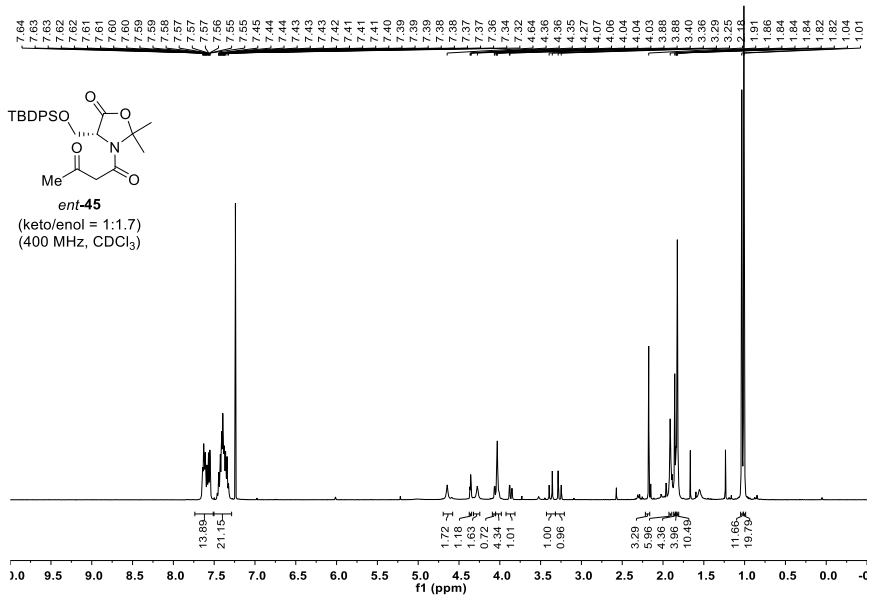
^{1}H NMR (400 MHz, DMSO-*d6*) of cinnabaramide F (**11**)



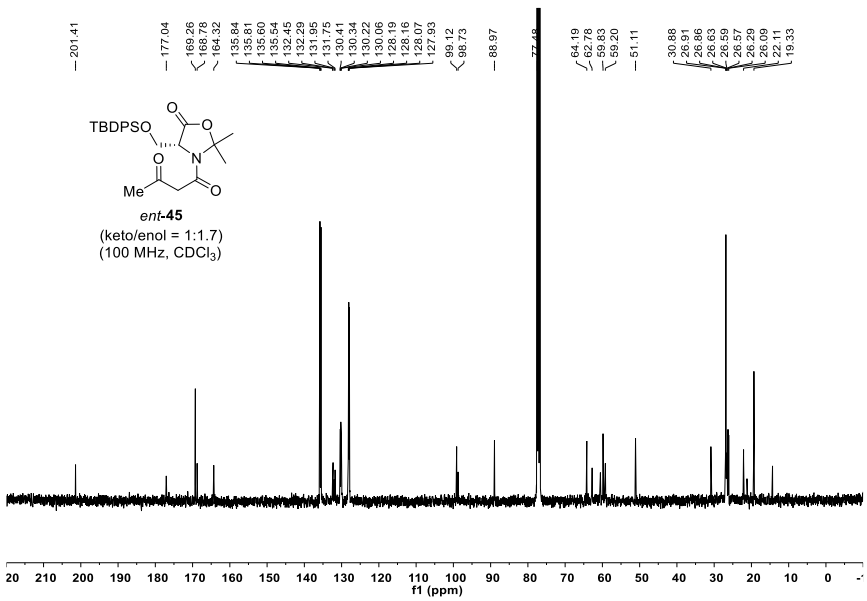
^{13}C NMR (214 MHz, DMSO-*d6*) of cinnabaramide F (**11**)



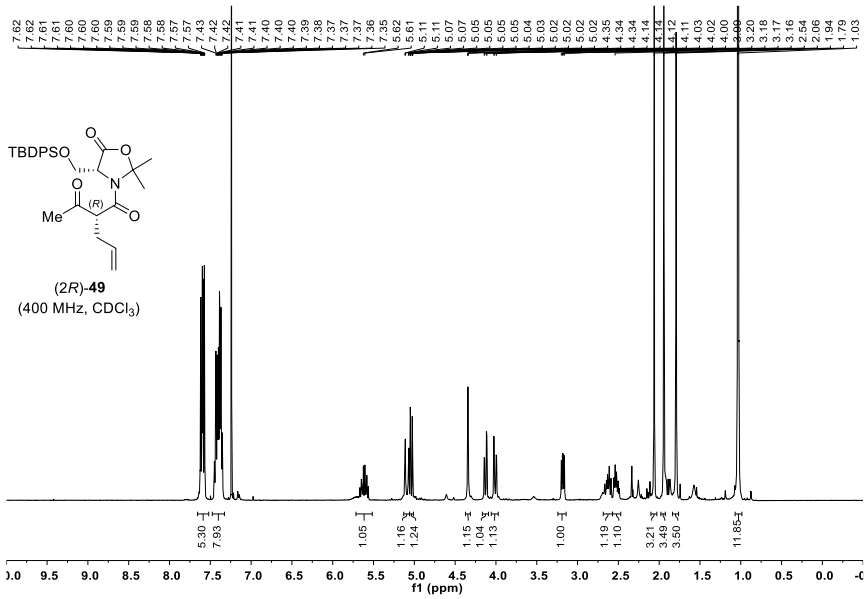
^{1}H NMR (400 MHz, $CDCl_3$) of *ent*-**45**



