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Stereoselective total synthesis of (3Z)- and (3E)-elatenynes†

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We describe here the highly stereoselective total synthesis of the *Laurencia* C₁₅ acetogenins (3Z)- and (3E)-elatenynes having a 7,12-dibromo-6,9-*cis*-10,13-*cis* adjacent bis-tetrahydrofuran (THF) core. The present synthesis features a highly stereoselective, protecting group-dependent, chelate-controlled intramolecular amide enolate alkylation (IAEA) for the synthesis of key intermediate 7-hydroxy-6,7-*cis*-6,9-*cis*-THF intermediate **10**, deployment of the sequential ate complex (*n*-BuLi/DIBAL-H) reduction/Keck allylation/cross metathesis (CM) protocol for the stereoselective introduction of the C(10)–C(15) unit, a sequential Sharpless asymmetric dihydroxylation (SAD)/intramolecular Williamson etherification for the construction of the 10,13-*cis*-THF ring, and a modified Nakata chloromethanesulfonate-mediated S_N2 displacement for the 7,12-dibromo functionality. Furthermore, our strategy based on chelate-controlled IAEA methodology would provide access to any member of the C₁₅ adjacent bis-THF acetogenin class.

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Marine algae produce a diverse set of oxacyclic C₁₅ acetogenins, among which some, as shown in Fig. 1, have a 2,2'-bifuranyl (adjacent bis-THF) core structure.¹ (3Z)-Elatenynine (**1a**) was first isolated from the marine algae *Laurencia elata* by Hall and Reiss in 1986,^{2a} and Erickson reported isolating (3E)-elatenynine (**1b**) from the marine alga *Laurencia majuscula* in 1989.^{2b} Later, **1a** was re-isolated from *Laurencia decumbens* by Wang in 2007 (ref. 2c) and from *Laurencia elata* by Urban in 2011.^{2d} The isolation of several closely related *Laurencia* C₁₅ acetogenins has been reported, including notoryne (**2**),³ chloroenyne (**3**) from *L. majuscula*,⁴ laurendecumenyne B (**4**),⁵ and laurefurenynes A (**5a**) and B (**5b**).⁶ It is worth mentioning at this point that the structures depicted in Fig. 1 have been revised or confirmed by total synthesis.^{2h,3c-e,6b,c}

Based on extensive ¹H and ¹³C NMR spectroscopic analyses, the structure of (3Z)-elatenynine (**1a**) was initially proposed by Hall and Reiss to have a pyrano[3,2-*b*]pyran core (fused bis-THP), as depicted in **1c**.^{2a} However, the **1c** structure was shown by Burton, *et al.*, to be incorrect through the total synthesis thereof.^{2e,f} The Burton and the Goodman groups collaborated to predict the correct 2,2'-bifuranyl skeleton (adjacent bis-THF) structure and relative stereochemistry of **1a** through comparison of the ¹³C NMR chemical shifts of **1a** with

the Boltzmann-weighted GIAO ¹³C NMR chemical shifts determined through DFT methods.^{2g} Later, a collaborative effort by the Kim and Burton groups achieved the total synthesis of **1a** and *ent*-**1a** utilizing a modular and biomimetic approach, respectively.^{2h} Despite the collaborative effort, the unequivocal

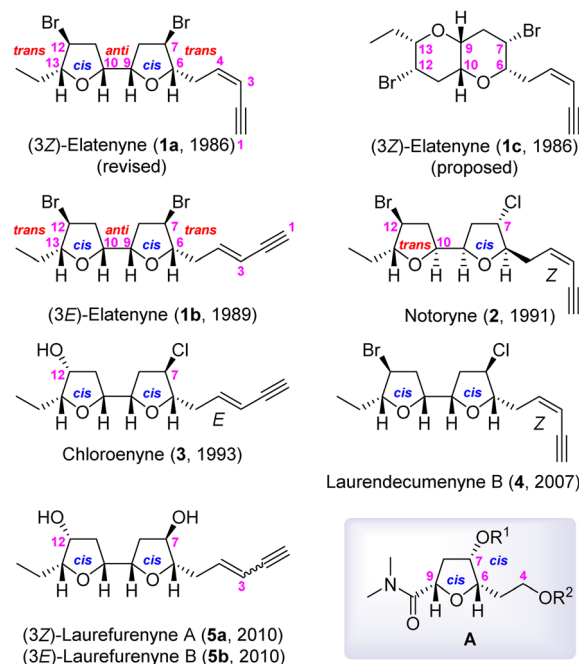


Fig. 1 *Laurencia* adjacent bis-tetrahydrofuranoid natural products.

