RSC Advances

PAPER

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Cite this: *RSC Adv.*, 2023, **13**, 35920

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

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Received 13th November 2023
Accepted 4th December 2023

DOI: 10.1039/d3ra07741a

rsc.li/rsc-advances

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

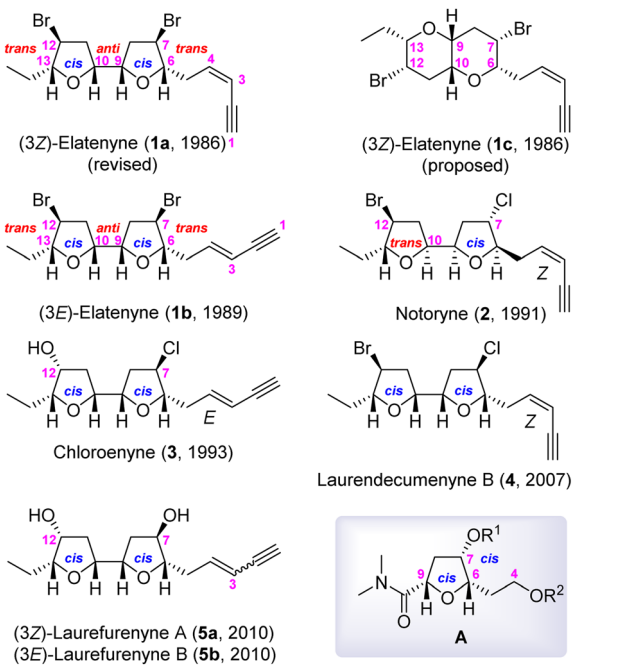

Fig. 1 *Laurencia* adjacent bis-tetrahydrofuranoid natural products.

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† Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d3ra07741a

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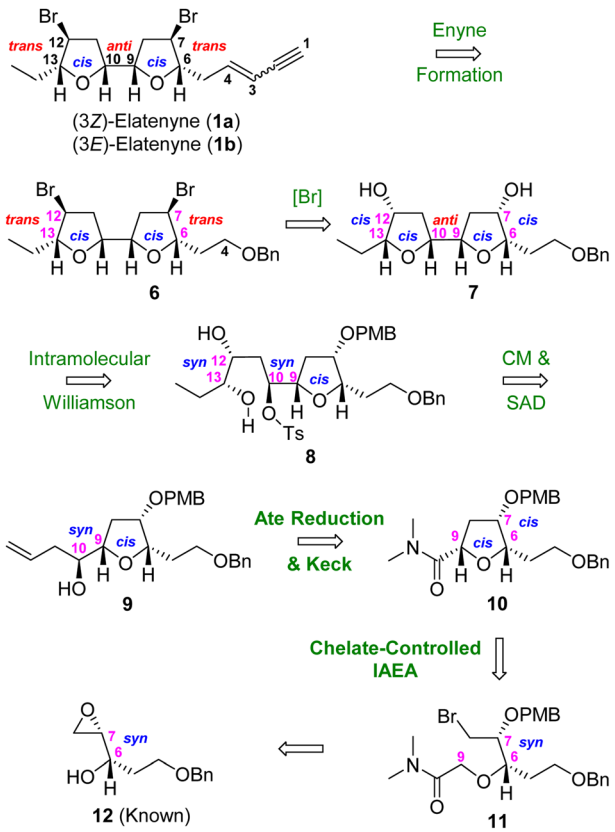
assignment of the absolute stereochemistry of **1a** was still not possible. Eventually, Urban and Fujita confirmed the absolute stereochemistry of **1a** as that shown in Fig. 1 using the crystalline sponge method.[2i]

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]

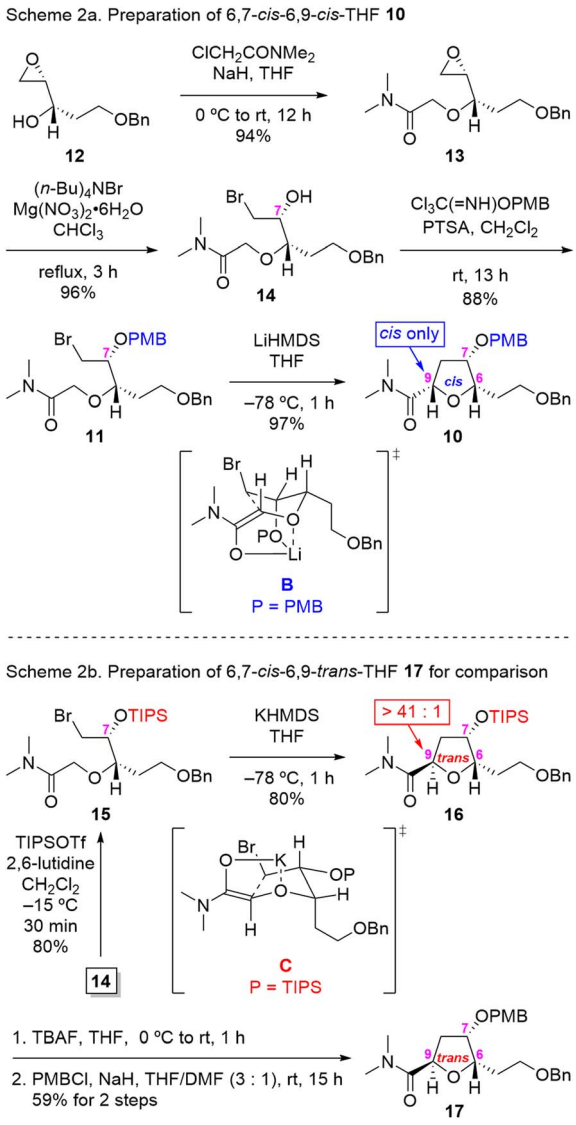
Based on the insights garnered from our highly stereoselective syntheses of oxylipids[7a] and asimitrin,[7b] we formulated a synthetic strategy which provides access to any member of this C_{15} adjacent bis-THF acetogenin class through a highly stereoselective construction of the 2,5-disubstituted-3-oxygenated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