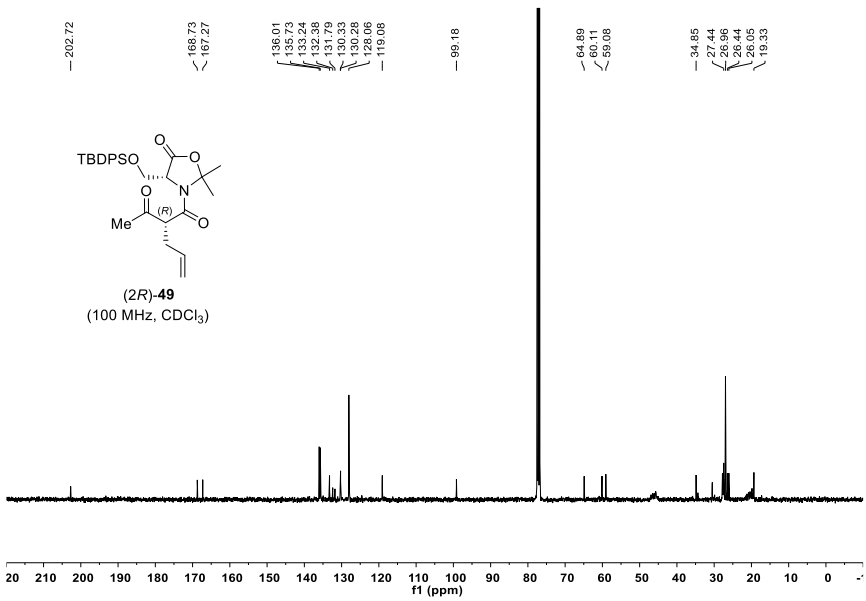
^{13}C NMR (100 MHz, $CDCl_3$) of *ent*-**45**



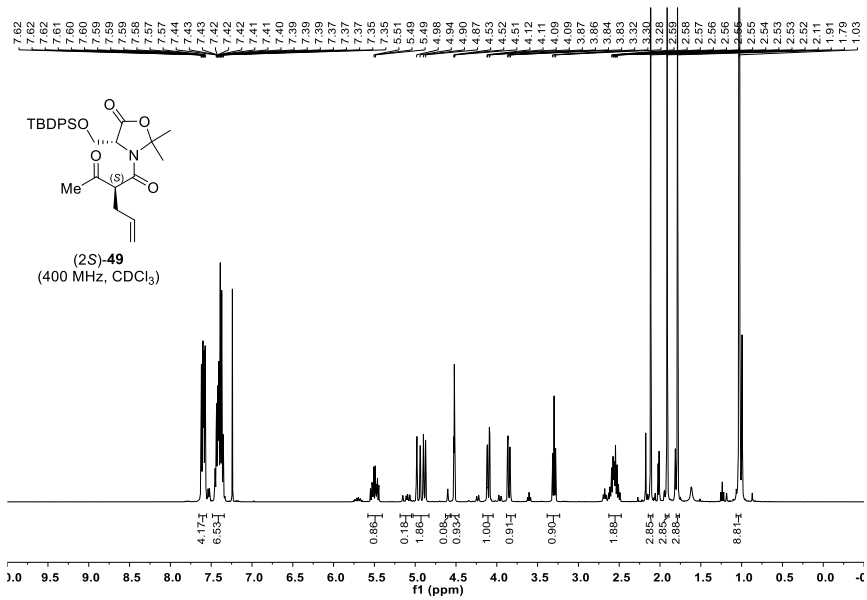
^{1}H NMR (400 MHz, $CDCl_3$) of (2*R*)-**49**



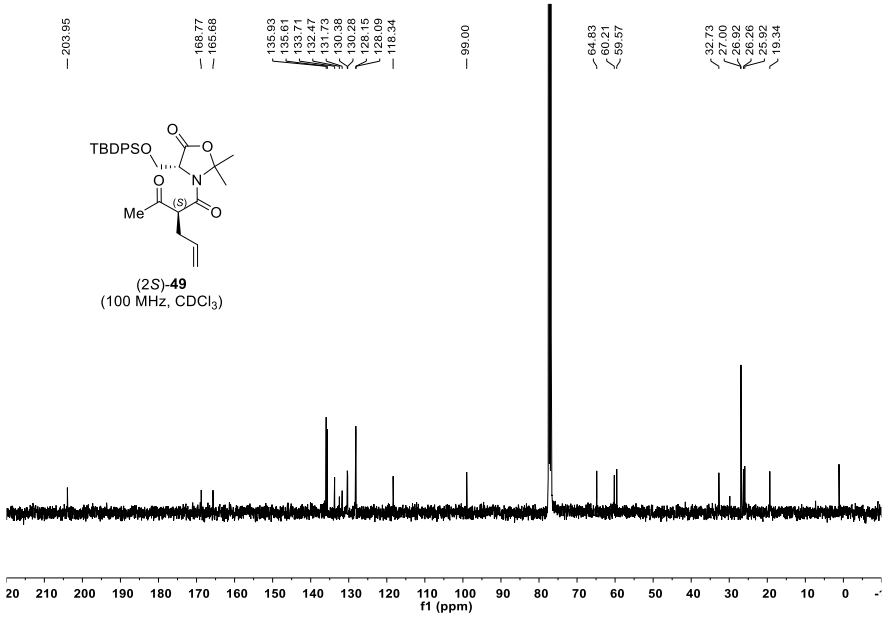
^{13}C NMR (100 MHz, $CDCl_3$) of (2*R*)-**49**



