약학박사 학위논문

해양천연물 (+)-Bermudenynol 의
Intramolecular Amide Enolate Alkylation 을 이용한 부제 전합성

Asymmetric Total Synthesis of (+)-Bermudenynol,
Through Intramolecular Amide Enolate Alkylation

2014 년 2 월

서울대학교 대학원
약학과 약품화학 전공
김 규 동

Abstract

A substrate-controlled asymmetric total synthesis of (+)-bermudenynol, a compact and synthetically challenging C_{15} *Laurencia* metabolite that contains several halogen atoms, is reported. The oxocene core, which contains a vinyl chloride, was constructed by an efficient and highly stereoselective intramolecular amide enolate alkylation (IAEA). This result showcases the broad utility of the IAEA methodology as a useful alternative for cases in which the ring-closing metathesis is inefficient.

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1. Introduction

Red algae of the genus *Laurencia* produce a diverse series of halogenated secondary metabolites.[1] (+)-Bermudenynol (**1**) was isolated from the red alga *Laurencia intricata* by Meinwald and co-workers in Castle Harbour, Bermuda in 1982.[2] The structure of **1** was elucidated on the basis of spectroscopic methods and further corroborated by X-ray crystallography. From a synthetic point of view, this acetogenin marine natural product bearing three halogen atoms possesses a unique vinyl chloride-containing eight-membered cyclic ether skeleton with five stereogenic centers in addition to a (*Z*)-enyne side chain in its compact C_{15} framework. Bermudenynol has not been synthesized to date, probably due to difficulties associated with construction of the vinyl chloride-containing oxocene core.
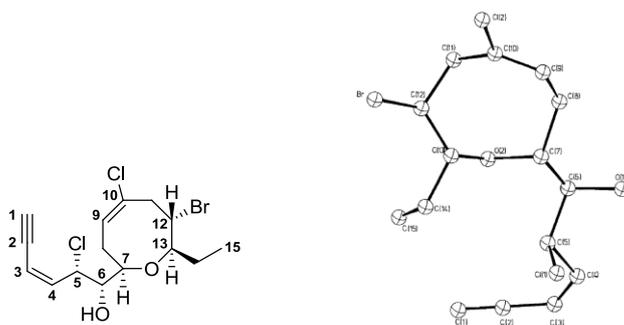
Figure 1. Structure of (+)-bermudenynol (**1**)

Ring-closing metathesis (RCM) has become established as a successful protocol for the construction of medium-ring oxacyclic skeletons, including those with either α,α'-*cis* or α,α'-*trans* disubstitution.[3] Notably, Weinreb and Chao reported RCM of olefinic vinyl chlorides to construct a variety of vinyl chloride-containing carbocyclic and heterocyclic five-, six-, and seven-membered rings in excellent yields.[4] And they also briefly investigated the possibility of forming larger rings by this process. Unfortunately, their attempt to construct a vinyl chloride-containing oxocene via RCM under their optimized RCM conditions (Scheme 1) was met with failure.
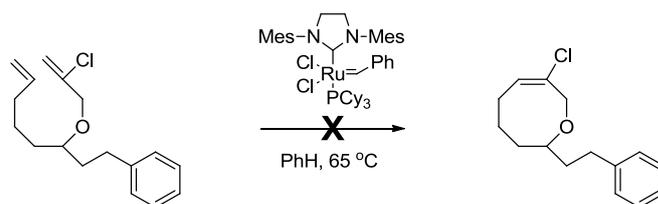
Scheme 1. Attempted RCM Cyclization to a Vinyl Chloride-Containing Oxocene.

Recently, we have demonstrated the potential of our "olefin geometry-dependent" intramolecular amide enolate alkylation (IAEA) methodology (Scheme 2) in the synthesis of medium-ring oxacyclic marine natural products with an α,α'-*cis*-disubstituted oxocene skeleton.[5]
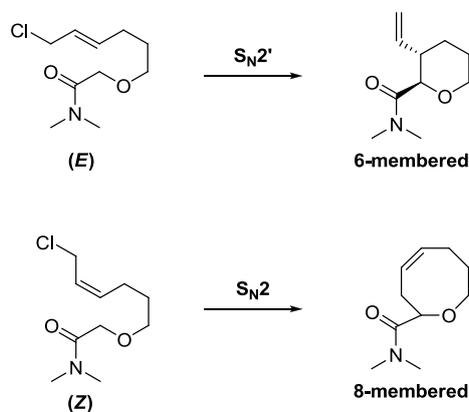
Scheme 2. Olefin Geometry-Dependent Intramolecular Amide Enolate Alkylation

More significantly, an extension of our methodology has served to complement a deficiency in RCM in the construction of (*E*)-oxonenes, as we demonstrated in our IAEA-based synthesis of (*E*)-cladiellin diterpenes.[6] (Figure 3)
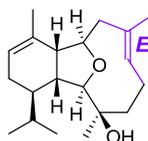
Figure 3. (*E*)-cladiellin diterpenes

Mindful that the abovementioned Weinreb study did not augur for success, we were still intrigued by the possibility that our olefin geometry-dependent IAEA strategy could be used to construct the crucial vinyl chloride-containing oxocene core of (+)-bermudenynol. This approach was ultimately successful, and this thesis reports our first asymmetric total synthesis of the *Laurencia* marine natural product.

2. Results and Discussion

2.1 Retrosynthetic plan for (+)-Bermudenynol
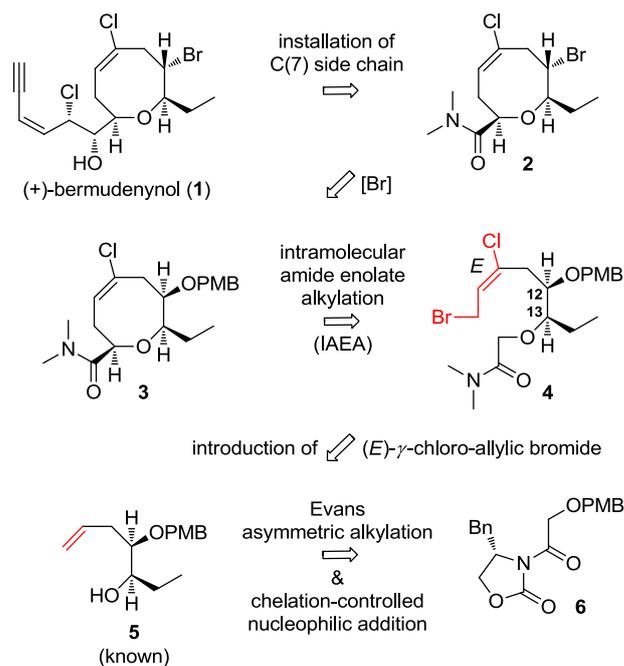
Scheme 3. Retrosynthetic Plan for (+)-Bermudenynol (**1**).
PMB = *p*-methoxybenzyl

As shown in our retrosynthetic plan (Scheme 3), we planned to introduce the C(7) side chain, which contains both a vicinal chlorohydrin and a (*Z*)-enyne, by elaboration of the α-alkoxy dimethylamide function in oxocene **2**. We were confident that the key vinyl chloride-containing bromo oxocene **2** could be secured by the IAEA of (*E*)-allylic bromide **4**, followed by bromination of the resultant

oxocene adduct **3** with inversion of configuration. We further envisaged that the requisite (*E*)-*γ*-chloro allylic bromide moiety in IAEA substrate **4** could be elaborated from the terminal alkene function in known C(12)/C(13)-*syn* diol derivative **5**, which was available in four steps from **6** by Evans alkylation and chelation-controlled nucleophilic addition.[7]

2.2 Synthesis of Key Bromo Oxocene 2

To commence the synthesis, α-alkoxy amide **7** was prepared by *O*-alkylation of known *syn*-diol derivative **5** by treatment with NaH and *N*,*N*-dimethyl chloroacetamide (Scheme 4). The terminal alkene function in **7** was used to install the (*E*)-*γ*-chloro allylic bromide moiety required in key IAEA substrate **4** as follows: one-pot cleavage of alkene **7** by a modified Lemieux-Johnson oxidation,[8] followed by Ohira-Bestmann alkynylation of the resultant aldehyde **8**, gave the desired alkyne **9** in good overall yield (78% yield for 3 steps from **5**).[9] Regio- and stereoselective hydrostannylation of propargylic ester **10**, prepared by palladium-catalyzed oxidative carbonylation of alkyne **9**,[10] was accomplished under the stannylcupration conditions described by Pancrazi and co-workers to afford the desired (*E*)-vinyl stannane **11** (53% for the two steps).[11] Chemoselective reduction of ester function in **11** in the presence of α-alkoxy dimethylamide by treatment with the ate complex generated from DIBAL-H and *n*BuLi[12a] (−78 ${}^{\circ}$C, then

NaBH$_4$/EtOH, −78 ^{o}C to RT), and subsequent tin-chlorine exchange[13] led to the desired (*E*)-γ-chloro allylic alcohol **13** (55% yield for the two steps). This same ate complex is used elsewhere to reduce an α-alkoxy dimethylamide function to the corresponding aldehyde at 0 ^{o}C to room temperature (vide infra), so the temperature effect makes the chemoselectivity here highly tunable. Finally, bromination of allylic alcohol via a modification of the Stork protocol[14] gave rise to the desired allylic bromide in nearly quantitative yield (96% for the two steps), setting the stage for the crucial intramolecular amide enolate alkylation.
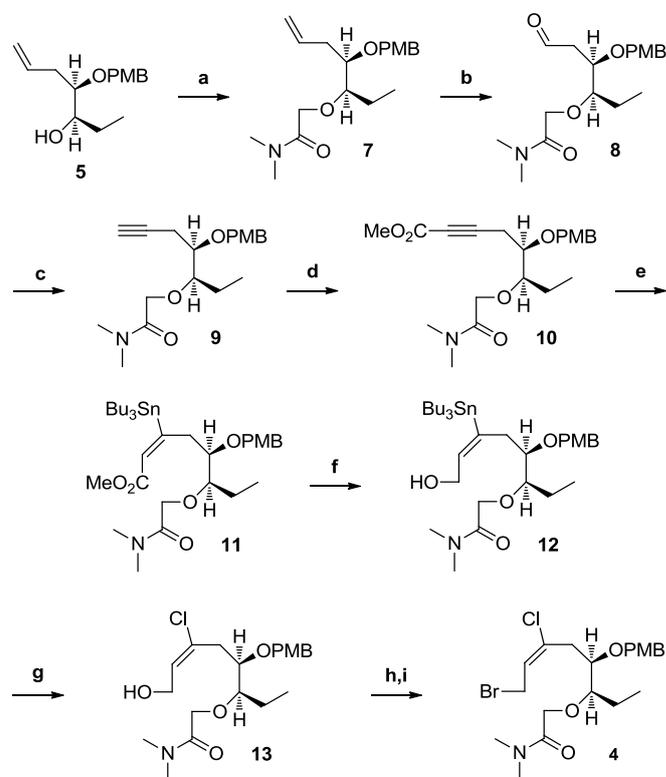
Scheme 4. Preparation of IAEA Substrate **4**: a) NaH, ClCH$_2$CONMe$_2$, THF/DMF (3:1), RT, 3 h, 94 %; b) i. OsO$_4$, NMO, acetone/H$_2$O, RT, 18 h, ii. NaIO$_4$, RT, 3 h, 92 %; c) CH$_3$COCN$_2$PO(OCH$_3$)$_2$, K$_2$CO$_3$, MeOH, RT, 18 h, 90 %; d) Pd(OAc)$_2$, PPh$_3$, MeOH, DMF, CO, O$_2$, RT, 25 h, 72 %; e) hexabutylditin, nBuLi, CuCN, MeOH, THF, −78 °C, 1 h, 73 %; f) DIBAL-H (3 equiv), nBuLi (3 equiv), THF, −78 °C, 10 min, then NaBH$_4$ (excess), EtOH, −78 °C to RT, 1 h, 77 % (BRSM 83%); g) CuCl$_2$, THF, 0 °C, 4 h, 71 %; h) Ms$_2$O, Et$_3$N, CH$_2$Cl$_2$, RT, 10 min; i) LiBr, THF, RT, 1 h, 96 % (2 steps).

THF = tetrahydrofuran, NMO = N-methylmorpholine-N-oxide, DMF = N,N-dimethylformamide, DIBAL-H = diisobutylaluminum hydride, Ms = methanesulfonyl.
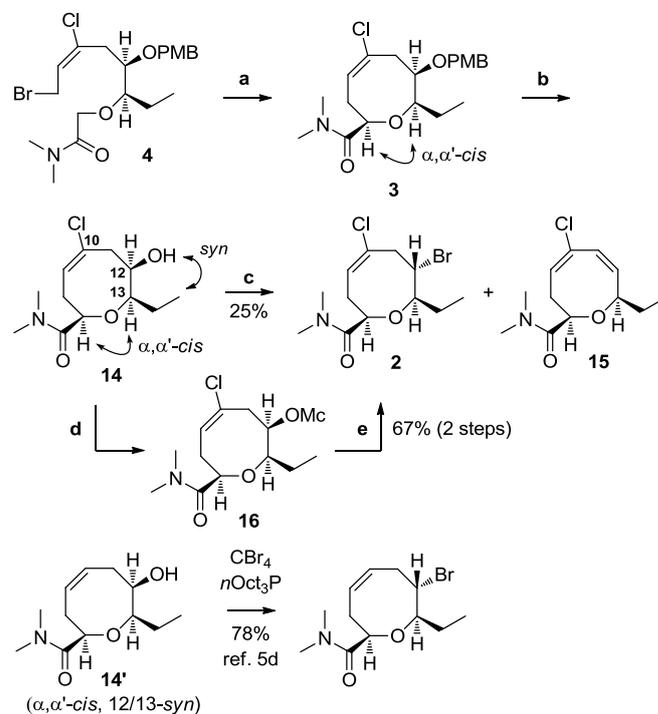
Scheme 5. Intramolecular Amide Enolate Alkylation and Bromination: a) LiHMDS, THF, −78 °C, 1 h, 80 %; b) DDQ, CH$_2$Cl$_2$/pH 7.4 buffer solution (9:1), RT, 7 h, 94 %; c) CBr$_4$, nOct$_3$P, 1-methyl cyclohexene, toluene, 70 °C, 12 h, 25 % for **2**, **2/15** = 1:1.2; d) McCl, 2,6-lutidine, CH$_2$Cl$_2$, 0 °C, 1 h; e) LiBr, Et$_2$O/THF (10:1), 40 °C, 6 d, 67 % for 2 steps, **2/15** = 7.3:1.
HMDS = hexamethyldisilazide, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, Mc = chloromethylsulfonyl.

