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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<sub>15</sub> 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<sub>N</sub>2 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<sub>15</sub> adjacent bis-THF acetogenin class.

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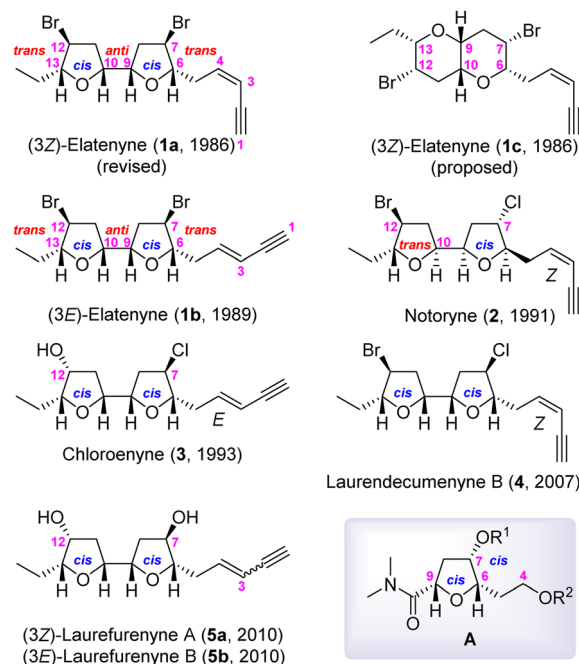
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Marine algae produce a diverse set of oxacyclic C<sub>15</sub> acetogenins, among which some, as shown in Fig. 1, have a 2,2'-bifuranyl (adjacent bis-THF) core structure.<sup>1</sup> (3*Z*)-Elatenyne (**1a**) was first isolated from the marine alga *Laurencia elata* by Hall and Reiss in 1986,<sup>2a</sup> and Erickson reported isolating (3*E*)-elatenyne (**1b**) from the marine alga *Laurencia majuscula* in 1989.<sup>2b</sup> Later, **1a** was re-isolated from *Laurencia decumbens* by Wang in 2007 (ref. 2c) and from *Laurencia elata* by Urban in 2011.<sup>2d</sup> The isolation of several closely related *Laurencia* C<sub>15</sub> acetogenins has been reported, including notoryne (**2**),<sup>3</sup> chloroenyne (**3**) from *L. majuscula*,<sup>4</sup> laurendecumenyne B (**4**),<sup>5</sup> and laurefurenynes A (**5a**) and B (**5b**).<sup>6</sup> It is worth mentioning at this point that the structures depicted in Fig. 1 have been revised or confirmed by total synthesis.<sup>2h,3c-e,6b,c</sup>

Based on extensive <sup>1</sup>H and <sup>13</sup>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**.<sup>2a</sup> However, the **1c** structure was shown by Burton, *et al.*, to be incorrect through the total synthesis thereof.<sup>2e,f</sup> 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 <sup>13</sup>C NMR chemical shifts of **1a** with

the Boltzmann-weighted GIAO <sup>13</sup>C NMR chemical shifts determined through DFT methods.<sup>2g</sup> 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.<sup>2h</sup> 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.<sup>2f</sup>

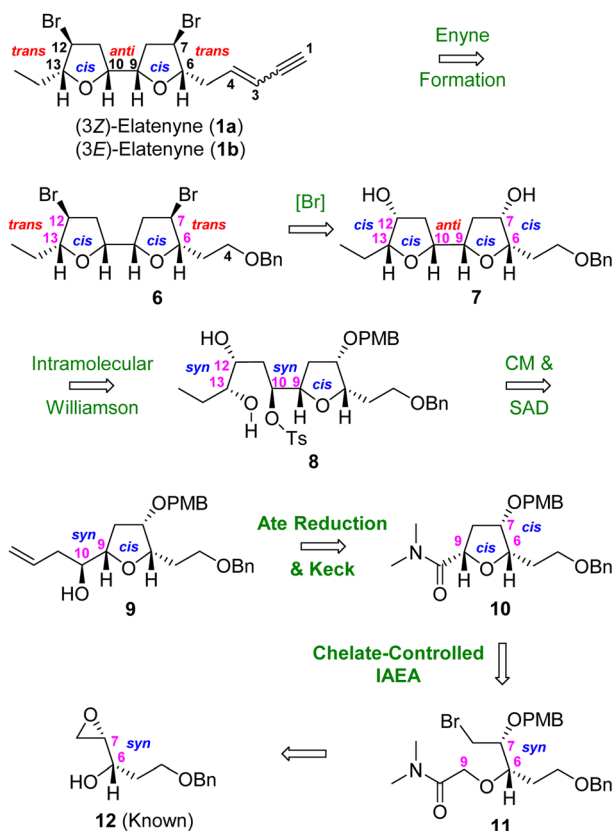
The structural features of these C<sub>15</sub> adjacent bis-THF acetogenins have received considerable attention from organic chemistry community, culminating to several total syntheses: the modular synthesis on the basis of analysis <sup>13</sup>C NMR chemical shifts,<sup>2h,e,3e,6b</sup> biomimetic approach,<sup>2e,h,3c,e</sup> the cyclization of chlorohydrin derived from anti-aldol reaction,<sup>6c</sup> the Sharpless asymmetric dihydroxylation (SAD)/Williamson cyclization sequence,<sup>4b</sup> and the bromo-etherification.<sup>3d</sup>

Based on the insights garnered from our highly stereoselective syntheses of oxylipids<sup>7a</sup> and asimitrin,<sup>7b</sup> we formulated a synthetic strategy which provides access to any member of this C<sub>15</sub> 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).<sup>7</sup> In addition, our strategy utilizes Marshall's protocol [cross metathesis (CM)/SAD/Williamson cyclization]<sup>9</sup> for the efficient construction of 2nd THF skeleton in the adjacent bis-THF unit.