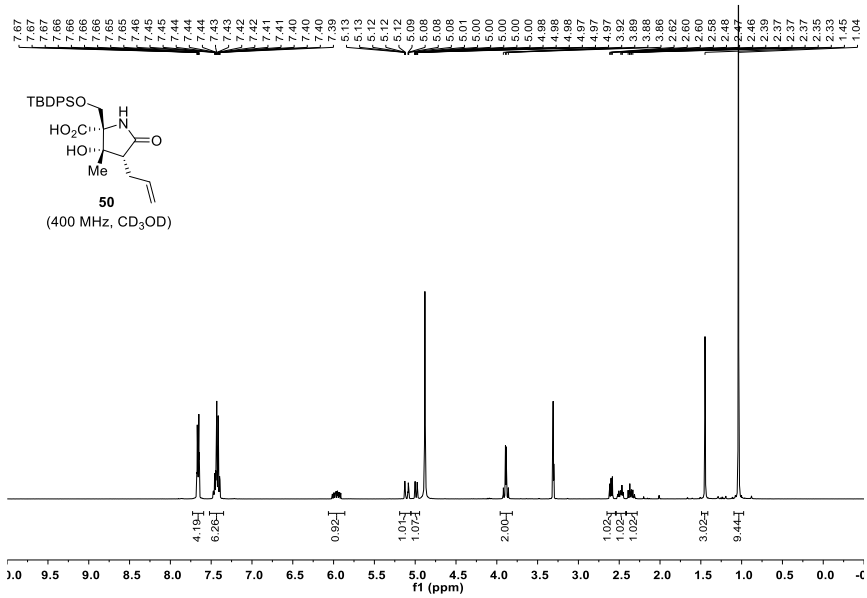
^{1}H NMR (400 MHz, $CDCl_3$) of (2*S*)-**49**



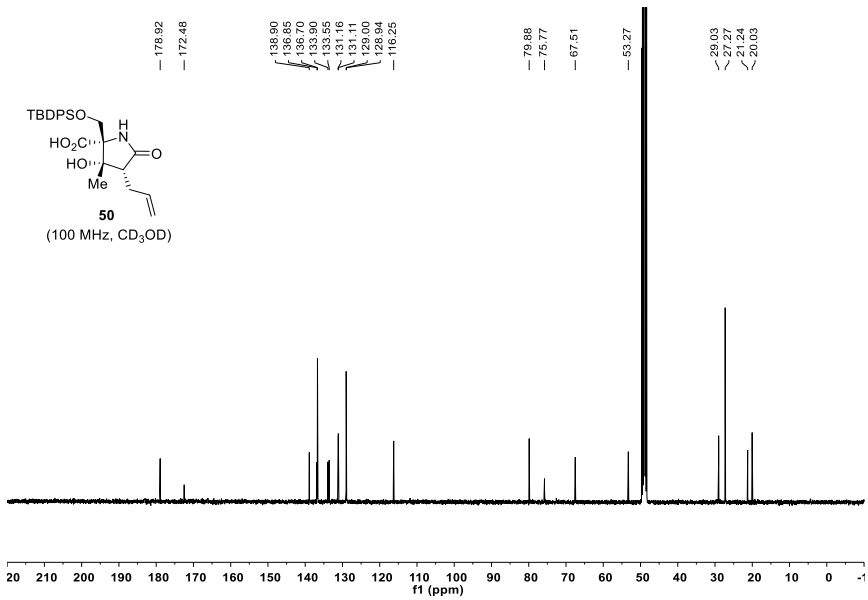
^{13}C NMR (100 MHz, $CDCl_3$) of (2*S*)-**49**