With the internal alkylation substrate in hand, we turned our attention to the much anticipated, pivotal IAEA of **4**.[5,6] To our delight, upon exposure to LiHMDS in THF at −78 °C for 1 h, the (*E*)-allylic bromide **4** gave rise to the key vinyl chloride-containing oxocene amide **3** in good yield (80%). This was an extremely welcome result because we had little confidence in an alternative route based on RCM, as mentioned earlier. Having gained access to the key vinyl chloride-containing

oxocene amide **3**, we next proceeded to address the crucial question of introducing the ring bromine, crucial because one of the most demanding tasks in the synthesis of oxocene marine natural products is introduction of the halogen atom with a defined stereochemistry. It is known that both the relative α,α'-stereochemistry and C(12)/C(13) stereochemistry in oxocenes can exert subtle conformational effects on halogenation with inversion of configuration. Our extensive experience in this area together with literature analogy suggested the diastereomeric oxocene alcohols with α,α'-*cis*-C(12)/C(13)-*syn* stereochemistry represent the most favorable substrates for halogenation with inversion.[15] For instance, α,α'-*cis*-C(12)/C(13)-*syn* oxocene alcohol **14'**[5d] {our laurefucin synthetic intermediate, and identical to **14** except for lacking the chlorine substituent at the C(10)} underwent efficient bromination with inversion of configuration upon exposure to CBr_4 and $nOct_3P$ (78%) under the Hooz conditions.[16] To our surprise and disappointment, however, bromination of key C(10)-chloro oxocene alcohol **14**, prepared in 96% yield by removal of the PMB protecting group in **3** under the Yonemitsu conditions,[17] produced a 1:1.2 mixture of the desired product **2** (25%) and the eliminated diene **15** under comparable conditions. We are still formulating an explanation for the subtle effect of the C(10) chlorine atom on the bromination behavior. Fortunately, the obstacle could be overcome by a modification of the Nakata two-step procedure via chloromethanesulfonate intermediate **16** to obtain

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the crucial bromo oxocene in good yield (67% for the two steps) with minimal

formation of diene **15**.[15,18]

2.3 Completion of the Synthesis
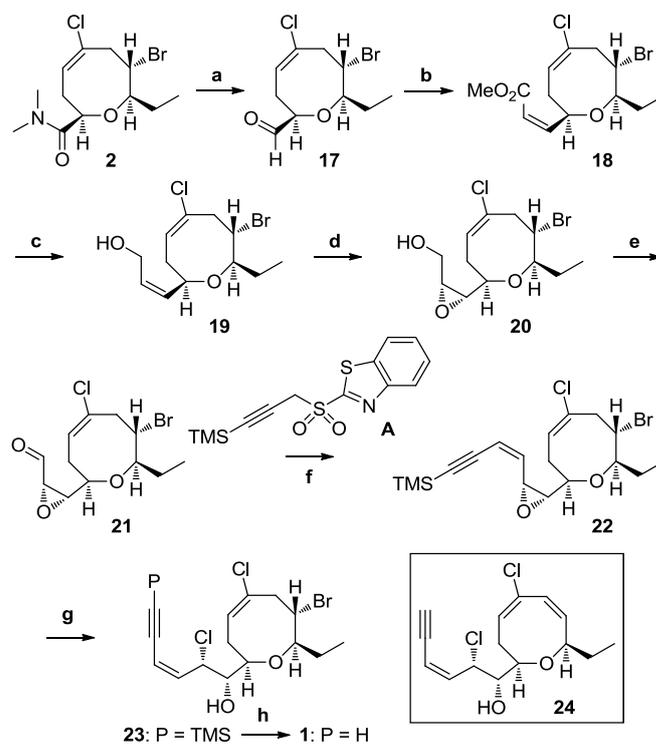
Scheme 6. Completion of the Synthesis: a) DIBAL-H (2 equiv), *n*BuLi (2 equiv), THF, 0 °C, 10 min, then RT, 50 min, 83 %; b) (CF$_3$CH$_2$O)$_2$POCH$_2$CO$_2$Me, KHMDS, 18-crown-6, THF, −78 °C, 15 h, 71 %, *Z/E* = 10 : 1; c) DIBAL-H, toluene, −78 °C, 30 min, 96 %; d) VO(acac)$_2$, *t*BuOOH, benzene, 40 °C, 15 h, α/β = 2.3 : 1, 70 % total yield; e) DMP, NaHCO$_3$, CH$_2$Cl$_2$, RT, 5 h, 96 %; f) **A**, KHMDS, THF, −78 °C, 30 min, 53%, *Z/E* = 16 : 1; g) TMSCl, DMAP, EtOAc, RT, 3 h, 76 %; h) TBAF, acetic acid, THF, 0 °C, 30 min, 90 %.
DMP = Dess-Martin periodinane, TMS = trimethylsilyl, DMAP = 4-dimethylaminopyridine, TBAF = tetra-*n*-butylammonium fluoride.

For installation of the challenging C(7) side chain, we envisioned that regioselective opening at the allylic position of *cis*-α-epoxy (*Z*)-enyne **22** by S$_N$2

displacement with chloride would produce the pivotal chlorohydrin in a stereo- and regioselective manner (Scheme 6). Taking advantage of the versatility of the α-alkoxy dimethylamide function,[5,6] reduction of oxocene amide **2** with the ate complex generated from DIBAL-H and *n*BuLi (0 °C to RT) produced the corresponding aldehyde **17** (83%),[12b] which was transformed into the requisite (*Z*)-enoate **18** with a good *Z/E* selectivity (10:1) via the Still-Gennari olefination (71%).[19] To generate the *cis*-α-epoxide functionality in the presence of the trisubstituted oxocene vinyl chloride, we decided on epoxidation of (*Z*)-allylic alcohol **19**, prepared by DIBAL-H reduction of (*Z*)-enoate **18** in excellent yield (96%). After some experimentation, we found that exposure of (*Z*)-allylic alcohol **19** to VO(acac)$_2$ and *tert*-butyl hydrogen peroxide under the Sharpless conditions afforded the desired *cis*-α-epoxide **20** with a modest degree of selectivity (α/*β* = 2.3:1, 70% total yield).[20-22] We were unable to assign the stereochemistry of the epoxide at that stage, but completion of the synthesis as described below established the fact that the major isomer corresponds to the desired α-epoxide.

The facial selectivity of epoxidation was probed through density functional theory (DFT) calculations, at the B3LYP/6-311+G(d,p) level of theory (Figure 1).[23] Competing transition structures were located for oxidation of either diastereoface of the allylic alcohol, according to a concerted mechanism involving a V^V-peroxy species as originally proposed by Sharpless et al.[20] and supported by

recent computational studies.[24] Due to the complexity of the substrate used experimentally, modeling studies used truncated substrate **C** to investigate the effect of the allylic stereocenter. In close agreement with experiment, a small free energy preference of 2.4 kJ/mol (i.e. 2.5:1 at 40 °C) is computed between TSs for epoxidation of either face of the C=C bond, favoring the *cis*-α-epoxide. This modest selectivity results from the difference in the hyperconjugative donating abilities of allylic C-C and C-O σ-bonds. In forming the major diastereomer, the allylic stereocenter is oriented so as to maximize σ_{C-C} and $\pi_{C=C}$ overlap, enhancing the electron density that may be donated towards the electrophilic oxidant in the TS. In the minor pathway this orientation is prohibited by the approach of the electrophile, and consequently there is less hyperconjugative donation from the σ_{C-C} bond. NBO calculations confirm this, showing greater $\sigma_{C-C} \rightarrow \pi^*_{C=C}$ delocalization in the favored TS, and greater $\sigma_{C=C} \rightarrow \sigma^*_{C-O}$ in the disfavored TS. Two different model systems **B** and **C** give the same relative free energies and similar conformations (see the Supporting Information for **B**), indicating that the selectivity is predominantly influenced by the allylic stereocenter, rather than by more remote stereoinductive effects.
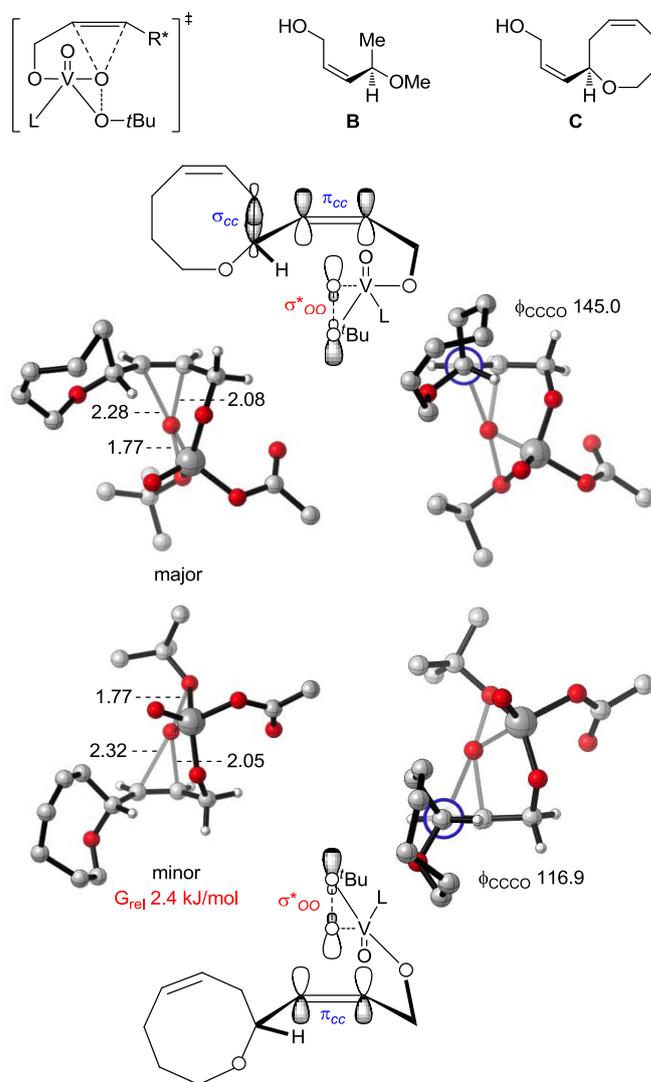
Figure 1. DFT Calculations on Diastereoselective Sharpless Epoxidation of **19**

Returning to Scheme 6, we focussed our attention on the introduction of the (*Z*)-enyne unit. Unfortunately, the use of the Yamamoto-Peterson reaction[25] on epoxy aldehyde **21**, generated from **20** by DMP oxidation in excellent yield (96%),[26] led to destruction of the starting material. To our delight, the desired (Z)-enyne unit

could be installed by application of the Julia-Kocienski procedure[27] to **21** with sulfone **A** to give the desired TMS-(*Z*)-enyne **22** in a serviceable yield and with a good stereoselectivity (53% isolated yield, *Z/E* = 16:1). Finally, regioselective opening of allylic epoxide **22** with chloride,[28] followed by removal of the TMS group in the resultant chlorohydrin **23** by exposure to TBAF under acidic conditions, delivered bermudenynol (**1**) in good overall yield for the two steps (68 %). It is imperative to run the desilylation with fluoride under slightly acidic conditions, since otherwise diene **24** is formed as the major product. Both the spectral characteristics and optical rotation of our synthetic material **1** were in good agreement with those reported for the natural bermudenynol: $[\alpha]^{25}_D$ +194.3 (*c* 0.75, CHCl$_3$) [natural: lit.[2] $[\alpha]^{25}_D$ +187 (*c* 0.756, CHCl$_3$)]. In particular, the ^{13}C NMR (125 MHz, acetone-d_6) spectral data were in excellent agreement with the resonances listed in the original isolation paper (20 MHz, acetone-d_6), and bermudenynol was fully characterized by 1D and 2D NMR spectroscopy (COSY, HSQC, HMBC, and NOESY). In addition, the measured rotation of our synthetic material supports the conclusion that the absolute configuration of (+)-bermudenynol is that represented by the structure **1**.

3. Conclusions

In summary, we have accomplished a substrate-controlled asymmetric total synthesis of (+)-bermudenynol (**1**), a compact and synthetically challenging C_{15} *Laurencia* metabolite that is laced with halogen atoms, in 21 steps from the known and readily available *syn*-diol intermediate **5**. The vinyl chloride-containing oxocene core in the natural product was constructed by an efficient and highly stereoselective intramolecular amide enolate alkylation, which showcases the broad utility of our IAEA methodology as a useful alternative for cases in which the ring-closing metathesis is inefficient.

