Natural Product Synthesis

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Asymmetric Total Synthesis of (+)-Bermudenynol, a C_{15} *Laurencia* Metabolite with a Vinyl Chloride Containing Oxocene Skeleton, through Intramolecular Amide Enolate Alkylation**

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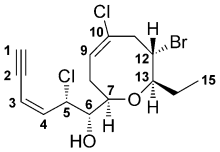
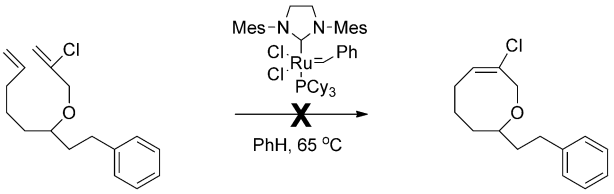
Abstract: *A substrate-controlled asymmetric total synthesis of (+)-bermudenynol, a compact and synthetically challenging C_{15} Laurencia metabolite that contains several halogen atoms, is reported. The oxocene core, which contains a vinyl chloride, was constructed by an efficient and highly stereoselective 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.*

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 that bears 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 owing to the difficulties associated with construction of the vinyl chloride containing oxocene core.



(+)-bermudenynol (**1**)

Ring-closing metathesis (RCM) has become established as a successful method 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 the 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] They also briefly investigated the possibility of forming larger rings by this process. Unfortunately, their attempt to construct a vinyl chloride containing oxocene by using RCM under their optimized RCM conditions failed (Scheme 1).



Scheme 1. Attempted RCM cyclization to a vinyl chloride containing oxocene.

Recently, we demonstrated the potential of our "olefin-geometry-dependent" intramolecular amide enolate alkylation (IAEA) methodology in the synthesis of medium-ring oxacyclic marine natural products with an α,α′-*cis*-disubstituted oxocene skeleton.[5] 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] Mindful that the above-mentioned 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; we report herein the first asymmetric total synthesis of this *Laurencia* marine natural product.

As shown in our retrosynthetic plan (Scheme 2), 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 functionality 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 functionality in known C(12)/C(13)-*syn* diol derivative **5**, which was accessed in four steps from **6** by Evans alkylation and chelation-controlled nucleophilic addition.[7]

To commence the synthesis, α-alkoxy amide **7** was prepared by O-alkylation of the known *syn*-diol derivative **5** by treatment with NaH and *N*,*N*-dimethyl chloroacetamide (Scheme 3). The terminal alkene functionality 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

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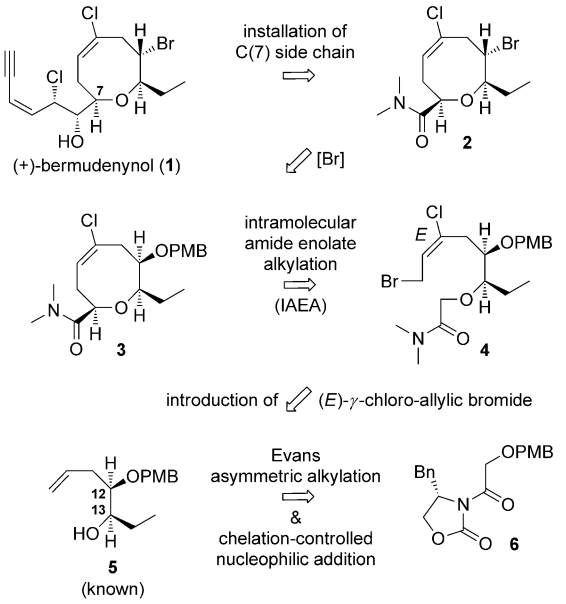
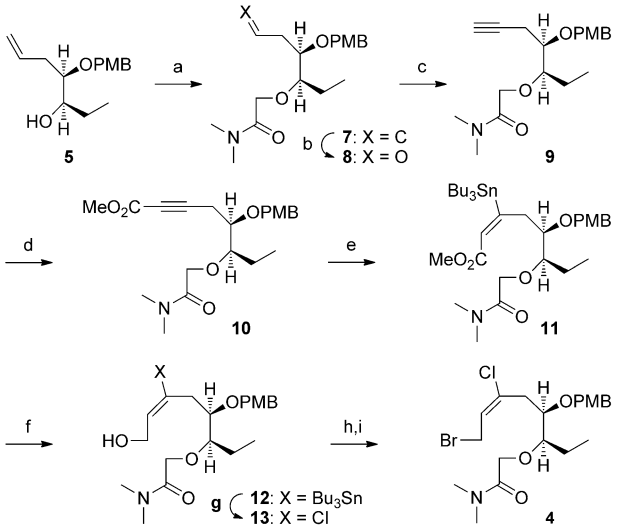