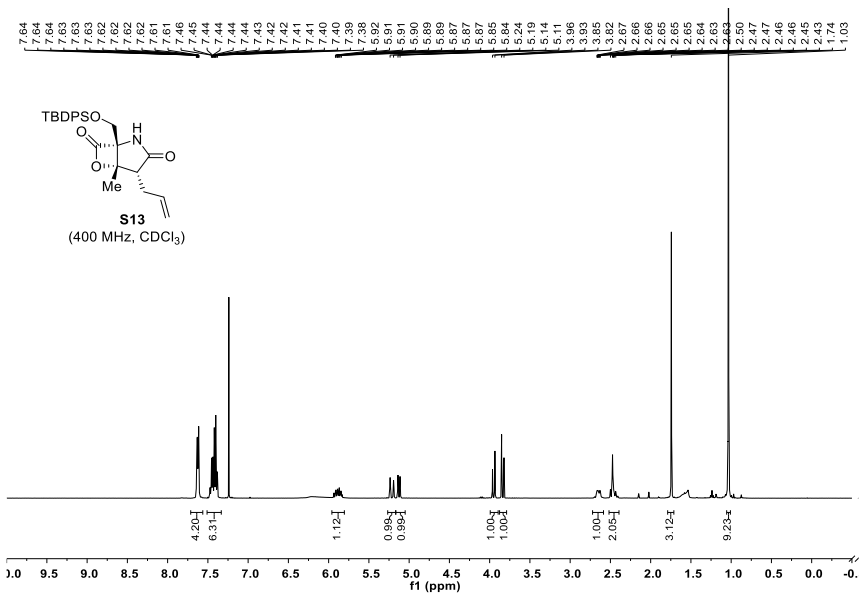
^{1}H NMR (400 MHz, CD_3OD) of **50**



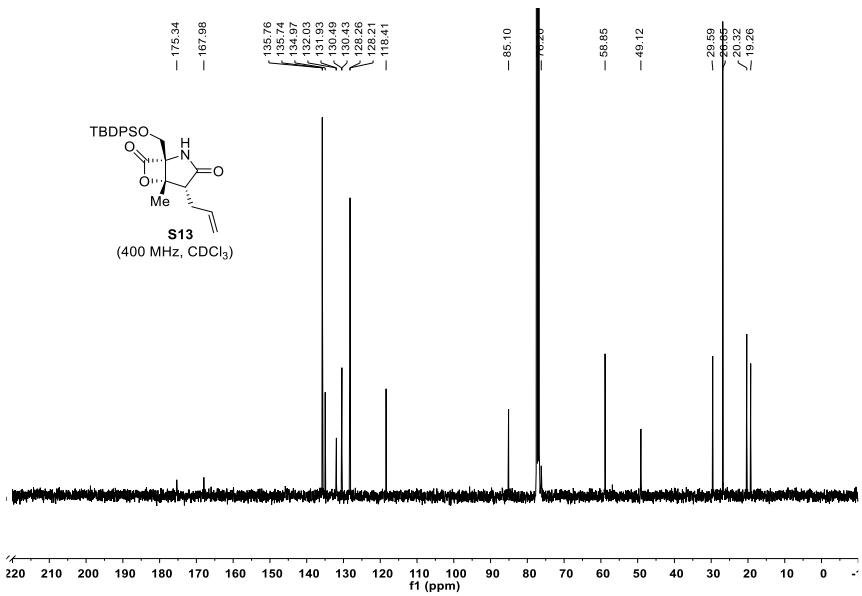
^{13}C NMR (100 MHz, CD_3OD) of **50**



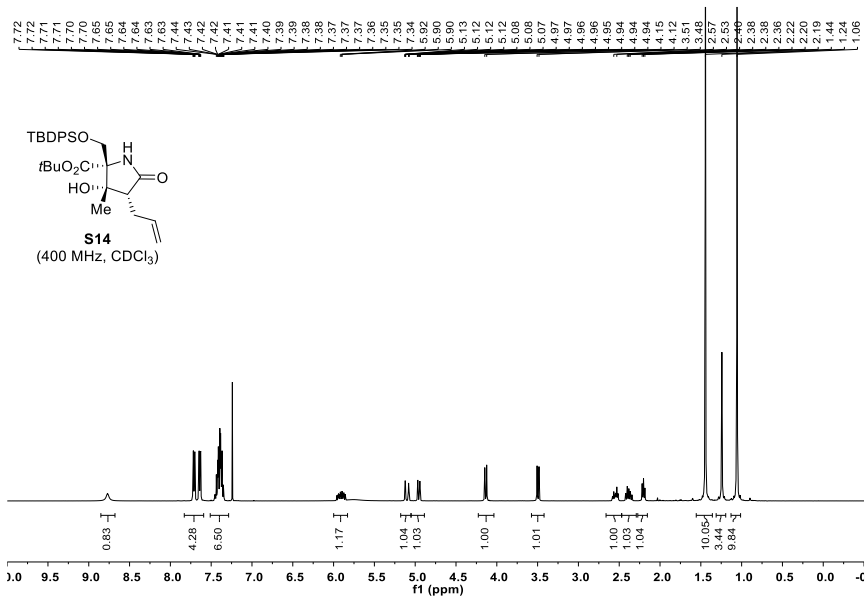
^{1}H NMR (400 MHz, $CDCl_3$) of **S13**



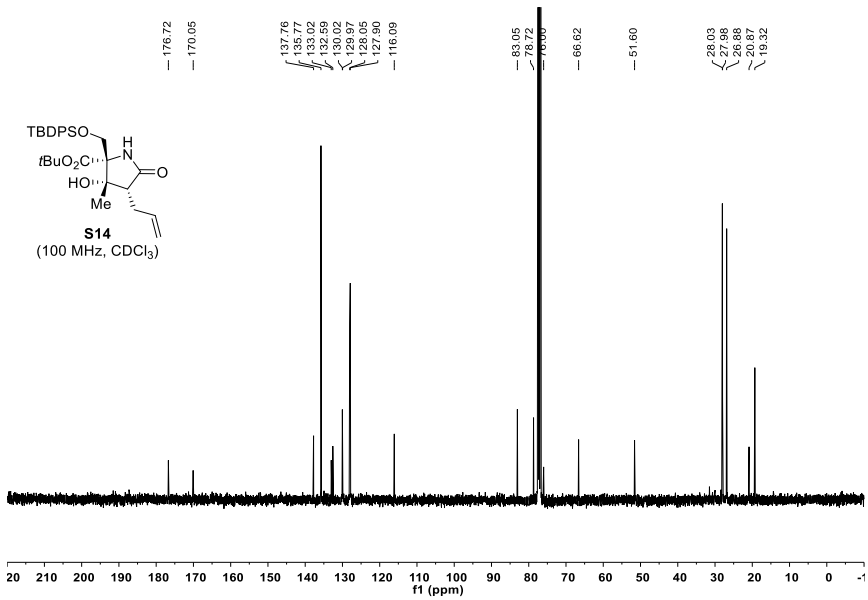
^{13}C NMR (100 MHz, $CDCl_3$) of **S13**



