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

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We describe here the highly stereoselective total synthesis of the *Laurencia* C_{15} acetogenins (3*Z*)- and (3*E*)-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 C_{15} adjacent bis-THF acetogenin class.

Marine algae produce a diverse set of oxacyclic C_{15} acetogenins, among which some, as shown in Fig. 1, have a 2,2′-bifuranyl (adjacent bis-THF) core structure.[1] (3*Z*)-Elatenyne (**1a**) was first isolated from the marine algae *Laurencia elata* by Hall and Reiss in 1986,[2a] and Erickson reported isolating (3*E*)-elatenyne (**1b**) from the marine alga *Laurencia majuscule* in 1989.[2b] Later, **1a** was re-isolated from *Laurencia decumbens* by Wang in 2007 (ref. 2*c*) and from *Laurencia elata* by Urban in 2011.[2d] The isolation of several closely related *Laurencia* C_{15} acetogenins has been reported, including notoryne (**2**),[3] chloroenyne (**3**) from *L. majuscule*,[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 ^{1}H and ^{13}C NMR spectroscopic analyses, the structure of (3*Z*)-elatenyne (**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 ^{13}C NMR chemical shifts of **1a** with the Boltzmann-weighted GIAO ^{13}C 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

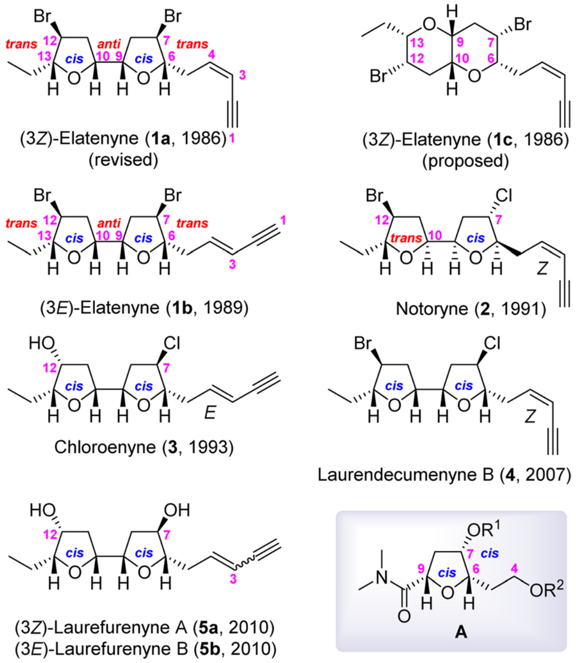

Fig. 1 *Laurencia* adjacent bis-tetrahydrofuranoid natural products.

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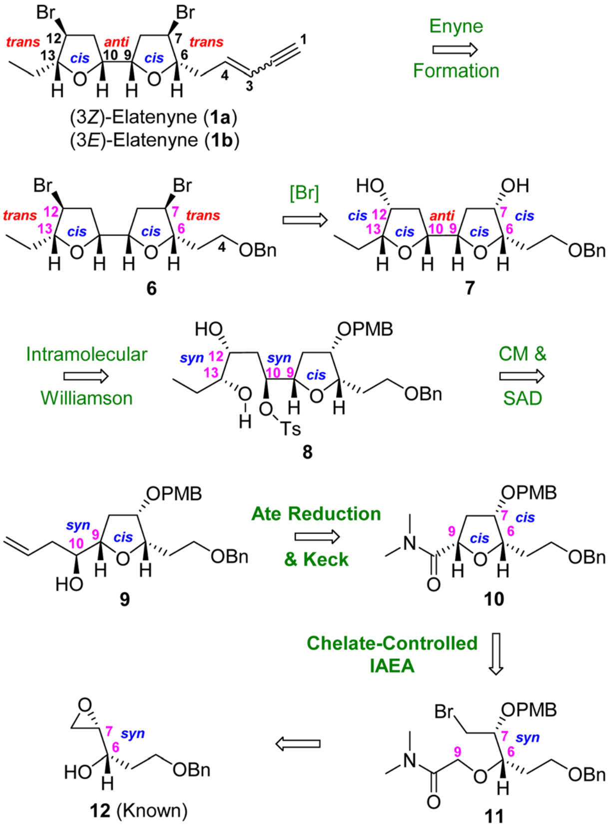
assignment of the absolute stereochemistry of **1a** was still not possible. Eventually, Urban and Fujita confirmed the absolute stereochemistry of **1a** as that shown in Fig. 1 using the crystalline sponge method.[2i]

The structural features of these C_{15} 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 ^{13}C 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]