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assignment of the absolute stereochemistry of **1a** was still not possible. Eventually, Urban and Fujita confirmed the absolute stereochemistry of **1a** as that shown in Fig. 1 using the crystal-line sponge method.²ⁱ

The structural features of these C₁₅ adjacent bis-THF acetogenins have received considerable attention from organic chemistry community, culminating to several total syntheses: the modular synthesis on the basis of analysis ¹³C NMR chemical shifts,^{2h,e,3e,6b} biomimetic approach,^{2e,h,3c,e} the cyclization of chlorohydrin derived from anti-aldol reaction,^{6c} the Sharpless asymmetric dihydroxylation (SAD)/Williamson cyclization sequence,^{4b} and the bromo-etherification.^{3d}

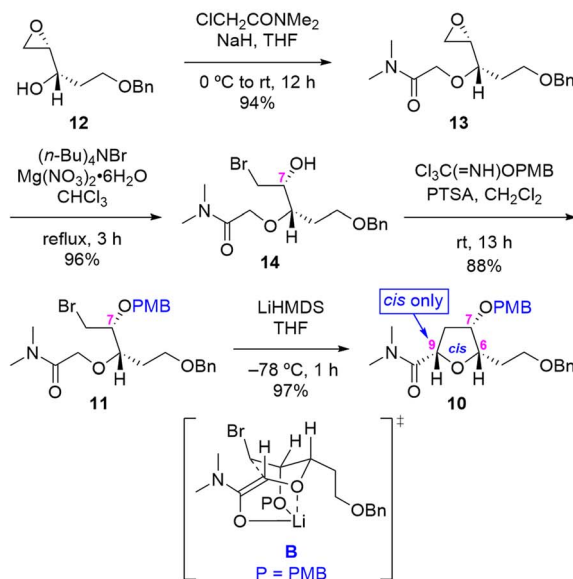
Based on the insights garnered from our highly stereoselective syntheses of oxylipids^{7a} and asimitrin,^{7b} we formulated a synthetic strategy which provides access to any member of this C₁₅ adjacent bis-THF acetogenin class through a highly stereoselective construction of the 2,5-disubstituted-3-oxygenated tetrahydrofuran moiety **A** (Fig. 1) *via* intramolecular amide enolate alkylation (IAEA).⁷ In addition, our strategy utilizes Marshall's protocol [cross metathesis (CM)/SAD/Williamson cyclization]⁸ for the efficient construction of 2nd THF skeleton in the adjacent bis-THF unit.

To demonstrate the synthetic potential of this strategy, we describe herein the asymmetric total synthesis of (3*Z*)-elatenyne (**1a**) and (3*E*)-elatenyne (**1b**) featuring a highly stereoselective and chelate-controlled IAEA for constructing key intermediate 7-hydroxy-6,7-*cis*-6,9-*cis*-THF **10**. This is followed by a sequential

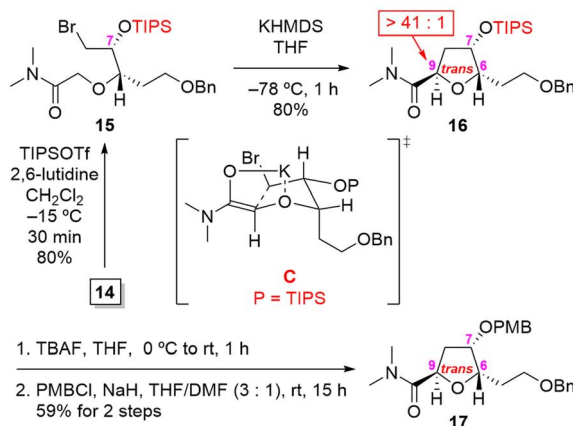
ate complex (*n*-BuLi/DIBAL-H) reduction/Keck allylation/cross metathesis (CM) protocol for stereoselective introduction of the C(10)–C(15) unit.