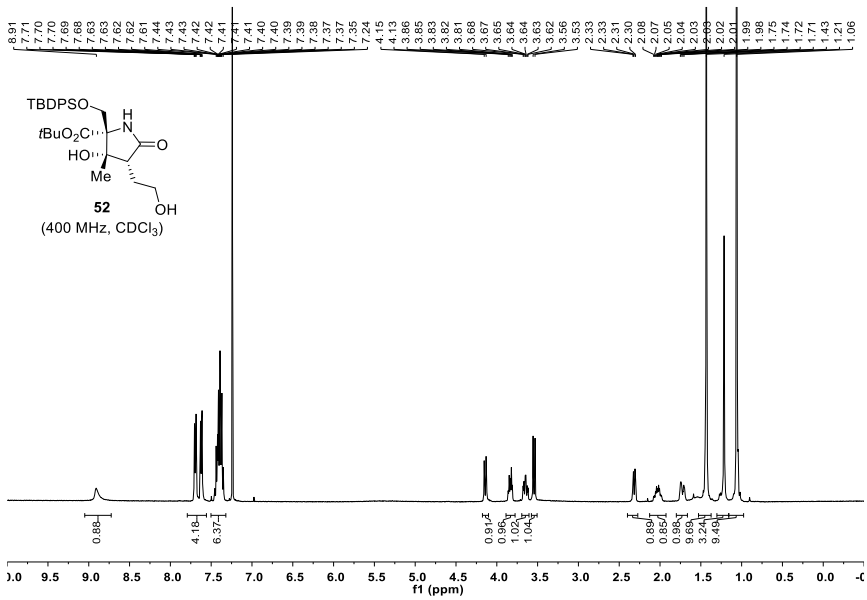
^{1}H NMR (400 MHz, $CDCl_3$) of **S14**



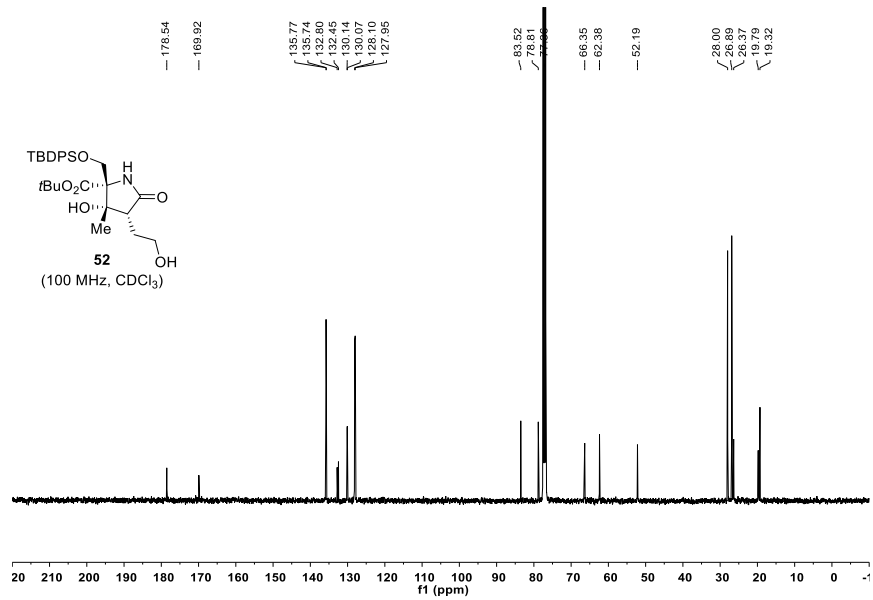
^{13}C NMR (100 MHz, $CDCl_3$) of **S14**