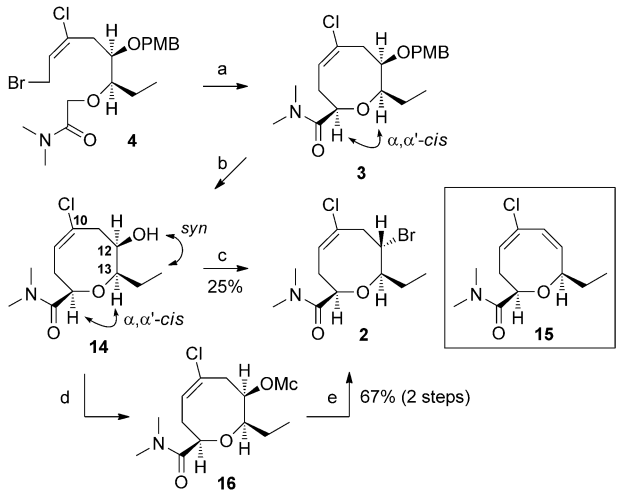
Scheme 2. Retrosynthetic plan for (+)-bermudenynol (**1**). PMB = *p*-methoxybenzyl.



Scheme 3. Preparation of IAEA substrate **4**: a) NaH, $ClCH_2CONMe_2$, THF/DMF (3:1), RT, 3 h, 94%; b) 1. OsO_4, NMO, acetone/H_2O, RT, 18 h, 2. $NaIO_4$, RT, 3 h, 92%; c) $CH_3COCN_2PO(OCH_3)_2$, K_2CO_3, MeOH, RT, 18 h, 90%; d) $Pd(OAc)_2$, PPh_3, MeOH, DMF, CO, O_2, RT, 25 h, 72%; e) hexabutylditin, *n*BuLi, CuCN, MeOH, THF, −78 °C, 1 h, 73%; f) DIBAL-H (3 equiv), *n*BuLi (3 equiv), THF, −78 °C, 10 min, then $NaBH_4$ (excess), EtOH, −78 °C to RT, 1 h, 77% (83% BRSM); g) $CuCl_2$, THF, 0 °C, 4 h, 71%; h) Ms_2O, Et_3N, CH_2Cl_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, BRSM = based on recovered starting material.

Ohira–Bestmann alkynylation[9] of the resultant aldehyde **8**, gave the desired alkyne **9** in good overall yield (78% yield for 3 steps from **5**). 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 the ester in **11** in the presence of α-alkoxy dimethylamide by treatment with the ate complex generated from DIBAL-H and *n*BuLi[12a] (−78 °C, then $NaBH_4$/EtOH, −78 °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 group to the corresponding aldehyde at 0 °C to room temperature (see below), so the temperature effect makes the chemoselectivity here highly tunable. Finally, bromination of the allylic alcohol through a modification of the Stork method[14] gave rise to the desired allylic bromide in nearly quantitative yield (96% for the two steps), thus setting the stage for the crucial intramolecular amide enolate alkylation.