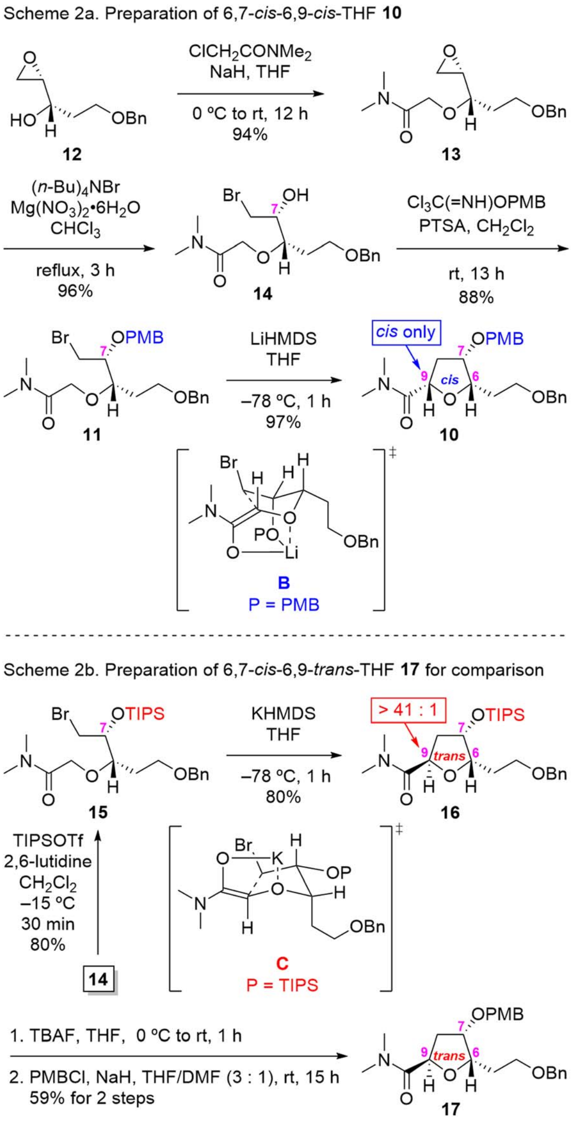
Based on the insights garnered from our highly stereoselective syntheses of oxylipids[7a] and asimitrin,[7b] we formulated a synthetic strategy which provides access to any member of this C_{15} adjacent bis-THF acetogenin class through a highly stereoselective construction of the 2,5-disubstituted-3-oxygenated 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 tetrahydrofuranyl *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, (10*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 1 Retrosynthetic plan.



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

(*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**.

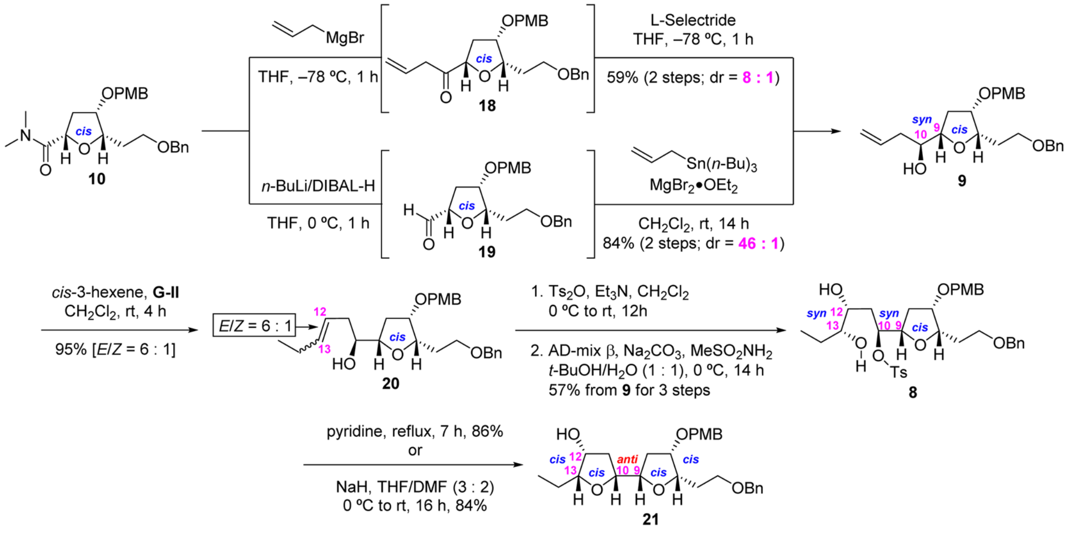
Our synthesis began with the preparation of IAEA substrate **11**, as outlined in Scheme 2. Thus, known epoxy alcohol **12** (ref. 9) was subjected to *O*-alkylation with *N*,*N*-dimethyl chloroacetamide to afford the desired epoxy α-alkoxy amide **13** in 94% yield. The regioselective opening of the terminal epoxide **13** was achieved through the action of (*n*-Bu)$_4$NBr in the presence of $\mathrm{Mg(NO_3)_2 \cdot 6H_2O}$ 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 ^{1}H 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.