As shown in our retrosynthetic plan (Scheme 1), we envisioned that respective total syntheses of (3*Z*)-elatenyne (**1a**) and (3*E*)-elatenyne (**1b**) could be readily accomplished through stereoselective incorporation of the (*Z*)- and (*E*)-enyne units into 7,12-dibromo-adjacent bis-THF **6**. This intermediate could be accessed by bis-bromination of the adjacent 7,12-dihydroxy-bis-THF **7**, which in turn could be constructed from the tetrahydrofuran *syn*-diol **8** through an intramolecular Williamson etherification. We planned to synthesize **8** from homoallylic alcohol **9** by employing cross metathesis (CM) and Sharpless asymmetric dihydroxylation (SAD) as key steps. By this route, (1*S*)-9,10-*syn* homoallylic alcohol **9** could be stereoselectively prepared through application of ate complex (*n*-BuLi/DIBAL-H) reduction/Keck allylation protocols to yield α -alkoxy amide **10**

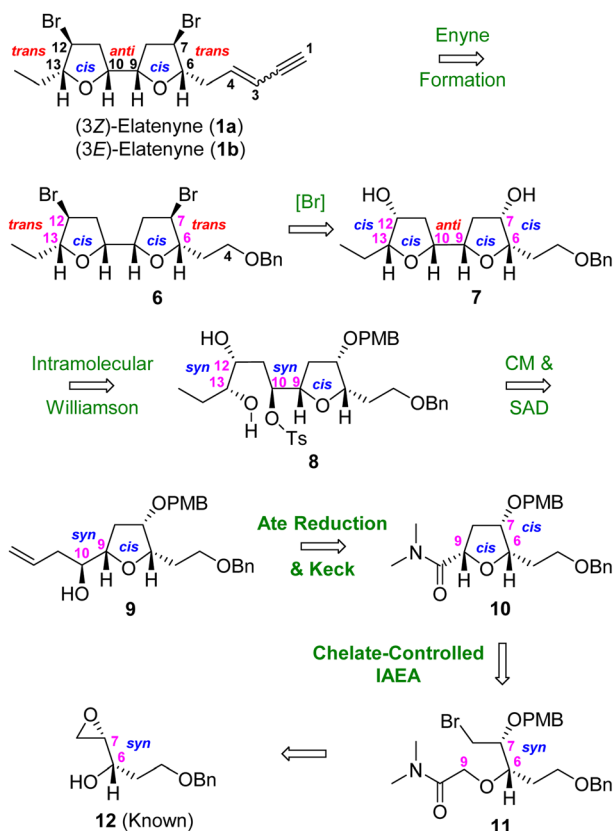
Scheme 2a. Preparation of 6,7-*cis*-6,9-*cis*-THF **10**



Scheme 2b. Preparation of 6,7-*cis*-6,9-*trans*-THF **17** for comparison



Scheme 2 Stereoselective synthesis of 6,9-*cis*-THF **10** and 6,9-*trans*-THF **17** *via* IAEA.



Scheme 1 Retrosynthetic plan.



(*vide infra*). Based on our previous work,⁷ we were confident that key 6,7-*cis*-6,9-*cis*-THF intermediate **10** could be accessed by subjecting 6,7-*syn*- ω -bromo- α -alkoxy amide **11** to our stereoselective chelate-controlled IAEA reaction. Finally, we imagined that IAEA substrate **11** could be prepared in a straightforward manner from the known 6,7-*syn* epoxy alcohol **12**.

Our synthesis began with the preparation of IAEA substrate **11**, as outlined in Scheme 2. Thus, known epoxy alcohol **12** (ref. 9) was subjected to *O*-alkylation with *N,N*-dimethyl chloroacetamide to afford the desired epoxy α -alkoxy amide **13** in 94% yield. The regioselective opening of the terminal epoxide **13** was achieved through the action of (*n*-Bu)₄NBr in the presence of Mg(NO₃)₂·6H₂O to furnish the 6,7-*syn*-bromoamide **14** with an excellent 96% yield.¹⁰ Protection of the hydroxyl group in **14** as the PMB ether with 4-methoxybenzyl 2,2,2-trichloroacetimidate in the presence of a catalytic amount of *p*-toluenesulfonic acid (PTSA)¹¹ gave rise to key IAEA substrate **11** in good yield (88%).