With the internal alkylation substrate in hand, we turned our attention to the pivotal IAEA of **4** (Scheme 4).[5,6] Upon exposure to LiHMDS in THF at −78 °C for 1 h, the (*E*)-allylic



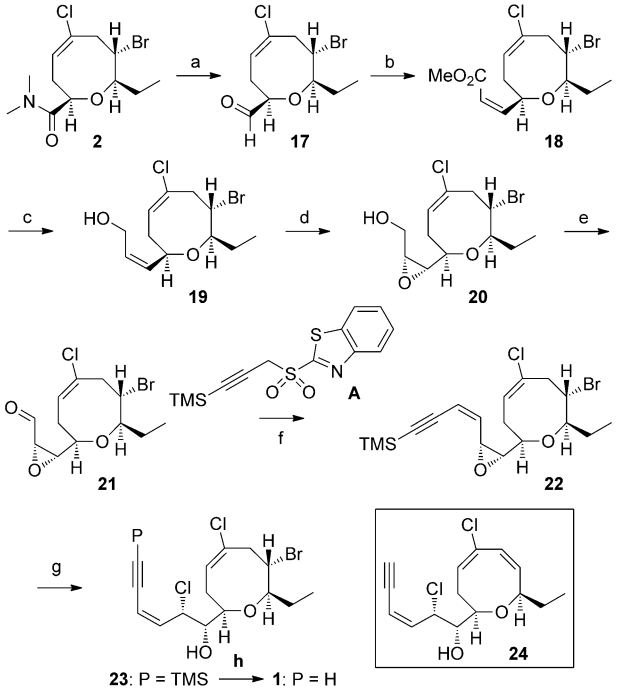
Scheme 4. Intramolecular amide enolate alkylation and bromination: a) LiHMDS, THF, −78 °C, 1 h, 80%; b) DDQ, CH_2Cl_2/pH 7.4 buffer solution (9:1), RT, 7 h, 94%; c) CBr_4, $nOct_3P$, 1-methyl cyclohexene, toluene, 70 °C, 12 h, 25% for **2**, **2**/**15** = 1:1.2; d) McCl, 2,6-lutidine, CH_2Cl_2, 0 °C, 1 h; e) LiBr, Et_2O/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.

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 were initially confident about the problem of introducing the ring bromine. Our extensive experience in this area together with literature analogy suggested that diastereomeric oxocene alcohols with α,α′-*cis*-C(12)/C(13)-*syn* stereochemistry are the most favorable substrates for halogenation with inversion.[15] For instance, the α,α′-*cis*-C(12)/C(13)-*syn* oxocene alcohol that is identical to **14** except for lacking the C(10) chlorine underwent efficient

bromination with inversion of configuration upon exposure to CBr_4 and $nOct_3P$ under the Hooz conditions (78%).[5d,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 the crucial bromo oxocene in good yield (67% for the two steps) with minimal formation of diene **15**.[15,18]

For installation of the challenging C(7) side chain, we envisioned that regioselective opening at the allylic position of the *cis*-α-epoxy (*Z*)-enyne **22** by S_N2 displacement with chloride would produce the pivotal chlorohydrin in a stereo- and regioselective manner (Scheme 5). Taking advantage of the versatility of the α-alkoxy dimethylamide functionality,[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) through a 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 ($\alpha/\beta = 2.3{:}1$, 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 (TSs) were located for oxidation of the two diastereofaces of the allylic alcohol according to a concerted mechanism involving a vanadium(V) peroxy species, as originally proposed by Sharpless et al.[20] and supported by recent computational studies.[24] Owing to the complexity of the substrate used experimentally, modeling studies were carried out with truncated substrate **C** to investigate the effect of the allylic stereocenter. In close agreement with experimental observations, a small free energy preference of 2.4 kJ mol^{-1} (i.e. 2.5:1 at 40°C) is computed between the



Scheme 5. Completion of the synthesis: a) DIBAL-H (2 equiv), *n*BuLi (2 equiv), THF, 0°C, 10 min, then RT, 50 min, 83%; b) $(CF_3CH_2O)_2POCH_2CO_2Me$, 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, $\alpha/\beta = 2.3{:}1$, 70% total yield; e) DMP, $NaHCO_3$, CH_2Cl_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.