− Experimentals: Part A −

Experimental Procedures and Product Characterization

General Procedures Proton (^{1}H) and carbon (^{13}C) NMR spectra were obtained on a Jeol JNM-LA300 (300/75 MHz), Bruker AV 400 (400/100 MHz), Bruker AMX 500 (500/125 MHz), Jeol JNM-ECA600 (600/150 MHz), or AVANCE II 900 (900/225 MHz) spectrometer. Chemical shifts are reported in ppm units with Me$_4$Si or CHCl$_3$ as the internal standard. All reactions were routinely carried out under an inert atmosphere of dry nitrogen or argon. Reactions were checked by thin layer chromatography (Kieselgel 60 F254, Merck). Spots were detected by viewing under a UV light, and by colorizing with charring after dipping in a *p*-anisaldehyde solution or phosphomolybdic acid solution. In aqueous work-up, all organic solutions were dried over anhydrous sodium sulfate and filtered prior to rotary evaporation at water pump pressure. The crude compounds were purified by column chromatography on a silica gel (Kieselgel 60, 70-230 mesh, Merck). Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. All solvents were purified and dried by standard techniques just before use. THF and Et$_2$O were freshly distilled from sodium and benzophenone. Methylene chloride, toluene, and benzene were purified by refluxing with CaH$_2$. Hexanes and ethylacetate were purified by simple distillation.

Preparation of α-Alkoxy Amide 7
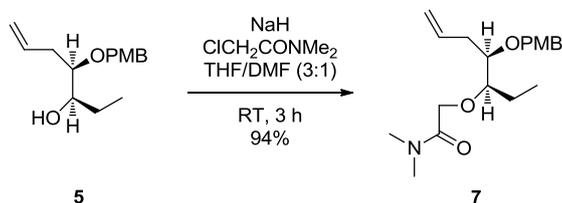
To a cooled (0 °C) solution of the known alcohol **5**[1] (420.0 mg, 1.678 mmol) in anhydrous THF/DMF (3:1, total 8.4 mL, 0.2 M) was added in one portion sodium hydride (168.0 mg, 60% dispersion in mineral oil, 4.2 mmol), followed by dropwise addition of 2-chloro-*N,N*-dimethylacetamide (0.52 mL, 5.034 mmol) after 10 min. After being stirred at the room temperature for 3 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL), and diluted with Et_2O (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic layers were washed successively with H_2O and saturated brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo.* The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 2/1 to 1/1) to give α-alkoxy amide **7** (530.0 mg, 94%): R_f 0.30 (hexanes/EtOAc, 1/1); colorless oil; $[\alpha]_D^{25}$ = +6.14 (*c* 1.02, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.6 Hz, 2 H), 6.85 (d, *J* = 8.7 Hz, 2 H), 5.81-5.89 (m, 1 H), 5.07 (ddd, *J* = 1.5, 18.3, 27.8 Hz, 2 H), 4.51 (ddd, *J* = 11.2, 11.2, 11.2 Hz, 2 H), 4.21 (ddd, *J* = 13.2, 13.2, 13.2 Hz, 2 H), 3.79 (s, 3 H), 3.53 (ddd, *J* = 4.9, 4.9, 7.4 Hz, 1 H), 3.36 (ddd, *J* = 4.8, 4.8, 7.7 Hz, 1 H), 2.98 (s, 3 H), 2.92 (s, 3 H), 2.36-2.41 (m, 1 H), 2.24 (ddd, *J* = 7.4, 7.4, 14.6 Hz, 1 H), 1.63-1.71 (m, 1 H), 1.45-1.54 (m, 1

H), 0.91 (dd, J = 7.4, 7.4, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 169.5, 159.1, 135.3, 130.8, 129.4, 116.8, 113.6, 82.8, 79.4, 72.1, 70.3, 55.2, 36.6, 35.3, 34.7, 22.7, 10.1; IR (neat) 2929, 2874, 1651, 1613, 1514, 1249, 1106, 1036 cm^{-1}; HRMS (FAB) found 336.2168 [calcd for C$_{19}$H$_{30}$NO$_4^+$ (M+H)$^+$ 336.2175].

Preparation of Aldehyde 8
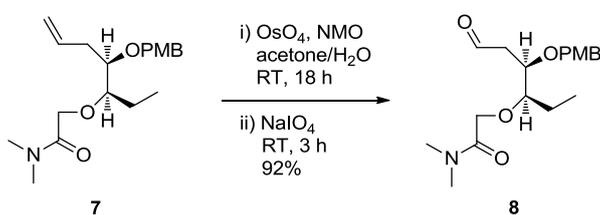
To a solution of terminal alkene **7** (512.0 mg, 1.526 mmol) in acetone (7.6 mL, 0.2 M) was dropwise added successively osmium tetroxide (1.6 mL, 0.5 wt% in H$_2$O, 0.031 mmol) and *N*-methylmorpholine-*N*-oxide (1.07 mL, 50 wt% in H$_2$O, 4.579 mmol) at room temperature, and the mixture was stirred for 18 h at the same temperature. To the reaction mixture was then added sodium periodate (653.0 mg, 3.053 mmol) in one portion. After being stirred at room temperature for 3 h, the reaction mixture was diluted with H$_2$O (10 mL) and CH$_2$Cl$_2$ (10 mL). The layers were separated, and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 × 10 mL). The combined organic layers were washed successively with H$_2$O and saturated brine, dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated *in vacuo*. The residue was purified by filtration through a short column of silica gel (hexanes/EtOAc, 1/1 to 1/2) to give aldehyde **8** (474.0 mg,

92%): R_f 0.30 (EtOAc only); colorless oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.77 (dd, J = 1.7, 1.7 Hz, 1 H), 7.24 (d, J = 8.5 Hz, 2 H), 6.86 (d, J = 8.6 Hz, 2 H), 4.52 (ddd, J = 11.3, 11.3, 11.3 Hz, 2 H), 4.13-4.22 (m, 3 H), 3.79 (s, 3 H), 3.46 (ddd, J = 4.4, 4.4, 8.3 Hz, 1 H), 2.96 (s, 3 H), 2.93 (s, 3 H), 2.79 (ddd, J = 1.4, 4.4, 16.7 Hz, 1 H), 2.62 (ddd, J = 2.3, 7.7, 16.7 Hz, 1 H), 1.65-1.73 (m, 1 H), 1.42-1.53 (m, 1 H), 0.94 (dd, J = 7.3, 7.3 Hz, 3 H).

Preparation of Terminal Alkyne 9
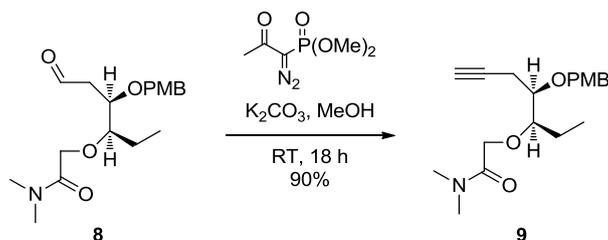
To a cooled (0 °C) solution of aldehyde **8** (144.1 mg, 0.427 mmol) in anhydrous MeOH (4.3 mL, 0.1 M) was dropwise added dimethyl-1-diazo-2-oxopropylphosphonate (0.1 mL, 0.666 mmol), followed by addition of potassium carbonate (118.1 mg, 0.854 mmol) in one portion, under Ar. After being stirred at room temperature for 18 h, the reaction mixture was quenched with saturated aqueous NaHCO$_3$ (10 mL) at 0 °C, and diluted with Et$_2$O (10 mL). The layers were separated, and the aqueous layer was extracted with Et$_2$O (2 × 50 mL). The combined organic layers were washed successively with H$_2$O and saturated brine, dried over anhydrous Na2SO4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel,

hexanes/EtOAc, 2/1 to 1/1) to give terminal alkyne **9** (127.6 mg, 90%): R_f 0.50 (EtOAc

only); colorless oil; $[\alpha]_D^{25} = -24.78$ (c 0.43, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ

7.29 (d, J = 8.6 Hz, 2 H), 6.86 (d, J = 8.7 Hz, 2 H), 4.68 (d, J = 11.4 Hz, 1 H), 4.51 (d, J

= 11.3 Hz, 1 H), 4.23 (ddd, J = 13.3, 13.3, 13.3 Hz, 2 H), 3.80 (s, 3 H), 3.65 (ddd, J =

5.9, 5.9, 5.9 Hz, 1 H), 3.45-3.49 (m, 1 H), 2.99 (s, 3 H), 2.92 (s, 3 H), 2.57 (ddd, J = 2.7,

5.6, 17.0 Hz, 1 H), 2.43 (ddd, J = 2.6, 6.3, 17.0 Hz, 1 H), 1.99 (dd, J = 2.6, 2.6 Hz, 1 H),

1.62-1.70 (m, 1 H), 1.50-1.59 (m, 1 H), 0.88 (dd, J = 7.5, 7.5, 3 H); ^{13}C NMR (125 MHz,

CDCl$_3$) δ 169.3, 159.3, 130.4, 129.6, 113.7, 82.2, 81.5, 77.7, 72.3, 70.1, 69.8, 55.3, 36.6,

35.3, 22.4, 20.3, 10.0; IR (neat) 3286, 3245, 2962, 2935, 2877, 1650, 1514, 1249, 1106,

823 cm^{-1}; HRMS (FAB) found 334.2025 [calcd for C$_{19}$H$_{28}$NO$_4^+$ (M+H)$^+$ 334.2018].

Preparation of Propargylic Ester 10
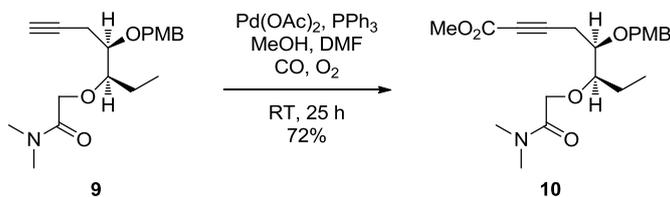
To a cooled (0 °C) solution of palladium acetate (26.8 mg, 0.120 mmol) and

triphenylphosphine (62.7 mg, 0.239 mmol) in anhydrous DMF (4 mL) was dropwise

added terminal alkyne **9** (102.5 mg, 0.398 mmol) in anhydrous MeOH (0.4 mL, 9.885

mmol). After being stirred for 25 h at room temperature under the atmoshphere of

carbon monoxide and oxygen (1:1), the reaction mixture was quenched with H$_2$O (10

mL) at 0 °C, and diluted with Et$_2$O (10 mL). The layers were separated, and the aqueous

layer was extracted with Et$_2$O (2 × 50 mL). The combined organic layers were washed successively with H$_2$O and saturated brine, dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 3/1 to 2/1) to give propargylic ester **10** (90.4 mg, 72%): R*f* 0.33 (hexanes/EtOAc, 1/2); colorless oil; $[\alpha]_D^{25} = -3.68$ (*c* 0.90, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.29 (d, *J* = 8.6 Hz, 2 H), 6.87 (d, *J* = 8.7 Hz, 2 H), 4.66 (d, *J* = 11.3 Hz, 1 H), 4.53 (d, *J* = 11.3 Hz, 1 H), 4.20 (s, 2 H), 3.80 (s, 3 H), 3.76 (s, 3 H), 3.72-3.75 (m, 1 H), 3.43 (ddd, *J* = 4.8, 4.8, 7.4 Hz, 1 H), 2.98 (s, 3 H), 2.93 (s, 3 H), 2.73 (dd, *J* = 4.9, 17.4 Hz, 1 H), 2.56 (dd, *J* = 7.1, 17.4 Hz, 1 H), 1.63-1.72 (m, 1 H), 1.46-1.57 (m, 1 H), 0.9 (dd, J = 7.4, 7.4 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 169.2, 159.3, 154.0, 130.0, 129.7, 113,8, 87.2, 82.2, 76.9, 74.0, 72.5, 69.7, 55.3, 52.6, 36.5, 35.4, 22.2, 20.7, 10.1; IR (neat) 2917, 2240, 1714, 1655, 1514, 1253, 1076, 771 cm^{-1}; HRMS (FAB) found 392.2064 [calcd for C$_{21}$H$_{30}$NO$_6^+$ (M+H)$^+$ 392.2073].