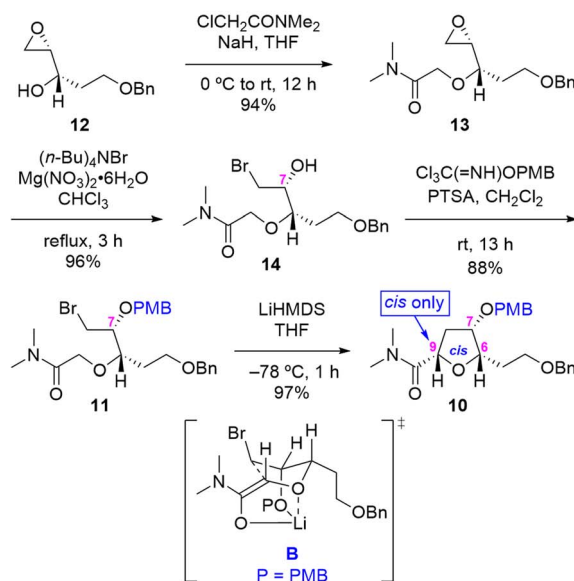
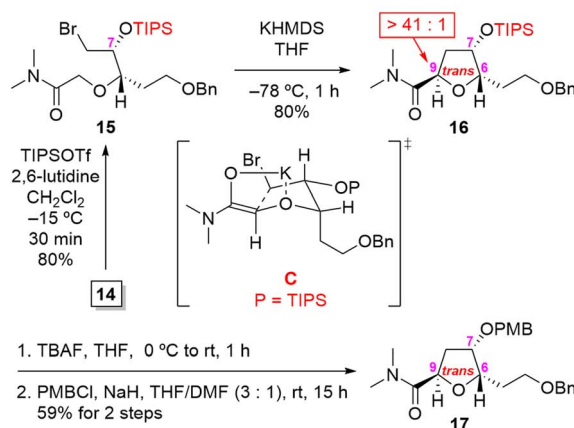
To demonstrate the synthetic potential of this strategy, we describe herein the asymmetric total synthesis of (3*Z*)-elatenyne (**1a**) and (3*E*)-elatenyne (**1b**) featuring a highly stereoselective and chelate-controlled IAEA for constructing key intermediate 7-hydroxy-6,7-*cis*-6,9-*cis*-THF **10**.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



Scheme 1 Retrosynthetic plan.

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

(*vide infra*). Based on our previous work,<sup>7</sup> we were confident that key 6,7-*cis*-6,9-*cis*-THF intermediate **10** could be accessed by subjecting 6,7-*syn*- $\omega$ -bromo- $\alpha$ -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  $\alpha$ -alkoxy amide **13** in 94% yield. The regioselective opening of the terminal epoxide **13** was achieved through the action of (*n*-Bu)<sub>4</sub>NBr in the presence of Mg(NO<sub>3</sub>)<sub>2</sub>·6H<sub>2</sub>O to furnish the 6,7-*syn*-bromoamide **14** with an excellent 96% yield.<sup>10</sup> 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)<sup>11</sup> gave rise to key IAEA substrate **11** in good yield (88%).

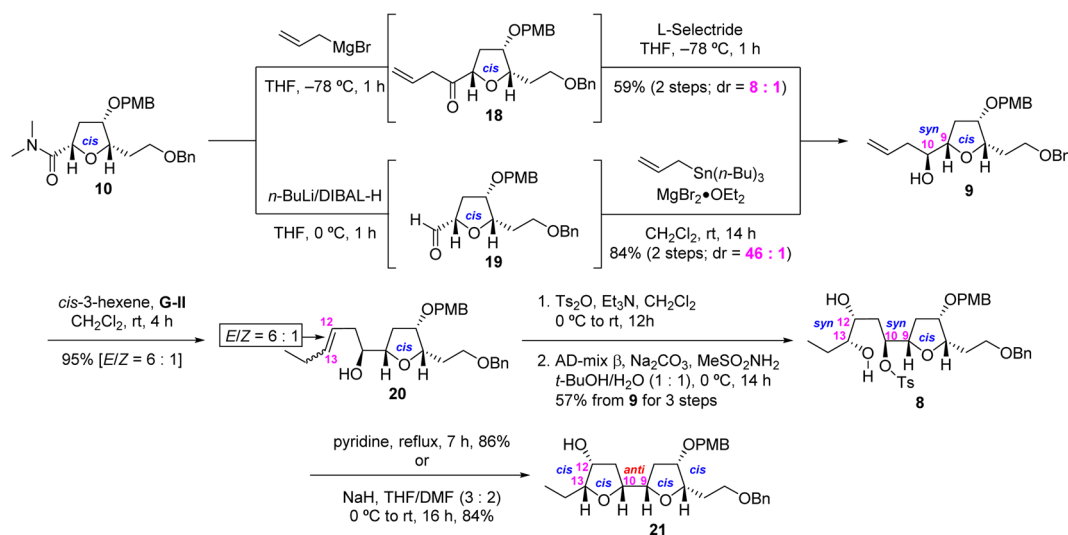
With IAEA substrate **11** in hand, we proceeded to address the pivotal stereoselective IAEA reaction of PMB-protected bromo  $\alpha$ -alkoxy amide **11** for the construction of key intermediate **10**. Treatment of **11** with LiHMDS in THF at -78 °C for 1 h led to the desired 6,7-*cis*-6,9-*cis*-THF **10** in 97% yield as a single stereoisomer (by <sup>1</sup>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  $\alpha$ -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 <sup>1</sup>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).