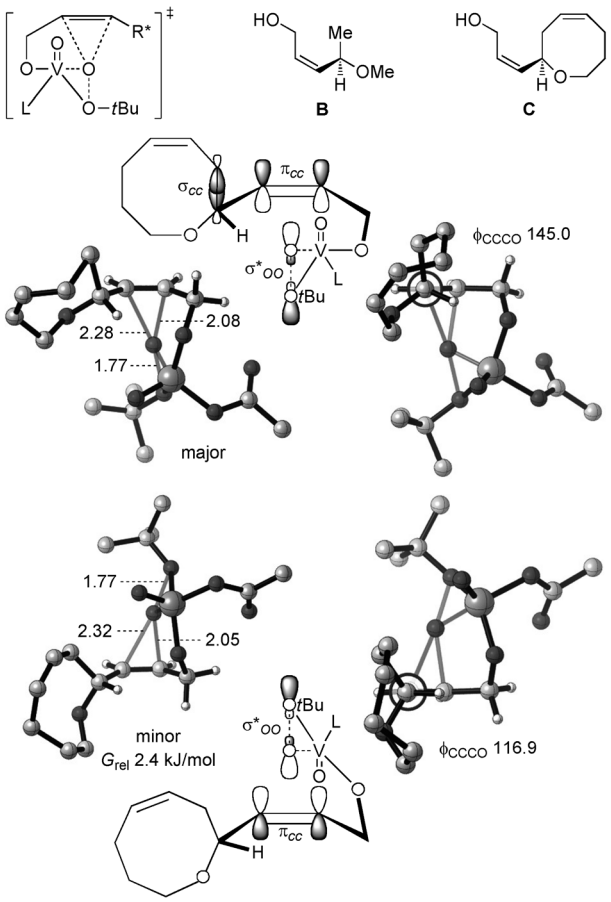


Figure 1. DFT calculations on diastereoselective Sharpless epoxidation of **19**.

TSs for epoxidation of the two faces of the C=C bond, with the *cis*-α-epoxide being favored. 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, thereby 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 (natural bond orbital) calculations confirm this, showing greater $\sigma_{C-C} \rightarrow \pi^*_{C=C}$ delocalization in the favored TS, and greater $\pi_{C=C} \rightarrow \sigma^*_{C-O}$ 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**), thus indicating that the selectivity is predominantly influenced by the allylic stereocenter rather than by more remote stereoinductive effects.

Returning to Scheme 5, we focused our attention on the introduction of the (*Z*)-enyne unit. After considerable experimentation, we found that the desired (*Z*)-enyne unit could be installed by application of the Julia–Kocienski procedure,[25] in which coupling of epoxy aldehyde **21**, generated from **20** by DMP oxidation in excellent yield (96%),[26] with sulfone **A** gave the desired TMS-(*Z*)-enyne **22** in serviceable yield with good stereoselectivity (53% yield of isolated product, $Z/E = 16{:}1$). Finally, regioselective opening of allylic epoxide **22** with chloride,[27] 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 diene **24** is otherwise 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 natural bermudenynol: $[\alpha]_D^{25} = +194.3$ ($c = 0.75$, $CHCl_3$) [natural: $[\alpha]_D^{25} = +187$ ($c = 0.756$, $CHCl_3$)[2]]. In particular, the ^{13}C NMR (125 MHz, [D$_6$]acetone) spectral data were in excellent agreement with the resonances listed in the original isolation paper (20 MHz, [D$_6$]acetone), 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**.

In summary, we have accomplished a substrate-controlled asymmetric total synthesis of (+)-bermudenynol (**1**), a compact and synthetically challenging C_{15} *Laurencia* metabolite that contains several 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, a result that showcases the broad utility of our IAEA methodology as a useful alternative for cases in which the ring-closing metathesis is inefficient.

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