Preparation of (*E*)-*β*-Stannyl Enoate 11
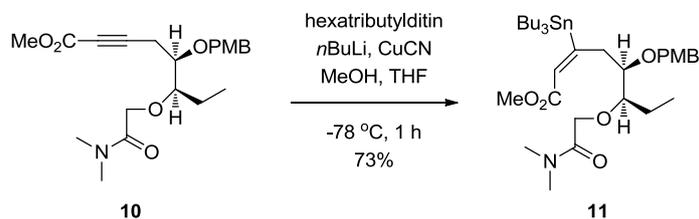
To a cooled (−78 °C) solution of hexatributylditin (759.0 mg, 1.309 mmol) in anhydrous THF (1.5 mL) was dropwise added *n*-butyllithium (0.78 mL, 1.6 M solution in hexanes, 1.243 mmol) under Ar, and the resulting solution was stirred at −40 °C for 30 min. To a cooled (−78 °C) suspension of CuCN (58.6 mg, 0.654 mmol) in anhydrous THF (1.5 mL) was dropwise added the above-generated solution via cannular, and the resulting mixture was stirred for 30 min at −78 °C until obtention of a yellow solution. Upon dropwise addition of MeOH (0.4 mL) at −78 °C, the yellow solution turned to a red gel, which was stirred at −10 °C for 30 min until obtention of a red solution. To a cooled (−78 °C) red solution of $Bu_3Sn(Bu)CuCNLi_2$ (1.2 mL, 0.179 mmol) was dropwise added propargylic ester **10** (22.0 mg, 0.056 mmol) in anhydrous THF (0.5 mL). After being stirred at same temperature for 1 h, the reaction mixture was quenched with saturated aqueous NH4Cl (10 mL), and diluted with EtOAc (20 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed successively with H2O and saturated brine, dried over anhydrous Na2SO4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 5/1 to 3/1) to give (*E*)-*β*-stannyl enoate **11**

(28.0 mg, 73%): R*f* 0.30 (hexanes/EtOAc, 1/1); colorless oil; $[\alpha]_D^{25}$ = +50.80 (*c* 0.40, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.18 (d, *J* = 8.6 Hz, 2 H), 6.82 (d, *J* = 8.6 Hz, 2 H), 6.05 (d, *J* = 31.9, 31.9 Hz, 1 H), 4.34-4.48 (m, 3 H), 4.10 (d, *J* = 13.3 Hz, 1 H), 3.79 (s, 3 H), 3.74 (ddd, *J* = 3.6, 3.6, 8.5 Hz, 1 H), 3.65 (s, 3 H), 3.40 (ddd, *J* = 4.2, 4.2, 8.4 Hz, 1 H), 3.15 (dd, *J* = 10.2, 12.7 Hz, 1 H), 3.02-3.06 (m, 1 H), 3.00 (s, 3 H), 2.92 (s, 3 H), 1.65-1.75 (m, 1 H), 1.41-1.55 (m, 6 H), 1.23-1.31 (m, 6 H), 0.85-0.97 (m, 19 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 171.8, 169.6, 164.4, 158.9, 131.0, 129.4, 129.0, 113.4, 83.0, 80.0, 72.3, 69.9, 55.2, 50.8, 36.7, 35.4, 35.3, 28.9, 27.4, 22.7, 13.6, 10.5, 10.3; IR (neat) 2955, 2927, 1715, 1654, 1514, 1463, 1249, 1171, 1077, 822 cm^{-1}; HRMS (FAB) found 684.3293 [calcd for C$_{33}$H$_{58}$NO$_6$Sn$^+$ (M+H)$^+$ 684.3286].

Preparation of (*E*)-γ-Stannyl Allylic Alcohol 12
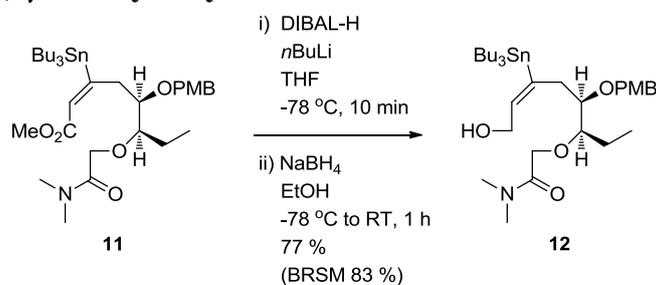
An ate complex (0.3 M solution in hexanes/THF) was generated by dropwise addition of *n*-buthyllithium (1.0 mL, 1.6 M solution in hexanes, 1.6 mmol) to DIBAL-H (1.6 mL, 1.0 M solution in hexanes, 1.6 mmol) in anhydrous THF (2.6 mL) at 0 °C under Ar, followed by stirring for 30 min at 0 °C. To a cooled (–78 °C) solution of (*E*)-β-stannyl

enoate **11** (12.0 mg, 0.018 mmol) in anhydrous THF (0.8 mL, 0.023 M) was dropwise added the above-generated ate complex solution (0.18 mL, 0.054 mmol) under Ar, and the resulting mixture was stirred for 10 minutes at the same temperature. To the mixture was dropwise added sodium borohydride (0.53 mL, 0.3 M in dry ethanol solution, 0.159 mmol). The reaction mixture was warmed to room temperature over 1 h with stirring, quenched with saturated aqueous NH_4Cl (10 mL), and diluted with EtOAc (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3×20 mL). The combined organic layers were washed successively with H_2O and saturated brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo.* The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 2/1 to 1/1) to give (*E*)-γ-stannyl allylic alcohol **12** (8.9 mg, 77%, 83% BRSM): Rf 0.20 (hexanes/EtOAc, 1/1); colorless oil; $[\alpha]_D^{25}$ = +20.96 (*c* 0.76, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.23 (d, *J* = 8.4 Hz, 2 H), 6.85 (d, *J* = 8.4 Hz, 2 H), 5.95-6.12 (m, 1 H), 4.48 (ddd, *J* = 11, 11, 11 Hz, 2 H), 4.18 (ddd, *J* = 13.1, 13.1, 13,1 Hz, 2 H), 4.09-4.15 (m, 1 H), 4.02-4.07 (m, 1 H), 3.79 (s, 3 H), 3.49 (ddd, *J* = 3.8, 3.8, 8.2 Hz, 1 H), 3.44 (ddd, *J* = 4.5, 4.5, 8.0 Hz, 1 H), 3.13 (s, 1 H, OH), 2.99 (s, 3 H), 2.94 (s, 3 H), 2.69 (dd, *J* = 9.5, 13.5 Hz, 1 H), 2.49 (dd, *J* = 3.7, 13.5 Hz, 1 H), 1.66-1.73 (m, 1 H), 1.55-1.61 (m, 1 H), 1.40-1.54 (m, 6 H), 1.27-1.34 (m, 6 H), 0.94-0.96 (m, 3 H), 0.87-0.90 (m, 15 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 169.3, 159.3, 144.3, 142.6, 129.9, 129.6, 113.7, 82.0, 78.8, 72.6, 69.3, 57.8, 55.2, 36.6, 35.4, 33.6, 29.1, 27.5, 13.7, 10.5, 9.7; IR (neat) 3438, 2955, 2927, 2871,

1654, 1514, 1249, 1073, 822 cm^{-1}; HRMS (FAB) found 656.3337 [calcd for

$C_{32}H_{58}NO_5Sn^+$ (M+H)$^+$ 656.3337].

Preparation of (*E*)-γ-Chloro Allylic Alcohol 13 at 0 °C

12   **13**
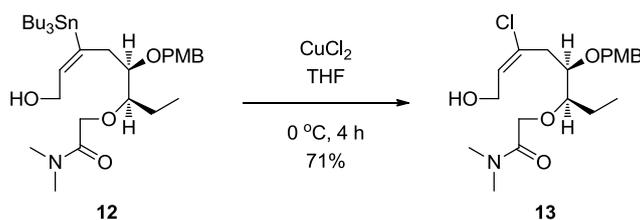
To a cooled (0 °C) solution of (*E*)-γ-stannyl allylic alcohol **12** (10.4 mg, 0.016 mmol) in

anhydrous THF (2.0 mL, 0.008 M) was added copper chloride (42.7 mg, 0.318 mmol)

in one portion. After being stirred at the same temperature for 4 h, the reaction mixture

was quenched with saturated aqueous NH$_4$Cl (10 mL), diluted with EtOAc (10 mL), and

stirred for 3 h at room temperature. The layers were separated, and the aqueous layer

was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed

successively with H2O and saturated brine, dried over anhydrous Na$_2$SO$_4$, filtered, and

concentrated *in vacuo.* The residue was purified by column chromatography (silica gel,

hexanes/EtOAc, 2/1) to give (*E*)-γ-chloro allylic alcohol **13** (4.5 mg, 71%): R$_f$ 0.20

(EtOAc only); colorless oil; [α]$_D^{25}$ = −7.61 (*c* 0.51, CHCl$_3$); ^{1}H NMR (500 MHz,

CDCl$_3$) δ 7.25 (d, *J* = 8,2 Hz, 2 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 6.04 (dd, *J* = 7.4, 7.4 Hz, 1

H), 4.53 (s, 2 H), 4.25 (d, *J* = 13.2 Hz, 1 H), 4.14 (d, *J* = 13.2 Hz, 1 H), 3.99-4.10 (m, 2

H), 3.91 (ddd, *J* = 4.8, 4.8, 8.6 Hz, 1 H), 3.80 (s, 3 H), 3.49 (ddd, *J* = 4.7, 4.7, 8.0 Hz, 1

H), 3.21 (dd, J = 6.6, 6.6 Hz, 1 H, OH), 3.00 (s, 3 H), 2.94 (s, 3 H), 2.65-2.75 (m, 2 H), 1.65-1.72 (m, 1 H), 1.51-1.57 (m, 1 H), 0.92 (dd, J = 7.4, 7.4 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 169.4, 159.5, 135.1, 129.9, 129.7, 113.8, 81.4, 75.7, 72.7, 68.8, 58.2, 55.2, 36.6, 35.4, 34.8, 22.0, 10.3; IR (neat) 3414, 2963, 2935, 2876, 1650, 1613, 1514, 1105, 1034 cm^{-1}; HRMS (FAB) found 400.1895 [calcd for $C_{20}H_{31}ClNO_5^+$ (M+H)$^+$ 400.1891].

Preparation of (*E*)-γ-Chloro Allylic Alcohol 13 at –40 to –5 ^{o}C

To a cooled (–40 ℃) solution of (*E*)-γ-stannyl allylic alcohol **12** (22.0 mg, 0.034 mmol) in anhydrous THF (2 mL, 0.017 M) was added in one portion copper chloride (91.6 mg, 0.681 mmol). After being stirred for 90 h at –40 ℃, the reaction mixture was stirred at –5 ℃ for additional 10 h to complete the reaction, quenched with saturated aqueous NH$_4$Cl (10 mL), diluted with EtOAc (10 mL), and stirred for 3 h at room temperature. The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed successively with H2O and saturated brine, dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated *in vacuo.* The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 2/1) to afford (*E*)-γ-chloro allylic alcohol **13** (10.8 mg, 79%).

[**Note**] The tin-chlorine exchange reaction had been carried out at –40 to –5 ℃ (100 h, 79%) until it was found out that the lower temperature was not necessary (0 ℃, 4 h,

71%) at the final stage of synthesis. The experiment at 0 $^{\circ}$C was carried out only once and the yield was not optimized.

Preparation of (*E*)-*γ*-Chloro Allylic Bromide 4
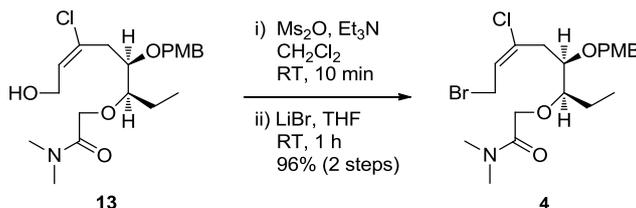
[Mesylation] To a solution of (*E*)-*γ*-chloro allylic alcohol **13** (50.1 mg, 0.125 mmol) in anhydrous CH2Cl2 (2 mL, 0.063 M) was dropwise added triethylamine (0.052 mL, 0.375 mmol), followed by addition of methanesulfonic anhydride (34.0 mg, 0.188 mmol) in one portion at room temperature under Ar. After being stirred at the same temperature for 10 min, the reaction mixture was quenched with saturated aqueous NH4Cl (10 mL), and diluted with CH2Cl2 (10 mL). The layers were separated and the aqueous layer was extracted with CH2Cl2 (2 × 20 mL). The combined organic layers were washed successively with H2O and saturated brine, dried over anhydrous Na2SO4, filtered, and concentrated *in vacuo*. The crude product was used for the next step without further purification.

[Bromination] To a solution of the crude mesylate in THF (2 mL) was added lithium bromide (109.0 mg, 1.253 mmol) in one portion at room temperature. After being stirred at the same temperature for 1 h, the reaction mixture was quenched with H$_2$O (10 mL), and diluted with EtOAc (10 mL). The layers were separated, and the aqueous layer

was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed successively with H2O and saturated brine, dried over anhydrous Na2SO4, filtered, and concentrated *in vacuo*. The residue was purified by filtration through a short column of silica gel (hexanes/EtOAc, 1/1 to 1/2) to give (*E*)-γ-chloro allylic bromide **4** (55.7 mg, 96% for 2 steps): R_f 0.40 (EtOAc only); colorless oil; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.22 (d, *J* = 8.6 Hz, 2 H), 6.85 (d, *J* = 8.6 Hz, 2 H), 6.00 (dd, *J* = 7.9, 9.5 Hz, 1 H), 4.50 (s, 2 H), 4.19 (ddd, *J* = 13.3, 13.3, 13.3 Hz, 2 H), 4.07 (dd, *J* = 10.5, 10.5 Hz, 1 H), 3.85-3.88 (m, 2 H), 3.79 (s, 3 H), 3.41 (ddd, *J* = 4.4, 4.4, 8.2 Hz, 1 H), 3.00 (s, 3 H), 2.94 (s, 3 H), 2.78 (dd, *J* = 9.3, 14.5 Hz, 1 H), 2.54 (dd, *J* = 2.7, 14.5 Hz, 1 H), 1.64-1.72 (m, 1 H), 1.45-1.54 (m, 1 H), 0.93 (dd, *J* = 7.4, 7.4 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 169.2, 159.2, 137.8, 130.4, 129.6, 126.2, 113.6, 82.3, 76.3, 73.0, 69.5, 55.2, 36.6, 35.6, 35.4, 27.4, 22.3, 10.3; IR (neat) 2934, 1650, 1514, 1249, 1104, 1082 cm^{-1}; HRMS (FAB) found 462.1045 [calcd for C$_{20}$H$_{30}$BrClNO$_4^+$ (M+H)$^+$ 462.1047].