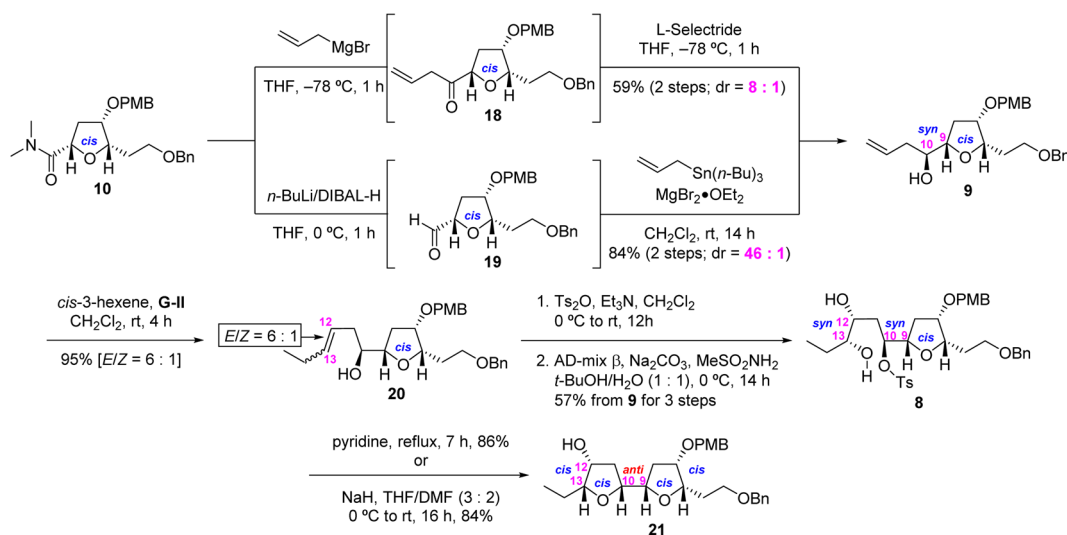
With IAEA substrate **11** in hand, we proceeded to address the pivotal stereoselective IAEA reaction of PMB-protected bromo α -alkoxy amide **11** for the construction of key intermediate **10**. Treatment of **11** with LiHMDS in THF at –78 °C for 1 h led to the desired 6,7-*cis*-6,9-*cis*-THF **10** in 97% yield as a single stereoisomer (by ¹H NMR analysis, see ESI† for details), presumably *via* chelated transition state geometry **B**. The NOE interaction between protons on [C(6) and C(7)] and [C(6) and C(9)] in **10** was supportive of the assigned *cis* relative stereochemistry.

To establish the diastereoselectivity of the IAEA reaction in a rigorous manner, we decided to synthesize the corresponding 6,9-*trans* isomer **17** for comparison purposes as shown at the bottom of Scheme 2. To this end, subjection of TIPS-protected bromo α -alkoxy amide **15** (prepared by TIPS protection of alcohol **14**) to KHMDS in THF at –78 °C for 1 h gave rise to the desired 6,9-*trans*-THF **16** in 80% yield as the major isomer (dr > 41 : 1 by ¹H NMR analysis), presumably *via* transition state **C**. Deprotection of the TIPS protecting group in **16** by exposure to TBAF and subsequent protection of the resultant alcohol as the

PMB ether provided the 6,9-*trans*-THF **17** in 59% yield (two steps).

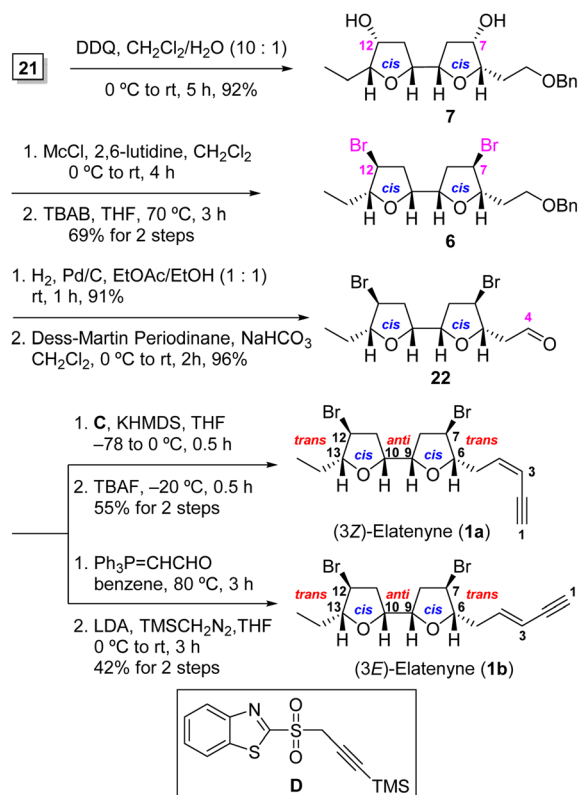
Having accomplished a highly stereoselective synthesis of the desired 6,9-*cis*-THF **10**, we turned our attention to the construction of the crucial adjacent bis-THF **21** as shown in Scheme 3. This requires the stereoselective synthesis of 9,10-*syn* homoallylic alcohol **9** from α -alkoxy amide **10** through application of our direct ketone synthesis/L-Selectride protocol.⁷ Thus, the Grignard reaction of **10** with CH₂=CHCH₂MgBr, and the subsequent L-Selectride reduction of the resulting ketone **18**, afforded the desired 9,10-*syn*-homoallylic alcohol **9** in moderate yield (59% for two steps) and good selectivity (dr = 8 : 1 by ¹H NMR analysis). In an alternative approach, **10** was reduced using the ate complex derived from *n*-BuLi and DIBAL-H¹² and subjected to Keck allylation¹³ to afford homoallylic alcohol **9** in improved yield (75% for two steps) and improved selectivity (dr = 46 : 1 by ¹H NMR analysis)¹⁴ CM reaction of the alcohol **9** with *cis*-3-hexene in the presence of Grubbs second-generation catalyst [G-II, (H₂IMes)(Cy₃P)Cl₂Ru=CHPh]¹⁵ afforded alkene **20** as an inseparable mixture of stereoisomers (95% total yield, *E/Z* = 6 : 1 by ¹H NMR analysis). Tosylation of alkene **20** (*E/Z* = 6 : 1) and subsequent AD-mix β -mediated SAD reaction¹⁶ of the resulting tosylate afforded the pure *syn*-diol **8** in 57% overall yield from **9** (three steps) after separation. Internal Williamson cyclization of **8** in refluxing pyridine or NaH in THF/DMF (3 : 2) furnished the desired adjacent bis-THF **21** in 86% or 84% yield, respectively.