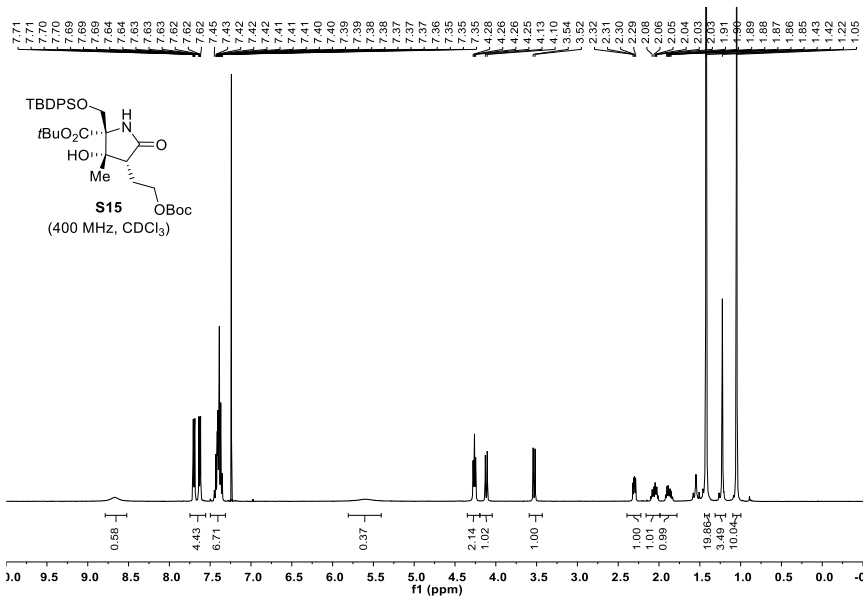
^{1}H NMR (400 MHz, $CDCl_3$) of **52**



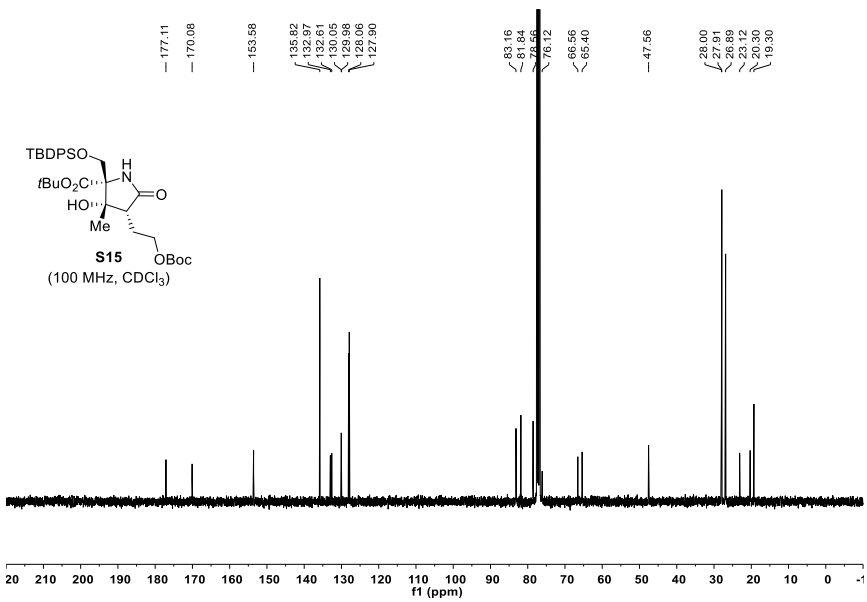
^{13}C NMR (100 MHz, $CDCl_3$) of **52**



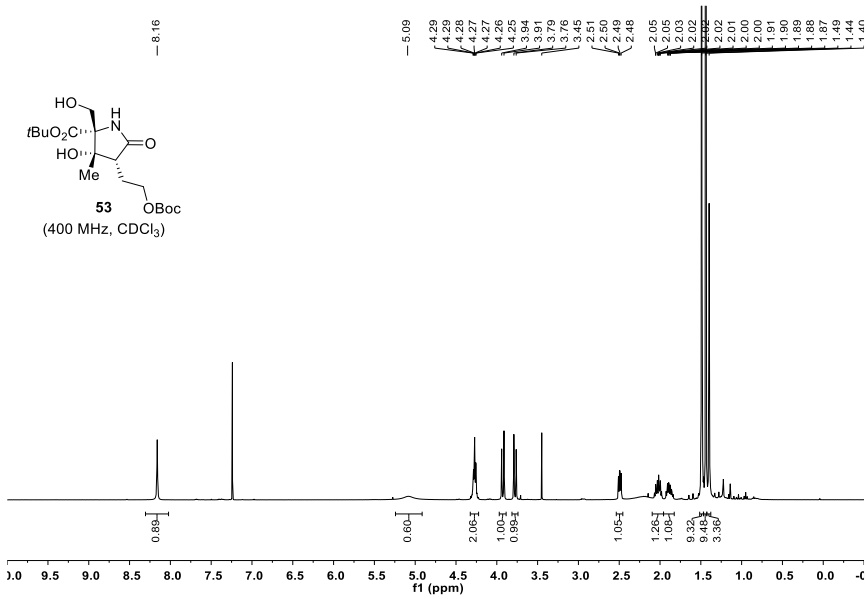
^{1}H NMR (400 MHz, $CDCl_3$) of **S15**



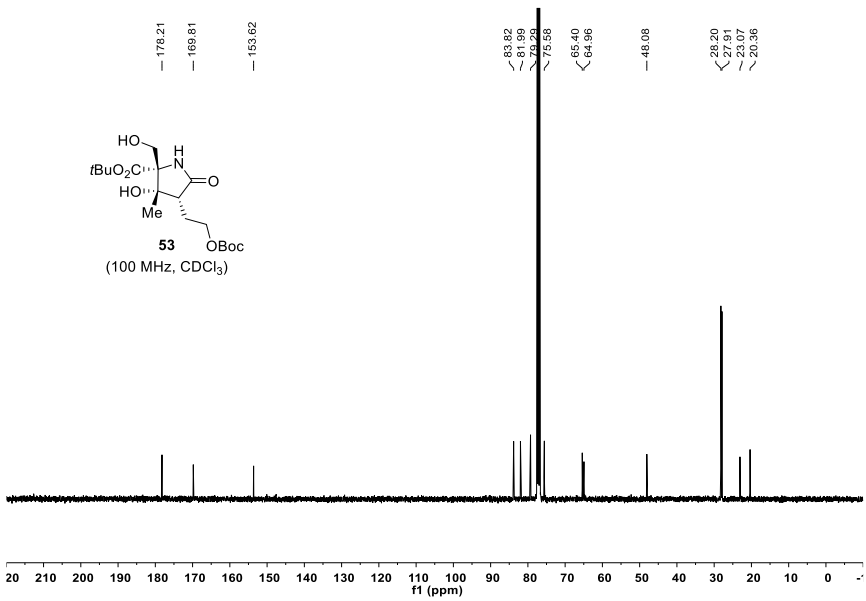
^{13}C NMR (100 MHz, $CDCl_3$) of **S15**