[**Note**] Two modifications of the original procedure (G. Stork, P. A. Grieco, M. Gregson, *Tetrahedron Lett*. **1969**, *10*, 1393-1395) were implemented: use of mesyl anhydride instead of mesyl chloride, and the target in the present case is a bromide, and not a chloride as in the original work. The use of methanesulfonyl chloride as described in the original procedure produced a small amount of the corresponding allylic chloride, which resulted in a lower yield during the subsequent intramolecular amide enolate alkylation.

Preparation of Oxocene Amide 3
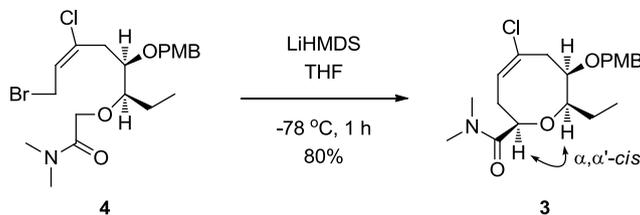
To a cooled (−78 °C) solution of (*E*)-γ-chloro allylic bromide **4** (15.2 mg, 0.033 mmol)

in anhydrous THF (7.2 mL, 0.005 M) was dropwise added LiHMDS (0.33 mL, 0.2 M

solution in THF, 0.066 mmol) under Ar. After being stirred at the same temperature for

1 h, reaction mixture was quenched with saturated aqueous NH_4Cl (20 mL), and diluted

with EtOAc (50 mL) and H_2O. The layers were separated, and the aqueous layer was

extracted with EtOAc (2 x 50 mL). The combined organic layers were washed

successively with H_2O and saturated brine, dried over anhydrous Na_2SO_4, filtered, and

concentrated *in vacuo*. The residue was purified by column chromatography (silica gel,

hexanes/EtOAc, 3/1 to 2/1) to give oxocene amide **3** (10.1 mg, 80%): R*f* 0.20

(hexanes/EtOAc, 1/1); colorless oil; $[\alpha]_D^{25} = +22.15$ (*c* 0.37, CHCl$_3$); ^{1}H NMR (500

MHz, CDCl$_3$) δ 7.26 (d, *J* = 8.6 Hz, 2 H), 6.87 (d, *J* = 8.7 Hz, 2 H), 5.95 (dd, *J* = 7.5,

8.9 Hz, 1 H), 4.62 (d, *J* = 11.5 Hz, 1 H), 4.40 (d, *J* = 11.6 Hz, 1 H), 4.17 (dd, *J* = 1.2,

10.2 Hz, 1 H), 3.80 (s, 3 H), 3.76-3.79 (m, 1 H), 3.51 (ddd, *J* = 2.6, 6.3, 8.3 Hz, 1 H),

3.12-3.17 (m, 4 H), 2.93 (s, 3 H), 2.75 (ddd, *J* = 7.5, 10.2, 14.7 Hz, 1 H), 2.61 (dd, *J* =

4.6, 13.1 Hz, 1 H), 2.26 (ddd, *J* = 1.4, 9.0, 14.7 Hz, 1 H), 1.67-1.76 (m, 1 H), 1.50-1.59

(m, 1 H), 0.82 (dd, J = 7.4, 7.4 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 170.0, 159.2,

134.3, 130.3, 129.5, 125.5, 113.7, 84.3, 83.1, 78.8, 71.1, 55.3, 37.4, 36.9, 36.2, 33.0,

25.1, 10.4; IR (neat) 2965, 2936, 1649, 1613, 1513, 1250, 1076, 822 cm^{-1}; HRMS

(FAB) found 382.1787 [calcd for C$_{20}$H$_{29}$ClNO$_4^+$ (M+H)$^+$ 382.1785].

Preparation of α,α'-*cis*-C(12)/C(13)-*syn* Oxocene Alcohol 14
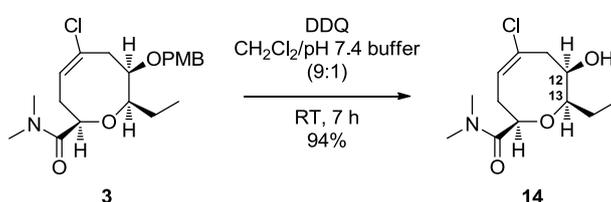
To a cooled (0 °C) solution of oxocene amide **3** (317.0 mg, 0.830 mmol) in CH$_2$Cl$_2$/pH

7.4 buffer solution (9:1, total 11 mL, 0.076 M) was added 2,3-dichloro-5,6-dicyano-1,4-

benzoquinone (471.0 mg, 2.075 mmol) in one portion. After being stirred vigorously at

room temperature for 7 h, the reaction mixture was quenched with saturated aqueous

NaHCO$_3$ (100 mL), and diluted with H$_2$O (40 mL) and CH$_2$Cl$_2$ (50 mL). The resulting

dark red mixture was stirred vigorously at room temperature for 2 h. The layers were

separated, and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 × 50 mL). The combined

organic layers were washed successively with H$_2$O and saturated brine, dried over

anhydrous Na$_2$SO$_4$, filtered, and concentrated *in vacuo*. The residue was purified by

column chromatography (silica gel, hexanes/EtOAc, 2/1 to 1/1) to give α,α'-*cis*-

C(12)/C(13)-*syn* oxocene alcohol **14** (204.0 mg, 94%): R$_f$ 0.15 (EtOAc only); colorless

oil; $[\alpha]_D^{25} = +19.47$ (c 0.079, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.95 (dd, $J = 7.9$, 7.9 Hz, 1 H), 4.27 (dd, $J = 1.5$, 9.6 Hz, 1 H), 4.00 (s, 1 H, OH), 3.51-3.54 (m, 1 H), 3.10 (s, 3 H), 3.05 (dd, $J = 10.2$, 13.3 Hz, 1 H), 2.95 (s, 3 H), 2.67-2.74 (m, 1 H), 2.62 (dd, $J = 4.8$, 13.2 Hz, 2 H), 2.21 (ddd, $J = 1.6$, 9.0, 14.8 Hz, 1 H), 1.65-1.73 (m, 1 H), 1.56-1.64 (m, 1 H), 0.91 (dd, $J = 7.5$, 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 170.1, 134.5, 124.9, 83.5, 80.3, 72.7, 40.9, 37.3, 36.0, 32.9, 25.1, 10.4; IR (neat) 3402, 2964, 1644, 1098, 1076 cm^{-1}; HRMS (FAB) found 262.1216 [calcd for C$_{12}$H$_{21}$ClNO$_3^+$ (M+H)$^+$ 262.1210].

Preparation of Chloromethanesulfonate 16

14 → **16**
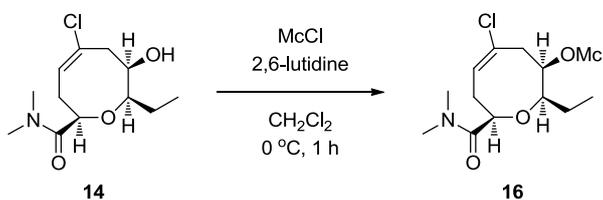
To a cooled (0 °C) solution of α,α'-cis-C(12)/C(13)-syn oxocene alcohol **14** (342.7 mg, 1.309 mmol) in anhydrous CH$_2$Cl$_2$ (13 mL, 0.1 M) were dropwise added successively 2,6-lutidine (1.53 mL, 13.093 mmol) and chloromethanesulfonyl chloride (0.58 mL, 6.547 mmol) under Ar. After being stirred at the same temperature for 1 h, the reaction mixture was quenched with saturated aqueous NH$_4$Cl (10 mL), and diluted with CH$_2$Cl$_2$ (30 mL). The layers were separated, and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 × 80 mL). The combined organic layers were washed successively with H$_2$O

and saturated brine, dried over anhydrous Na2SO4, filtered, and concentrated *in vacuo*.
The residue was filtered through a short column of silica gel (hexanes/EtOAc, 2/1 to
1/1) to give the crude chloromethanesulfonate **16** (583.0 mg, 119%), which was
immediately used for the next step: R_f 0.50 (EtOAc only); colorless solid.

Preparation of Bromo Oxocene Amide 2
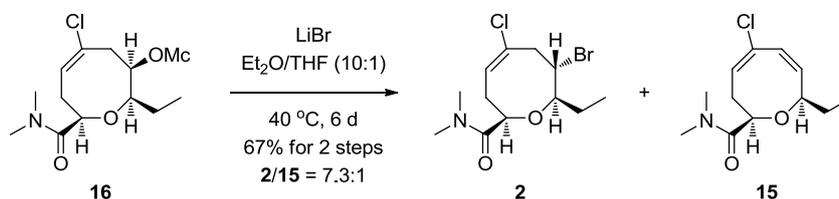
To a solution of the crude chloromethanesulfonate **16** (583.0 mg) in Et$_2$O/THF (10:1,
total 13 mL) was added lithium bromide (568.6 mg, 5.0 mmol) in one portion at room
temperature. After being heated at 40 °C (bath temperature) with stirring for 6 d, the
reaction mixture was cooled to room temperature, quenched with H$_2$O, and diluted with
EtOAc (100 mL). The layers were separated, and the aqueous layer was extracted with
EtOAc (2 × 50 mL). The combined organic layers were washed successively with H2O
and saturated brine, dried over anhydrous Na2SO4, filtered, and concentrated *in vacuo*.
The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 3/1 to
1/1) to give bromo oxocene amide **2** (284.8 mg, 67%, <u>isolated</u> yield for 2 steps) and
diene **15** (**2**/**15** = 7.3:1 by ^{1}H NMR analysis): **For Bromo Oxocene Amide 2**; R_f 0.25
(hexanes/EtOAc, 1/1); colorless solid; $[\alpha]_D^{25} = +24.36$ (*c* 0.55, CHCl$_3$); ^{1}H NMR (500

MHz, CDCl$_3$) δ 6.12 (dd, J = 7.2, 9.2 Hz, 1 H), 4.22 (dd, J = 1.8, 9.4 Hz. 1 H), 4.11 (ddd, J = 3.9, 3.9, 10.1 Hz, 1 H), 3.63 (dd, J = 3.9, 15.2 Hz, 1 H), 3.54 (ddd, J = 2.6, 8.1, 10.3 Hz, 1 H), 3.07 (s, 3 H), 2.96 (s, 3 H), 2.80 (dd, J = 3.8, 15.2 Hz, 1 H), 2.59-2.65 (m, 1 H), 2.28 (ddd, J = 1.8, 9.3, 14.9 Hz, 1 H), 2.03-2.11 (m, 1 H), 1.61-1.70 (m, 1 H), 0.94 (dd, J = 7.4, 7.4 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 169.9, 133.4, 126.2, 85.2, 79.9, 51.4, 40.2, 37.1, 36.1, 32.7, 26.6, 9.1; IR (neat) 2965, 2935, 1650, 1084, 1071 cm^{-1}; HRMS (FAB) found 324.0375 [calcd for C$_{12}$H$_{20}$BrClNO$_2$$^+$ (M+H)$^+$ 324.0366]; **For Diene 15**; R$_f$ 0.40 (hexanes/EtOAc, 1/1); colorless solid; ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.04 (dd, J = 8.6, 8.6 Hz, 1 H), 5.99 (d, J = 11.1 Hz. 1 H), 5.62 (dd, J = 7.2, 11.0 Hz, 1 H), 3.96 (dd, J = 1.5, 7.2 Hz, 1 H), 3.62 (ddd, J = 6.5, 6.5, 6.5 Hz, 1 H), 3.10 (s, 3 H), 2.96 (s, 3 H), 2.75 (ddd, J = 1.6, 9.0, 14.6 Hz, 1 H), 2.22 (ddd, J = 7.9, 7.9, 15.2 Hz, 1 H), 1.63-1.78 (m, 2 H), 0.94 (dd, J = 7.4, 7.4 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 170.0, 134.5, 132.0, 127.2, 127.1, 78.2, 73.6, 37.4, 36.0, 32.6, 29.7, 9.7; IR (neat) 3353, 2965, 2934, 2879, 1725, 1646, 1096, 755 cm^{-1}; HRMS (FAB) found 242.0951 [calcd for C$_{12}$H$_{17}$ClNO$_2$$^+$ (M+H)$^+$ 242.0948].

Preparation of Bromo Oxocene Amide 2 by the Hooz Protocol
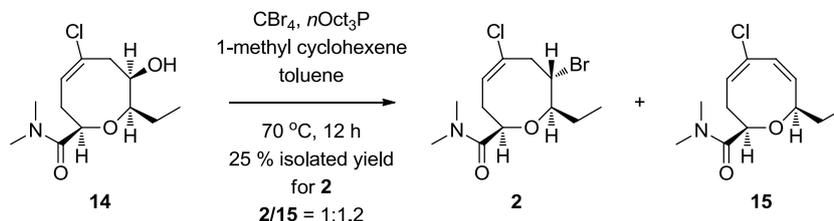
To a solution of α,α'-*cis*-C(12)/C(13)-*syn* oxocene alcohol **14** (7.0 mg, 0.027 mmol) in anhydrous toluene (0.5 mL, 0.053 M) was added in one portion carbon tetrabromide (10.6 mg, 0.032 mmol), followed by successive dropwise addition of *n*Oct$_3$P (0.03 mL, 90 %, 0.060 mmol) and 1-methyl cyclohexene (0.01 mL, 0.086 mmol) at room temperature. After being heated at 70 °C (bath temperature) with stirring for 12 h, the reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 3/1 to 1/1) to give bromo oxocene amide **2** (2.2 mg, 25% isolated yield) and diene **15** (**2/15** = 1:1.2 by ^{1}H NMR analysis).