Having acquired adjacent bis-THF **21**, we proceeded to introduce the bis-bromide functionality to both the C(7) and C(12) positions utilizing the two-step modified Nakata chloromethanesulfonate-mediated S_N2 displacement protocol^{2h,7b,17} (Scheme 4). To this end, treatment of bis secondary alcohol **7**, obtained from **21** after PMB deprotection (92%), with chloromethanesulfonyl chloride (MsCl) in the presence of 2,6-lutidine and subsequent exposure of the resulting sulfonate to (*n*-Bu)₄NBr in refluxing THF furnished the desired 7,12-dibromo-bis-THF **6** in an overall yield of 63% from **21** in two



Scheme 3 Construction of 7,12-dihydroxy adjacent bis-THF **21**.



Scheme 4 Completion of total synthesis of **1a** and **1b**.

steps. It is of note that the two-step Nakata protocol was superior to Hooz bromination in term of yield and purification in our hands [69% vs. 58%; see ESI† for details].¹⁸

Having successfully installed both the C(7) and C(12) bromide atoms in **1a** and **1b**, the remaining task was attaching the C(4) enyne appendages. Catalytic hydrogenolysis of benzyl ether **6**, followed by Dess–Martin oxidation¹⁹ of the resultant primary alcohol gave rise to aldehyde **22**. The stereoselective Julia–Kocienski olefination²⁰ of aldehyde **22** with benzothiazole sulfone **C** by treatment with KHMDS in THF at -78 to 0 $^\circ\text{C}$ for 0.5 h gave rise to the (3Z)-TMS-enyne (*Z/E* = 31 : 1 by ^1H NMR analysis), which was desilylated with TBAF to afford (3Z)-elatenyne (**1a**) in 55% overall yield for the two steps from **22**. For the second target, Wittig olefination of aldehyde **22** with $\text{Ph}_3\text{P=CHCHO}$ [(triphenylphosphoranylidene)acetaldehyde] gave exclusively the (*E*)- α,β -unsaturated aldehyde, which was then subjected to the condition of Colvin–Ohira homologation²¹ using trimethylsilyldiazomethane and LDA to afford (3E)-elatenyne (**1b**) in 42% overall yield for two steps. The spectral characteristics of our synthetic material **1a** and **1b** were in good agreement with those reported for both the natural and synthetic (3Z)-^{2a,d,h} and (3E)-^{2b,h}-elatenynes, respectively.

Conclusions

In summary, we have accomplished the total synthesis of both (3Z)-elatenyne (**1a**) and (3E)-elatenyne (**1b**), featuring the protecting group-dependent chelate-controlled IAEA methodology

for a highly stereoselective construction of key intermediate 6,7-*cis*-6,9-*cis*-THF **10**. Other key features of the synthesis include the sequential ate complex reduction/Keck allylation for stereoselective establishment of 9,10-*syn* configuration, the CM/SAD/Williamson cyclization sequence for the efficient construction of the bis-THF moiety, and the chloromethanesulfonate-mediated $\text{S}_{\text{N}}2$ displacement for installation of the 7,12-dibromo functionality. Application of our strategy on the basis of chelate-controlled IAEA and the Marshall's protocol to the synthesis of other members of the adjacent C₁₅ bis-THF acetogenin class in Fig. 1 is currently under investigation in our laboratories.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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