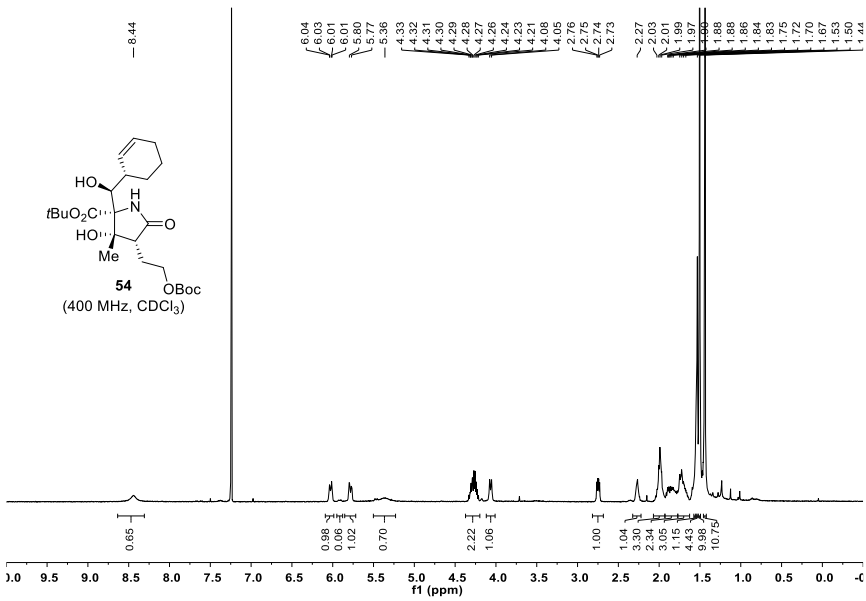
^{1}H NMR (400 MHz, $CDCl_3$) of **53**



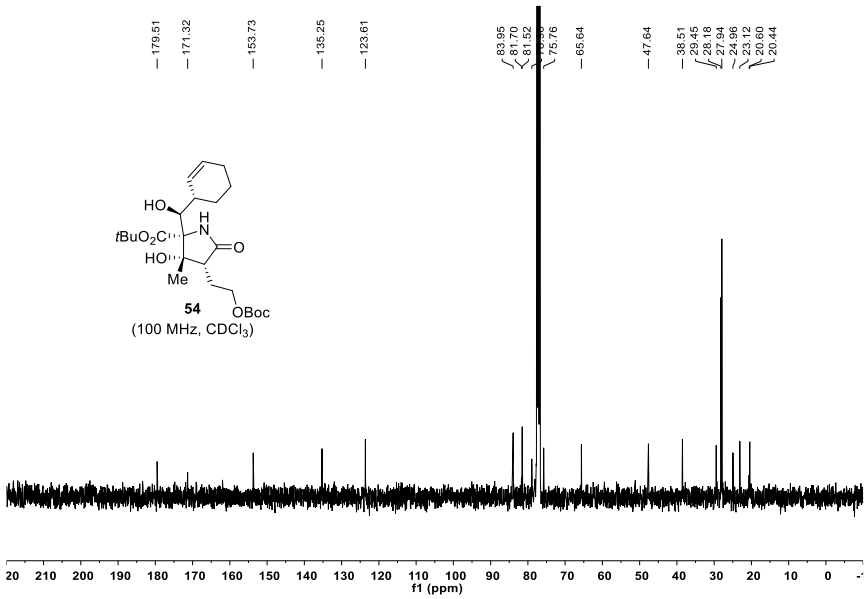
^{13}C NMR (100 MHz, $CDCl_3$) of **53**