Preparation of α-Alkoxy Aldehyde 17
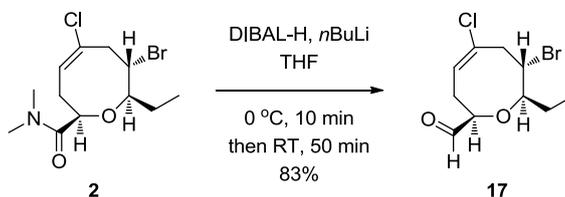
An ate complex (0.3 M solution in hexanes/THF) was generated by dropwise addition

of *n*-buthyllithium (1.0 mL, 1.6 M solution in hexanes, 1.6 mmol) to DIBAL-H (1.6 mL,

1.0 M solution in hexanes, 1.6 mmol) in anhydrous THF (2.6 mL) at 0 °C under Ar,

followed by stirring for 30 min at 0 °C. To a cooled (0 °C) solution of α-alkoxy

oxocene amide **2** (32.0 mg, 0.099 mmol) in anhydrous THF (1 mL, 0.1 M) was

dropwise added the above-generated ate complex (0.66 mL, 0.198 mmol) under Ar.

After being stirred at the same temperature for 10 min, the reaction mixture was stirred

at room temperature for additional 50 min, quenched with saturated aqueous NH_4Cl (30

mL), and diluted with EtOAc (30 mL). The layers were separated, and the aqueous layer

was extracted with EtOAc (2 × 30 mL). The combined organic layers were washed

successively with H_2O and saturated brine, dried over anhydrous Na_2SO_4, and

concentrated *in vacuo.* The residue was purified by filtration through a short column of

silica gel (hexanes/EtOAc, 20/1 to 15/1) to give α-alkoxy aldehyde **17** (23.0 mg, 83%),

which was used immediately for the next step: R_f 0.40 (hexanes/EtOAc, 3/1); colorless

solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.68 (s, 1 H), 6.05 (dd, *J* = 7.2, 9.1 Hz, 1 H), 4.08

(ddd, *J* = 4.1, 4.1, 10.1 Hz, 1 H), 3.76 (dd, *J* = 2.5, 9.4 Hz, 1 H), 3.50-3.56 (m, 2 H),

2.83 (dd, $J = 4.2$, 15.2 Hz, 1 H), 2.54 (ddd, $J = 2.5$, 9.3, 14.8 Hz, 1 H), 2.17-2.25 (m, 1

H), 1.59-1.65 (m, 1 H), 1.02 (dd, $J = 7.4$, 7.4 Hz, 3 H).

[**Note**] In their initial work (S. Kim, K. H. Ahn, *J. Org. Chem.* **1984**, *49*, 1717-1724),

Kim and Ahn reported that partial reduction of tertiary amides to the corresponding

aldehydes could be effected by using exactly one equivalent of the ate complex

generated from DIBAL-H and *n*BuLi, which precluded over-reduction to the primary

alcohol. With α-alkoxy dimethyl amide **2** in our case, an excess of the reagent could be

tolerated presumably since the partial reduction proceeds through a very stable metal-

chelated intermediate that resists over-reduction.

Preparation of (*Z*)-Enoate 18
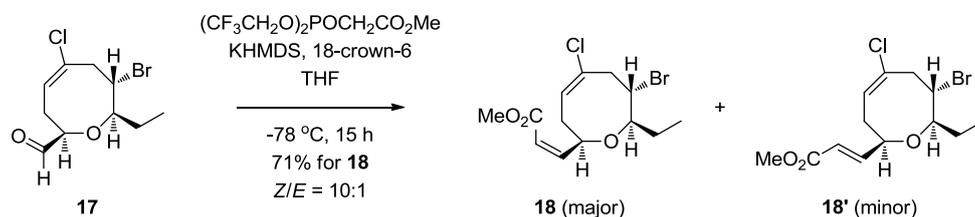
To a cooled (−78 °C) solution of $(CF_3CH_2O)_2POCH_2CO_2Me$ (114.0 mg, 95%, 0.340

mmol) and 18-crown-6 (377.0 mg, 1.426 mmol) in anhydrous THF (2 mL) was

dropwise added KHMDS (0.68 mL, 0.5 M solution in toluene, 0.340 mmol) under Ar,

and the resulting solution was stirred at the same temperature for 30 min. To a cooled (−

78 °C) solution of α-alkoxy aldehyde **17** (23.9 mg, 0.085 mmol) in anhydrous THF (1

mL, 0.085 M) was dropwise added the above-generated phosphonate anion solution

under Ar. After being stirred at the same temperature for 15 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL), and diluted with EtOAc (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed successively with H_2O and saturated brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 100/1 to 30/1) to give (*Z*)-enoate **18** (20.3 mg, 71% <u>isolated</u> yield) and (*E*)-enoate **18'** (*Z*/*E* = 10:1 by ^{1}H NMR analysis): **For (*Z*)-Enoate 18**; R_f 0.60 (hexanes/EtOAc, 10/1); colorless oil; $[\alpha]_D^{25} =$ +2.45 (*c* 0.21, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.21 (dd, *J* = 7.7, 11.8 Hz, 1 H), 6.13 (dd, *J* = 8.0, 8.0 Hz, 1 H), 5.76 (dd, *J* = 1.2, 11.9 Hz, 1 H), 4.96 (dd, *J* = 7.5, 7.5 Hz, 1 H), 3.99 (ddd, *J* = 4.0, 4.0, 9.9 Hz, 1 H), 3.73 (s, 3 H), 3.51-3.59 (m, 2 H), 2.80 (dd, *J* = 3.9, 15.1 Hz, 1 H), 2.25-2.35 (m, 2 H), 2.09-2.16 (m, 1 H), 1.36-1.45 (m, 1 H), 0.89 (dd, *J* = 7.3, 7.3 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 149.8, 132.7, 126.6, 118.0, 84.2, 78.9, 52.3, 51.4, 40.4, 35.4, 27.1, 9.6; IR (neat) 2963, 2925, 1721, 1642, 1438, 1208, 1068, 819 cm^{-1}; HRMS (CI) found 337.0206 [calcd for $C_{13}H_{19}BrClO_3^+$ (M+H)$^+$ 337.0206]; **For (*E*)-Enoate 18'**; R_f 0.40 (hexanes/EtOAc, 10/1); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (dd, *J* = 4.0, 15.6 Hz, 1 H), 6.03-6.10 (m, 2 H), 4.01-4.07 (m, 2 H), 3.75 (s, 3 H), 3.50-3.56 (m, 2 H), 2.80 (dd, *J* = 4.0, 15.1 Hz, 1 H), 2.09-2.37 (m, 3 H), 1.45-1.54 (m, 1 H), 0.93 (dd, *J* = 7.3, 7.3 Hz, 3 H).

Preparation of (Z)-Allylic Alcohol 19
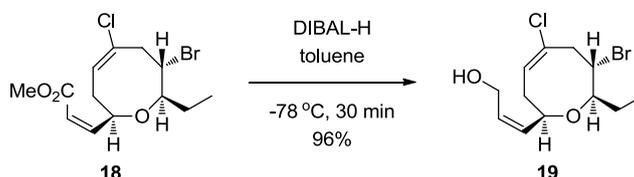
To a cooled (–78 °C) solution of (Z)-enoate **18** (11.0 mg, 0.033 mmol) in anhydrous

toluene (3 mL, 0.011 M) was dropwise added DIBAL-H (0.1 mL, 1.0 M solution in

hexanes, 0.1 mmol). After being stirred for 30 min at the same temperature, the reaction

mixture was quenched with saturated aqueous Rochelle's solution (10 mL), diluted with

EtOAc (20 mL), and stirred at room temperature for additional 2 h. The layers were

separated, and the aqueous layer was extracted with EtOAc (2 × 100 mL). The

combined organic layers were washed with saturated brine, dried over anhydrous

Na_2SO_4, filtered, and concentrated *in vacuo.* The residue was purified by column

chromatography (silica gel, hexanes/EtOAc, 10/1 to 5/1) to give (Z)-allylic alcohol **19**

(9.7 mg, 96%): R_f 0.40 (hexanes/EtOAc, 3/1); colorless oil; $[\alpha]_D^{25} = +21.96$ (*c* 0.68,

$CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.07 (dd, J = 7.3, 7.3 Hz, 1 H), 5.65 (ddd, J =

6.4, 6.4, 12.2 Hz, 1 H), 5.53 (dd, J = 8.0, 8.0 Hz, 1 H), 4.13-4.26 (m, 3 H), 4.00 (ddd, J

= 4.1, 4.1, 9.8 Hz, 1 H), 3.56 (dd, J = 3.4, 15.1 Hz, 1 H), 3.51 (ddd, J = 2.0, 9.8, 9.8 Hz,

1 H), 2.81 (dd, J = 4.0, 15.1 Hz, 1 H), 2.28-2.37 (m, 1 H), 2.11-2.22 (m, 2 H), 1.39-1.48

(m, 1 H), 0.93 (dd, J = 7.4, 7.4 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.9, 132.1,

129.1, 126.3, 84.5, 78.2, 58.9, 52.1, 40.4, 36.0, 27.2, 9.7; IR (neat) 3380, 2964, 2920,

2876, 1641, 1061, 1030, 942, 865, 836 cm^{-1}; HRMS (CI) found 309.0264 [calcd for

C$_{12}$H$_{19}$BrClO$_2^+$ (M+H)$^+$ 309.0257].

Preparation of *cis*-α-Epoxide 20
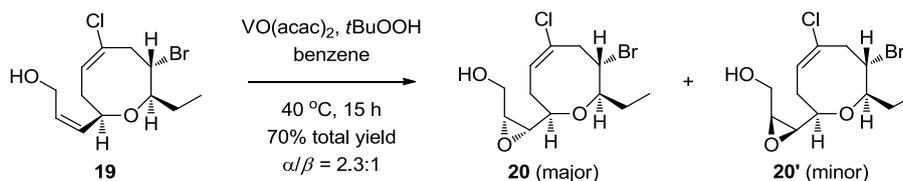
To a solution of (Z)-allylic alcohol **19** (4.1 mg, 0.013 mmol) in anhydrous benzene (2.0

mL, 0.007 M) was dropwise added *tert*-butyl hydroperoxide (0.01 mL, 5.5 M solution

in decane, 0.055 mmol), followed by vanadyl acetylacetonate (0.01 mL, 0.016 M in

benzene, 0.0002 mmol) at room temperature under Ar. The reaction mixture was heated

at 40 °C (bath temperature) with stirring for 15 h. The reaction mixture was quenched

with saturated aqueous Na$_2$S$_2$O$_4$ (10 mL), and diluted with EtOAc (10 mL). The layers

were separated, and the aqueous layer was extracted with EtOAc (2 × 50 mL). The

combined organic layers were washed successively with H2O and saturated brine, dried

over anhydrous Na2SO4, filtered, and concentrated *in vacuo*. The residue was purified

by column chromatography (silica gel, hexanes/EtOAc, 10/1) to give *cis*-α-epoxide **20**

and *cis*-β-epoxide **20'** (3.0 mg, 70% <u>total</u> yield, α/β = 2.3:1 by ^{1}H NMR analysis): **For**

***cis*-α-Epoxide 20**; R$_f$ 0.30 (hexanes/EtOAc, 3/1); colorless oil; [α]$_D^{25}$ = 2.36 (*c* 0.24,

CHCl$_3$); ^{1}H NMR (600 MHz, CDCl$_3$) δ 6.06 (dd, *J* = 7.3, 9.6 Hz, 1 H), 4.01 (ddd, *J* =

3.7, 4.6, 9.7 Hz, 1 H), 3.96 (ddd, J = 3.7, 6.4, 12.4 Hz, 1 H), 3.72 (ddd, J = 5.5, 5.5, 12.4 Hz, 1 H), 3.48-3.51 (m, 2 H), 3.39 (ddd, J = 2.3, 7.8, 7.8 Hz, 1 H), 3.26 (ddd, J = 4.1, 4.1, 6.8 Hz, 1 H), 2.95 (dd, J = 4.1, 7.8 Hz, 1 H), 2.85 (dd, J = 5.0, 15.1 Hz, 1 H), 2.47 (ddd, J = 2.3, 9.2, 14.6 Hz, 1 H), 2.33-2.38 (m, 1 H), 2.03-2.09 (m, 1 H), 1.56-1.63 (m, 1 H), 0.94 (dd, J = 7.4, 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 133.2, 125.6, 84.1, 77.6, 60.8, 57.8, 57.6, 51.3, 40.9, 33.2, 27.0, 9.0; IR (neat) 3438, 2966, 2925, 2877, 1743, 1643, 1097, 1076, 1065, 1038, 947 cm^{-1}; HRMS (CI) found 325.0197 [calcd for C$_{12}$H$_{19}$BrClO$_3$$^+$ (M+H)$^+$ 325.0206]; **For *cis*-β-Epoxide 20'**; R$_f$ 0.25 (hexanes/EtOAc, 3/1); colorless oil; [α]$_D$^{25} = +19.69 (*c* 0.47, CHCl$_3$); ^{1}H NMR (600 MHz, CDCl$_3$) δ 6.05 (dd, J = 7.3, 9.2 Hz, 1 H), 4.02 (ddd, J = 3.7, 3.7, 10.1 Hz, 1 H), 3.84 (dd, J = 4.1, 12.4 Hz, 1 H), 3.78 (dd, J = 5.5, 12.4 Hz, 1 H), 3.57 (dd, J = 3.7, 14.7 Hz, 1 H), 3.40-3.47 (m, 2 H), 3.19 (ddd, J = 4.6, 4.6, 4.6 Hz, 1 H), 3.08 (dd, J = 4.6, 8.2 Hz, 1 H), 2.79 (dd, J = 4.1, 15.1 Hz, 1 H), 2.31-2.36 (m, 1 H), 2.14-2.22 (m, 2 H), 1.68 (s, 1 H, OH), 1.46-1.53 (m, 1 H), 1.05 (dd, J = 7.3, 7.3 Hz, 3 H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 133.2, 125.5, 84.7, 80.6, 60.4, 59.2, 55.8, 52.1, 40.2, 32.7, 27.3, 9.7; IR (neat) 3438, 2962, 2930, 2877, 1714, 1642, 1072, 1038, 940 cm^{-1}; HRMS (FAB) found 325.0196 [calcd for C$_{12}$H$_{19}$BrClO$_3$$^+$ (M+H)$^+$ 325.0206].