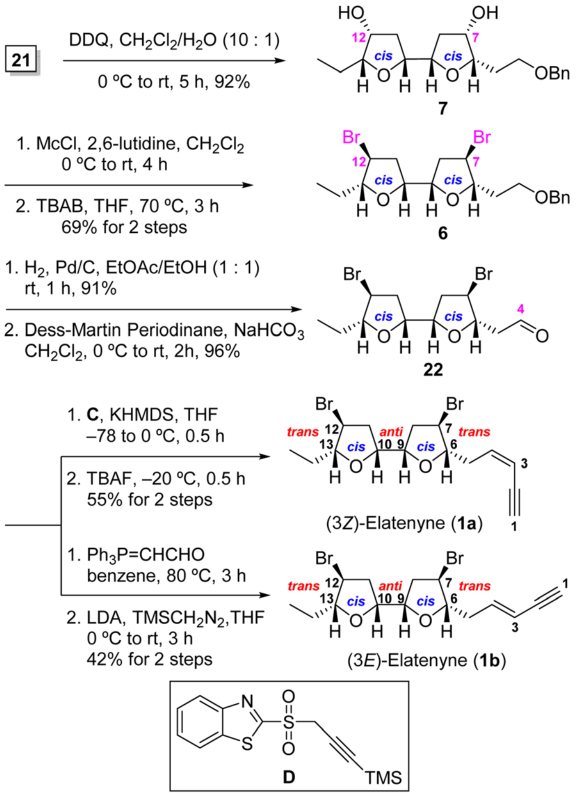
To establish the diastereoselectivity of the IAEA reaction in a rigorous manner, we decided to synthesize the corresponding 6,9-*trans* isomer **17** for comparison purposes as shown at the bottom of Scheme 2. To this end, subjection of TIPS-protected bromo α-alkoxy amide **15** (prepared by TIPS protection 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 ^{1}H 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 $\mathrm{CH_2{=}CHCH_2MgBr}$, 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 ^{1}H NMR analysis). In an alternative approach, **10** was reduced using the ate complex derived from *n*-BuLi and DIBAL-H[12] and subjected to Keck allylation[13] to afford homoallylic alcohol **9** in improved yield (75% for two steps) and improved selectivity (dr = 46 : 1 by ^{1}H NMR analysis)[14] CM reaction of the alcohol **9** with *cis*-3-hexene in the presence of Grubbs second-generation catalyst [G-II, $\mathrm{(H_2IMes)(Cy_3P)Cl_2Ru{=}CHPh}$][15] afforded alkene **20** as an inseparable mixture of stereoisomers (95% total yield, *E*/*Z* = 6 : 1 by ^{1}H NMR analysis). Tosylation of alkene **20** (*E*/*Z* = 6 : 1) and subsequent AD-mix β-mediated SAD reaction[16] 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 $\mathrm{S_N2}$ 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 (McCl) in the presence of 2,6-lutidine and subsequent exposure of the resulting sulfonate to (*n*-Bu)$_4$NBr 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 oxidation[19] of the resultant primary alcohol gave rise to aldehyde **22**. The stereoselective Julia–Kocienski olefination[20] of aldehyde **22** with benzothiazole sulfone **C** by treatment with KHMDS in THF at −78 to 0 °C for 0.5 h gave rise to the (3*Z*)-TMS-enyne (*Z*/*E* = 31 : 1 by ^{1}H NMR analysis), which was desilylated with TBAF to afford (3*Z*)-elatenyne (**1a**) in 55% overall yield for the two steps from **22**. For the second target, Wittig olefination of aldehyde **22** with $Ph_3P{=}CHCHO$ [(triphenylphosphoranylidene)acetaldehyde] gave exclusively the (*E*)-α,β-unsaturated aldehyde, which was then subjected to the condition of Colvin–Ohira homologation[21] using trimethylsilyldiazomethane and LDA to afford (3*E*)-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 (3*Z*)-[2a,d,h] and (3*E*)[2b,h]-elatenynes, respectively.

Conclusions

In summary, we have accomplished the total synthesis of both (3*Z*)-elatenyne (**1a**) and (3*E*)-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 S_N2 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 C_{15} 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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