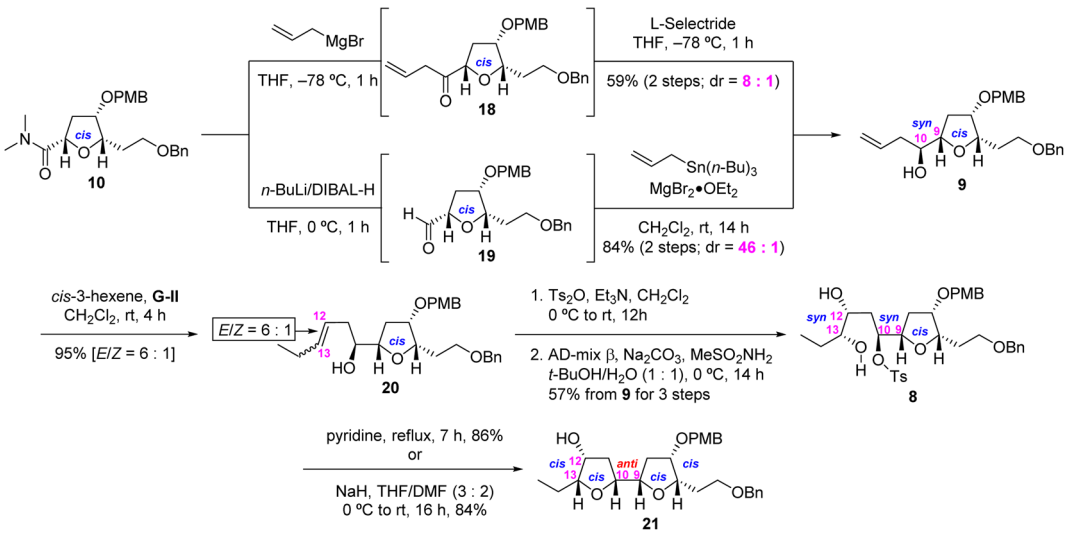
Our synthesis began with the preparation of IAEA substrate **11**, as outlined in Scheme 2. Thus, known epoxy alcohol **12** (ref. 9) was subjected to *O*-alkylation with *N*,*N*-dimethyl chloroacetamide to afford the desired epoxy α-alkoxy amide **13** in 94% yield. The regioselective opening of the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

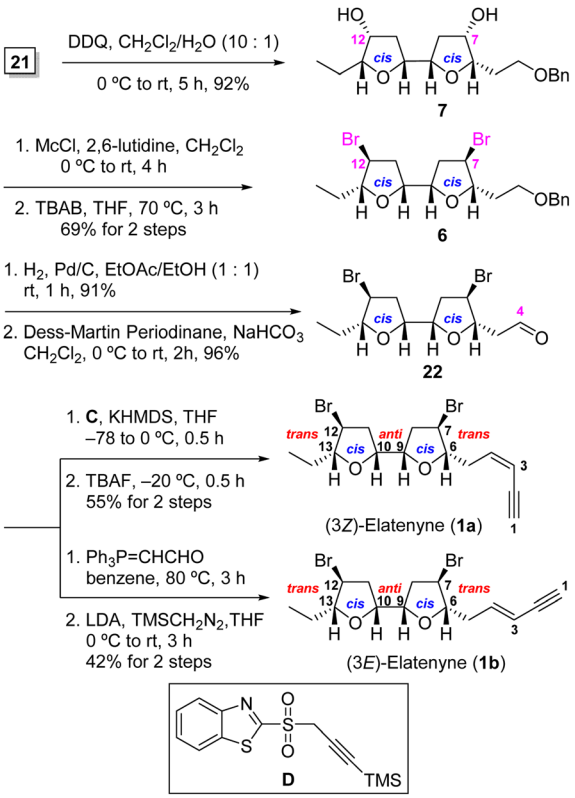
To establish the diastereoselectivity of the IAEA reaction in a rigorous manner, we decided to synthesize the corresponding 6,9-*trans* isomer **17** for comparison purposes as shown at the bottom of Scheme 2. To this end, subjection of TIPS-protected bromo α-alkoxy amide **15** (prepared by TIPS protection 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 $CH_2{=}CHCH_2MgBr$, 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, $(H_2IMes)(Cy_3P)Cl_2Ru{=}CHPh$][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 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 $(n\text{-Bu})_4\text{NBr}$ 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

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIT) (NRF-2020R1A2C2010329) and a grant (21153MFDS602 & 21163MFDS369) from the Ministry of Food and Drug Safety.

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