Preparation of *cis*-α-Epoxy Aldehyde 21
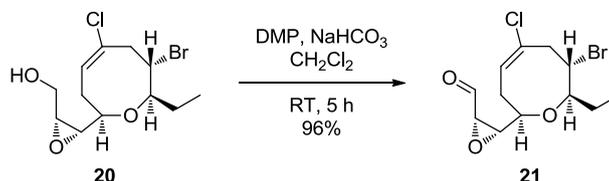
To a cooled (0 °C) solution of *cis*-α-epoxide **20** (16.7 mg, 0.051 mmol) in anhydrous

CH_2Cl_2 (3.0 mL, 0.017 M) were successively added $NaHCO_3$ (6.5 mg, 0.077mmol) and

Dess-Martin periodinane (109.0 mg, 0.256 mmol) under Ar. After being stirred at room

temperature for 5 h, the reaction mixture was quenched with H_2O (10 mL), and diluted

with CH2Cl2 (10 mL). The layers were separated, and the aqueous layer was extracted

with CH2Cl2 (2 × 50 mL). The combined organic layers were washed successively with

H2O and saturated brine, dried over anhydrous Na2SO4, filtered, and concentrated *in*

vacuo. The residue was purified by column chromatography (silica gel, hexanes/EtOAc,

10/1 to 5/1) to give *cis*-α-epoxy aldehyde **21** (15.9 mg, 96%): R_f 0.50 (hexanes/EtOAc,

3/1); colorless oil; ^{1}H NMR (600 MHz, CDCl$_3$) δ 9.54 (d, *J* =3.7, 1 H), 6.04 (dd, *J* = 7.4,

9.7, 1 H), 3.95 (ddd, *J* = 4.1, 4.1, 10.1 Hz, 1 H), 3.70 (ddd, *J* = 2.3, 4.6, 9.2, 1 H), 3.47

(ddd, *J* = 2.8, 8.7, 10.6, 1 H), 3.43 (dd, *J* = 4.1, 4.1 Hz, 1 H), 3.41 (dd, *J* = 4.6, 16 Hz, 1

H), 3.22 (dd, *J* = 4.6, 4.6 Hz, 1 H), 2.79 (dd, *J* = 4.6, 15.1 Hz, 1 H), 2.45 (ddd, *J* = 2.3,

9.7, 14.7, 1 H), 2.26-2.31 (m, 1 H), 2.05-2.11 (m, 1 H), 1.45-1.52 (m, 1 H), 0.96 (dd, *J* =

7.4, 7.4 Hz, 3 H).

Preparation of TMS-(Z)-Enyne 22
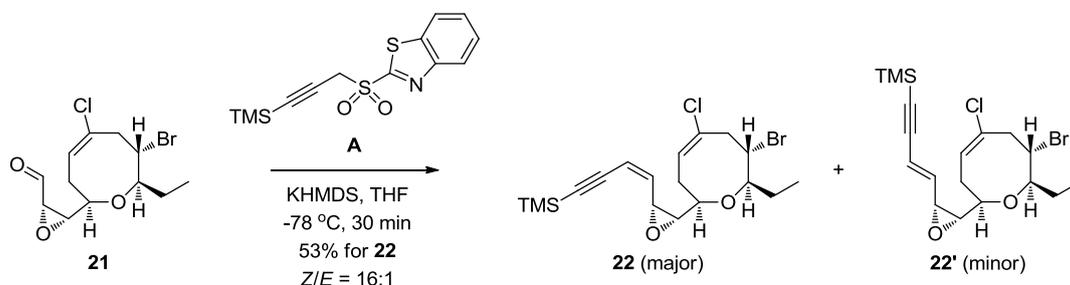
To a cooled (–78 °C) solution of *cis*-α-epoxy aldehyde **21** (2.7 mg, 0.008 mmol) and sulfone **A** (25.6 mg, 0.083 mmol) in anhydrous THF (2.0 mL, 0.0042 M) was dropwise added KHMDS (0.13 mL, 0.5 M solution in toluene, 0.067mmol) under Ar. After being stirred at –78 °C for 30 min, the reaction mixture was quenched with H_2O and diluted with EtOAc (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed successively with H_2O and saturated brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 80/1 to 50/1) to give TMS-(Z)-enyne **22** (1.8 mg, 53% <u>isolated</u> yield) and TMS-(E)-enyne **22'** (Z/E = 16:1 by ^{1}H NMR analysis): **For TMS-(Z)-Enyne 22**; colorless oil; R_f 0.50 (hexanes/EtOAc, 10/1); $[\alpha]_D^{25}$ = +46.69 (*c* 0.14, CHCl$_3$); ^{1}H NMR (600 MHz, CDCl$_3$) δ 6.07 (dd, *J* = 6.8, 9.1, 1 H), 5.84 (dd, *J* = 0.9, 11 Hz, 1 H), 5.69 (dd, *J* = 8.7, 11.0 Hz, 1 H), 4.06 (ddd, *J* = 0.9, 4.1, 8.7 Hz, 1 H), 4.01 (ddd, *J* = 4.1, 4.1, 10.1 Hz, 1 H), 3.52 (dd, *J* = 3.7, 4.2 Hz, 1 H), 3.45 (ddd, *J* = 2.7, 8.7, 10.5 Hz, 1 H), 3.26 (ddd, *J* = 2.3, 8.3, 8.3 Hz, 1 H), 3.11 (dd, *J* = 4.1, 7.8 Hz, 1 H), 2.83 (dd, *J* = 4.6, 15.1 Hz, 1 H),

2.47-2.50 (m, 1 H), 2.33-2.40 (m, 1 H), 2.01-2.09 (m, 1 H), 1.47-1.52 (m, 1 H), 0.90 (dd, J = 7.3, 7.3 Hz, 3 H), 0.20 (s, 9 H); ^{13}C NMR (225 MHz, CDCl$_3$) δ 136.9, 133.2, 125.9, 116.0, 102.2, 100.0, 84.4, 77.8, 59.7, 55.6, 51.7, 40.6, 33.1, 27.0, 9.4; IR (neat) 2962, 2924, 2149, 1251, 1097, 845, 772 cm^{-1}; HRMS (FAB) found 415.0506 [calcd for C$_{18}$H$_{25}$BrClO$_2$Si$^+$ (M+H)$^+$ 415.0496]; **For TMS-(E)-Enyne 22'**; colorless oil; R$_f$ 0.33 (hexanes/EtOAc, 10/1); ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.08 (dd, J = 7.3, 9.2 Hz, 1 H), 6.02 (dd, J = 6.6, 16 Hz, 1 H), 5.82 (dd, J = 0.7, 15.9 Hz, 1 H), 4.00 (ddd, J = 4.2, 4.2, 10.0 Hz, 1 H), 3.56 (ddd, J = 0.8, 4.1, 6.4 Hz, 1 H), 3.45-3.54 (m, 2 H), 3.19 (ddd, J = 2.5, 8.3, 8.3 Hz, 1 H), 3.04 (dd, J = 4.1, 8.1 Hz, 1 H), 2.83 (dd, J = 4.4, 15.1 Hz, 1 H), 2.34-2.47 (m, 2 H), 2.03-2.11 (m, 1 H), 1.45-1.52 (m, 1 H), 0.90 (dd, J = 7.4, 7.4 Hz, 3 H), 0.19 (s, 9 H).

Preparation of 1-TMS-Chlorohydrin 23
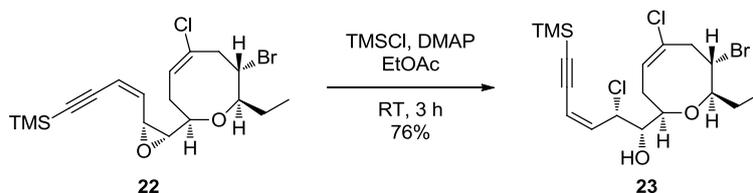
To a cooled (0 °C) solution of TMS-(Z)-enyne **22** (5.2 mg, 0.012 mmol) in anhydrous EtOAc (3 mL, 0.004 M) was dropwise added TMSCl (0.01 mL, 0.079 mmol), followed by addition of DMAP (0.15 mg, 0.001 mmol) under Ar. After being stirred at room temperature for 3 h, the reaction mixture was quenched with H$_2$O (2 mL), and diluted with EtOAc (10 mL). The layers were separated, and the aqueous layer was extracted

with EtOAc (2 × 30 mL). The combined organic layers were washed successively with

H_2O and saturated brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane/EtOAc, 20/1 to 15/1) to give 1-TMS-chlorohydrin **23** (4.3 mg, 76%): R*f* 0.10 (hexanes/EtOAc, 10/1); white solid; $[\alpha]_D^{25} = +84.41$ (*c* 0.071, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.11 (dd, *J* = 10.2, 10.7 Hz, 1 H), 6.03 (dd, *J* = 7.3, 9.3 Hz, 1 H), 5.68 (dd, *J* = 0.4, 10.9 Hz, 1 H), 5.33 (dd, *J* = 3.2, 9.9 Hz, 1 H), 4.07 (ddd, *J* = 4.0, 4.9, 10.0, 1 H), 3.61 (ddd, *J* = 3.0, 5.7, 13.2 Hz, 1 H), 3.52-3.57 (m, 1 H), 3.47 (dd, *J* = 3.8, 15.1 Hz, 1 H), 3.42 (ddd, *J* = 2.5, 7.6, 15.0 Hz, 1 H), 2.86 (dd, *J* = 5, 15.2, 1 H), 2.54 (ddd, *J* = 2.5, 9.4, 14.6 Hz, 1 H), 2.35 (ddd, *J* = 7.5, 7.5, 14.8 Hz, 1 H), 2.03-2.14 (m, 2 H), 1.74-1.85 (m, 1 H), 1.02 (dd, *J* = 7.4, 7.4 Hz, 3 H), 0.21 (s, 9 H), 0.97; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 132.9, 126.0, 112.7, 103.3, 99.3, 83.9, 80.3, 75.2, 60.9, 50.1, 41.0, 30.5, 26.3, 8.6; IR (neat) 3444, 2960, 2924, 2854, 2149, 1711, 1251, 1092, 845 cm^{-1}; HRMS (CI) found 453.0419 [calcd for $C_{18}H_{28}BrCl_2O_2Si^+$ $(M+H)^+$ 453.0419].

Preparation of (+)-Bermudenynol (1)
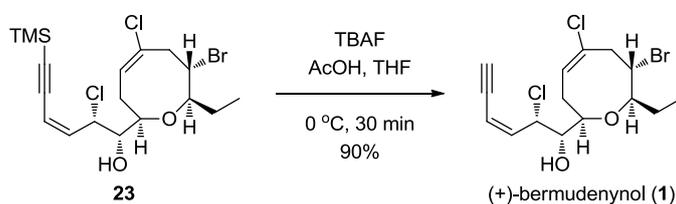
To a cooled (0 °C) solution of TBAF (10 mL, 1.0 M solution in THF, 10 mmol) was dropwise added acetic acid (0.5 mL), and the mixture was stirred at the same

temperature for 30 min. To a cooled (0 °C) solution of 1-TMS-chlorohydrin **23** (5.3 mg, 0.012 mmol) in dry THF (3 mL, 0.004 M) was dropwise added 3 drops of acetic acid, followed by the above acetic acid-pretreated TBAF (0.11 mL, 0.103 mmol). After being stirred at 0 °C for 30 min, the reaction mixture was quenched with H_2O (30 mL), and diluted with EtOAc (30 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic layers were washed successively with H_2O and saturated brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo.* The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 20/1 to 15/1) to give (+)-bermudenynol (**1**) (4.0 mg, 90%): R_f 0.36 (hexanes/EtOAc, 4/1); colorless oil; $[\alpha]_D^{25} = +194.3$ (*c* 0.75, $CHCl_3$) {(lit.[2] $[\alpha]_D^{25} = +187.0$ (*c* 0.756, $CHCl_3$)}; ^{1}H NMR (500 MHz, acetone-d_6) δ 6.41 (dd, *J* = 10.6, 10.6 Hz, 1 H), 6.12 (dd, *J* = 7.3, 9.4 Hz, 1 H), 5.75 (dd, *J* = 2.3, 10.6 Hz, 1 H), 5.50 (dd, *J* = 1.8, 10.5 Hz, 1 H), 4.60 (d, *J* = 8.2 Hz, 1 H, OH), 4.25-4.28 (m, 1 H), 3.93-3.94 (m, 1 H), 3.76 (ddd, *J* = 3.8, 3.8, 10.3 Hz, 1 H), 3.62 (ddd, *J* = 2.6, 8.2, 8.2 Hz, 1 H), 3.54 (dd, *J* = 3.2, 15.2 Hz, 1 H), 3.48 (ddd, *J* = 2.0, 8.3, 8.3 Hz, 1 H), 2.93 (dd, *J* = 4.9, 15.3 Hz, 1 H), 2.82 (s, 1 H), 2.73 (ddd, *J* = 2.6, 9.5, 14.4 Hz, 1 H), 2.38 (ddd, *J* = 7.5, 7.5, 14.7 Hz, 1 H), 2.02-2.09 (m, 1 H), 1.91-1.99 (m, 1 H), 1.05 (dd, *J* = 7.4, 7.4 Hz, 3 H); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.24 (dd, *J* = 10.6, 10.6, 1 H), 6.05 (dd, *J* = 7.3, 9.2 Hz, 1 H), 5.65 (dd, *J* = 2.3, 10.6 Hz, 1 H), 5.44 (dd, *J* = 2.8, 10.1 Hz, 1 H), 4.10 (ddd, *J* = 1.3, 1.3, 8.7 Hz, 1 H), 3.65 (ddd, *J* = 3.2, 4.6, 10.1 Hz, 1 H), 3.41 (ddd, *J* = 2.3, 7.8, 7.8 Hz, 1 H),