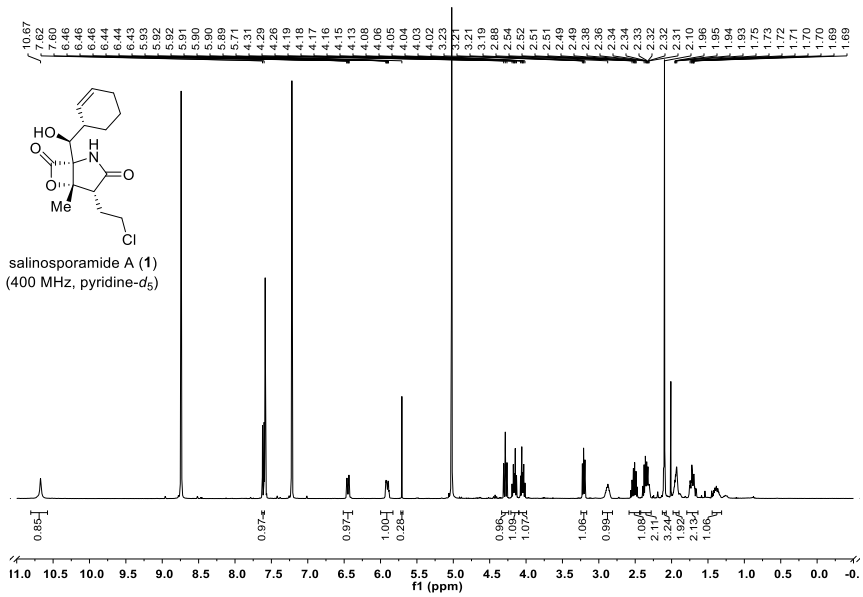
^{1}H NMR (400 MHz, $CDCl_3$) of **54**



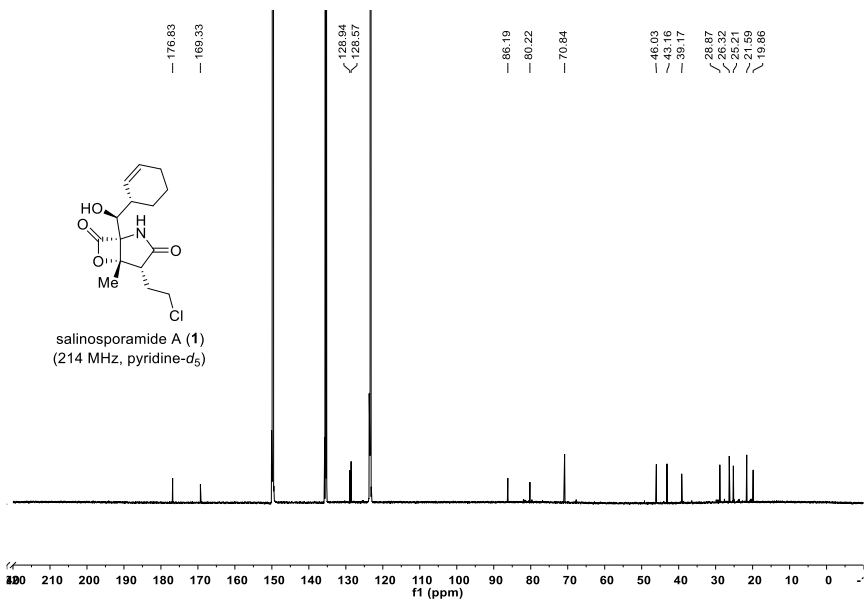
^{13}C NMR (100 MHz, $CDCl_3$) of **54**



^{1}H NMR (400 MHz, pyridine-d_5) of Salinosporamide A (**1**)



^{13}C NMR (214 MHz, pyridine-d_5) of Salinosporamide A (**1**)



국 문 초 록

Salinosporamide 계열 천연물들의 효율적인 전합성 수행 및 이를 위한 비대칭 합성법 개발

Salinosporamide 계열의 천연물은 독특한 화학적 구조와 우수한 20S proteasome 억제제로 알려져 있으며, 다양한 분야의 연구진들에게 많은 관심을 받아왔다. 현재까지 약 13편의 salinosporamide A의 전합성이 보고된 바 있으며, 대부분은 salinosporamide의 공통 키랄성 pyrrolidinone 골격을 구축하는 방법에 대한 연구가 논문의 주요 내용으로 보고되었다. 하지만, 대부분의 전합성 논문에서는 비대칭 pyrrolidinone의 골격을 효율적으로 합성하지 못하거나, 높은 입체선택성을 도입하기 힘들어서 salinosporamide 계열의 화합물이 비교적 단순함에도 불구하고, 대부분의 전합성 논문에서는 20 step 이상이 소요된다는 문제를 가지고 있다. 이에, 현재까지도 salinosporamide A 전합성에서는 chiral pyrrolidinone을 간결하고 효율적으로 구축할 수 있는 방법론이 요구되며, 다른 C-2 작용기를 가지는 다양한 salinosporamide 및 cinnabaramide 계열의 천연물을 합성하기 위해서는 C-2 위치에 다양한 작용기가 도입될 수 있는 확장성이 있는 방법론의 개발이 필요하다.

본 연구에서는, 천연 아미노산인 L-serine을 출발 물질로 하여, 5-oxazolidinone 골격을 가지는 알돌 기질을 확보하고, 알돌 고리화 반응과 가수분해를 동시에 수행하는 반응을 고안하여 3개의 인접한 입체 중심을 가지는 키랄성 pyrrolidinone 골격을 입체선택적으로 합성하였다. 위의 반응은 C-2 위치의 입체 중심이 에피머화 되지 않는 Evans' oxazolidinone 원리가 적용된 5-oxazolidinone의 화학적 특징과 'hydrolytic Dynamic kinetic resolution' 원리를 활용하여 C-3, C-4 위치의 입체 선택적으로 도입하는데 성공하였다. 추후, 위의 개발된 반응을 활용하여, C-2 위치에 다양한 작용기를 가지는 salinosporamide A/B 및 cinnabaramide A/E/F 모두 축약적이고 효율적인 비대칭 전합성을 성공적으로 수행하였다.

주요어: Aldol cyclization, Salinosporamide, Hydrolytic dynamic kinetic resolution, 5-oxazolidinone, Total synthesis

학번: 2012-31107