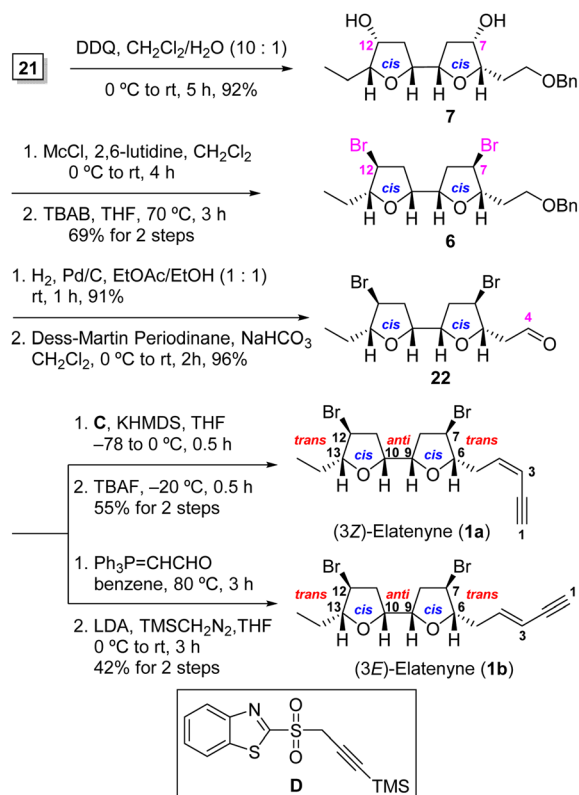
Having accomplished a highly stereoselective synthesis of the desired 6,9-*cis*-THF **10**, we turned our attention to the construction of the crucial adjacent bis-THF **21** as shown in Scheme 3. This requires the stereoselective synthesis of 9,10-*syn* homoallylic alcohol **9** from  $\alpha$ -alkoxy amide **10** through application of our direct ketone synthesis/*L*-Selectride protocol.<sup>7</sup> Thus, the Grignard reaction of **10** with CH<sub>2</sub>=CHCH<sub>2</sub>MgBr, 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 <sup>1</sup>H NMR analysis). In an alternative approach, **10** was reduced using the ate complex derived from *n*-BuLi and DIBAL-H<sup>12</sup> and subjected to Keck allylation<sup>13</sup> to afford homoallylic alcohol **9** in improved yield (75% for two steps) and improved selectivity (dr = 46 : 1 by <sup>1</sup>H NMR analysis)<sup>14</sup> CM reaction of the alcohol **9** with *cis*-3-hexene in the presence of Grubbs second-generation catalyst [G-II, (H<sub>2</sub>IMes)(Cy<sub>3</sub>P)Cl<sub>2</sub>Ru=CHPh]<sup>15</sup> afforded alkene **20** as an inseparable mixture of stereoisomers (95% total yield, *E/Z* = 6 : 1 by <sup>1</sup>H NMR analysis). Tosylation of alkene **20** (*E/Z* = 6 : 1) and subsequent AD-mix  $\beta$ -mediated SAD reaction<sup>16</sup> 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<sub>N</sub>2 displacement protocol<sup>2h,7b,17</sup> (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)<sub>4</sub>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].<sup>18</sup>

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<sup>19</sup> of the resultant primary alcohol gave rise to aldehyde **22**. The stereoselective Julia–Kocienski olefination<sup>20</sup> 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 (3Z)-TMS-enyne ( $Z/E = 31 : 1$  by <sup>1</sup>H 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 Ph<sub>3</sub>P=CHCHO [(triphenylphosphoranylidene)acetaldehyde] gave exclusively the (E)- $\alpha,\beta$ -unsaturated aldehyde, which was then subjected to the condition of Colvin–Ohira homologation<sup>21</sup> 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)-<sup>2a,d,h</sup> and (3E)<sup>2b,h</sup>-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 S<sub>N</sub>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 C<sub>15</sub> 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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