3.26 (dd, J = 1.0, 2.3 Hz, 1 H), 2.85 (dd, J = 4.6, 15.1 Hz, 1 H), 2.56 (ddd, J = 2.3, 9.6, 14.6 Hz, 1 H), 2.31 (ddd, J = 7.8, 7.8, 15.1, 1 H), 2.07 (d, J = 10.1, 1 H), 1.99-2.05 (m, 1 H), 1.85-1.92 (m, 1 H), 0.99 (dd, J = 7.3, 7.3 Hz, 3 H); ^{13}C NMR (125 MHz, Acetone-d_6) δ 142.3, 133.2, 127.8, 111.3, 86.5, 83.6, 81.0, 79.5, 74.9, 61.1, 50.8, 41.9, 31.5, 26.4, 7.5; IR (neat) 3546, 3297, 2965, 2925, 1091, 655, 627 cm^{-1}; HRMS (FAB) found 381.0013 [calcd for $C_{15}H_{20}BrCl_2O_2^+$ (M+H)$^+$ 381.0024].

Table I. ^{13}C NMR Comparison of (+)-Bermudenynol

Carbon No.	Natural (Meinwald)[2] (+)-Bermudenynol (20 MHz, acetone-d_6) δ (TMS = 0)	$\Delta\delta$ (Natural – Synthetic)	Synthetic (Kim) (+)-Bermudenynol (125 MHz, acetone-d_6) δ (acetone-d_6 = 206.19)
1	85.7	-0.8	86.5
2	78.7	-0.8	79.5
3	110.6	-0.7	111.3
4	141.6	-0.7	142.3
5	60.4	-0.7	61.1
6	74.1	-0.8	74.9
7	82.9	-0.7	83.6
8	30.8	-0.7	31.5
9	127.0	-0.8	127.8
10	132.5	-0.7	133.2
11	41.1	-0.8	41.9
12	50.0	-0.8	50.8
13	80.2	-0.8	81.0
14	25.6	-0.8	26.4
15	6.8	-0.7	7.5

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– Experimentals: Part B –

Spectroscopy Analysis

Oxocene Amide **3**
500 MHz ^{1}H NMR, CDCl$_3$

Oxocene Amide **3**
125 MHz ^{13}C NMR, CDCl$_3$

Peak labels (left to right): 169.9692, 159.2308, 134.3249, 130.2724, 129.4968, 125.4762, 113.7116, 84.3044, 83.0970, 78.7853, 77.2540, 76.9999, 76.7459, 71.1182, 55.2627, 37.4402, 36.8609, 36.2182, 32.9604, 25.0839, 10.3851, -0.0174

x-axis: 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

IAEA

Oxocene Amide **3**
500 MHz ^{1}H-^{1}H COSY NMR
CDCl$_3$

ppm

IAEA

H-9 H-7 H-13

H-13
H-12
H-7

Oxocene Amide **3**
500 MHz ^{1}H-^{1}H NOESY NMR
CDCl$_3$

Cl
OPMB
9 12
13
7
O
N
H
O
α,α'-*cis*

nOe
9
7
13
12
nOe
nOe

partial structure

54

(+)-Bermudenynol (1)
500 MHz ^{1}H NMR, acetone-d_6

1.0541 1.0000 1.0128 1.0591 0.8991 1.1005 0.9002 1.1711 1.1850 1.1410 1.2009 1.1623 4.0240 0.8065 1.1721 1.1710 1.1317 1.2555 1.8394 3.3717

(+)-Bermudenynol (**1**)
600 MHz ^{1}H NMR, CDCl$_3$

Comparison of ¹H NMR Spectra of Bermudenynol in CDCl₃ and in Acetone-d_6

(+)-Bermudenynol (**1**)
600 MHz ¹H NMR, CDCl₃

(+)-Bermudenynol (**1**)
500 MHz ¹H NMR, acetone-d_6
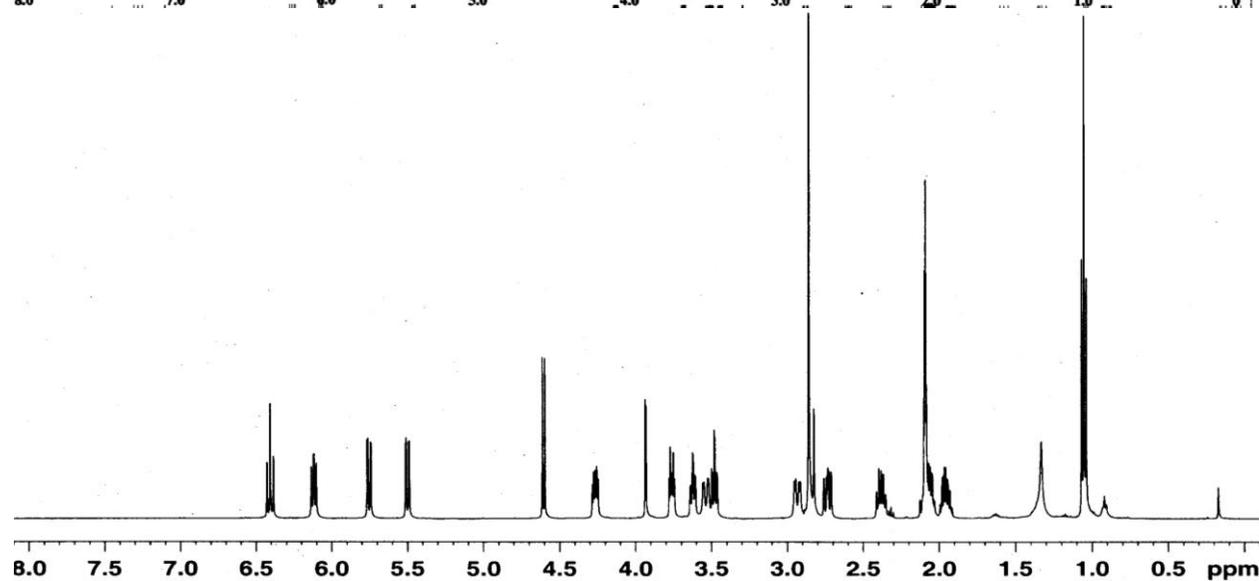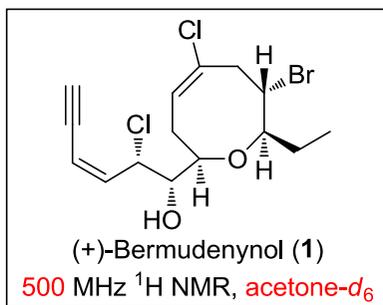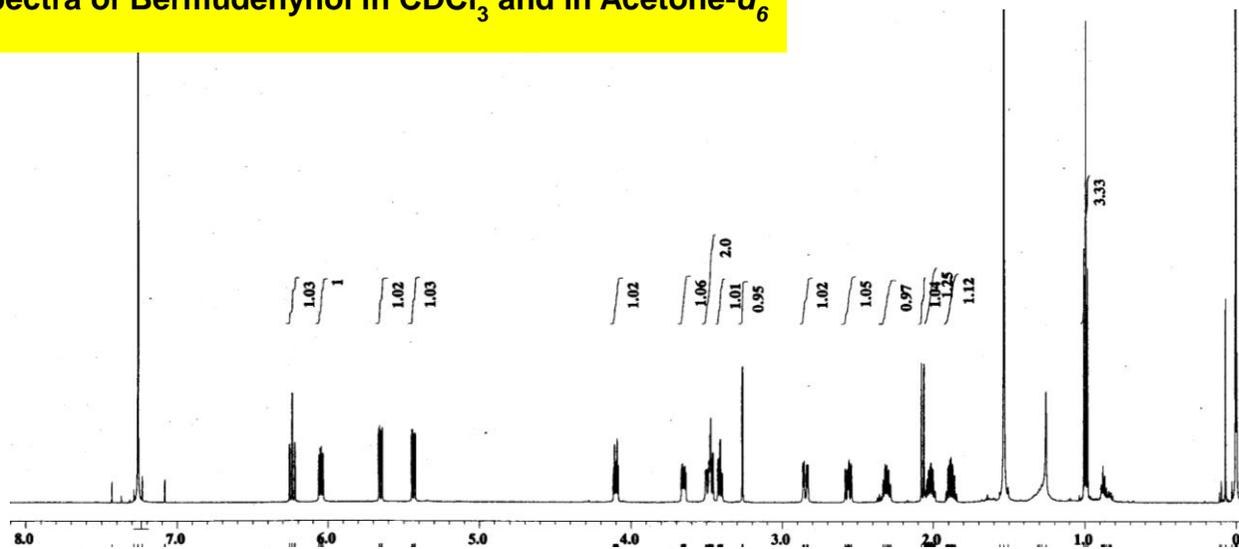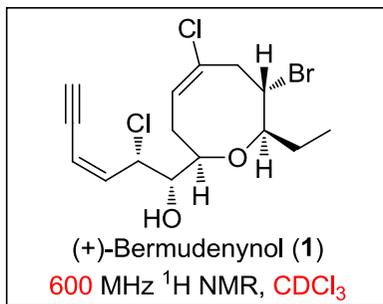
The width of the 500 MHz spectrum in acetone-d_6 was adjusted for comparison purpose.

206.3390
206.1853
206.0295
142.3146
133.2165
127.7713
111.3082
86.4766
83.6457
80.9772
79.4575
74.8923
61.1177
50.7770
41.8525
31.4649
30.3610
30.2070
30.0530
29.8993
29.7452
29.5913
29.4376
26.3626
7.5443

Cl
H
Br
Cl
O
H
HO
H

(+)-Bermudenynol (**1**)
125 MHz ^{13}C NMR, acetone-d_6

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

(+)-Bermudenynol

(+)-Bermudenynol (**1**)
500 MHz ^{1}H-^{13}C HSQC NMR
acetone-d_6

(+)-Bermudenynol

(+)-Bermudenynol (1)
500 MHz ¹H-¹H COSY NMR
acetone-d_6

(+)−Bermudenynol

(+)-Bermudenynol (**1**)
500 MHz ^{1}H-^{1}H NOESY NMR
acetone-d_6

61

(+)-Bermudenynol

(+)-Bermudenynol (**1**)
500 MHz ^{1}H-^{13}C HMBC NMR
acetone-d_6

62

^{13}C NMR Comparison of (+)-Bermudenynol

Carbon No.	Natural (+)-Bermudenynol (20 MHz, acetone-d_6) δ(TMS = 0)	$\Delta\delta$ (Natural – Synthetic)	Synthetic (+)-Bermudenynol (125 MHz, acetone-d_6) δ(acetone-d_6 = 206.19)
1	85.7	-0.8	86.5
2	78.7	-0.8	79.5
3	110.6	-0.7	111.3
4	141.6	-0.7	142.3
5	60.4	-0.7	61.1
6	74.1	-0.8	74.9
7	82.9	-0.7	83.6
8	30.8	-0.7	31.5
9	127.0	-0.8	127.8
10	132.5	-0.7	133.2
11	41.1	-0.8	41.9
12	50.0	-0.8	50.8
13	80.2	-0.8	81.0
14	25.6	-0.8	26.4
15	6.8	-0.7	7.5

(+)-Bermudenynol
125 MHz ^{13}C NMR, Acetone-d_6

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국문초록

본 연구는 C_{15} *Laurencia* 대사물질, (+)-bermudenynol (**1**)의 기질에 의해 조절되는 부제 전합성에 관한 내용이다. Vinyl Chloride Containing Oxocene 의 독특한 핵심 골격을 본 연구실의 Intramolecular Amide Enolate Alkylation 방법으로 입체선택적으로 합성했다. 이 연구는 Intramolecular Amide Enolate Alkylation 방법의 새로운 사용 범위에 대해 좋은 예를 제시해주며, 현재 Ring-Closing Metathesis 으로 극복할 수 없는 문제점에 대해 대안법을 제시해준다.

주요어: 천연물 전합성
    (+)-bermudenynol
    Intramolecular Amide Enolate Alkylation
    Vinyl Chloride Containing Oxocene