Natural Products

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Substrate-Controlled Asymmetric Total Synthesis and Structure Revision of (+)-Itomanallene A**

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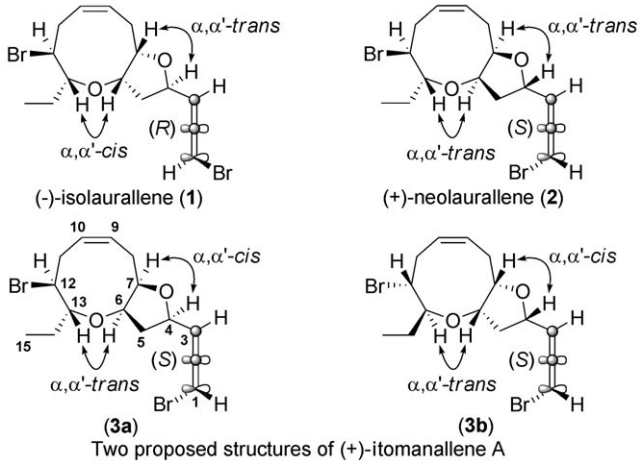
Species of the red algal genus *Laurencia* (Rhodomelaceae, Ceramiales) have been a prolific source of diverse halogenated secondary metabolites.[1] Since Kurata et al. reported the isolation of isolaurallene (**1**) from the red alga *Laurencia nipponica* in 1982,[2] new C_{15} acetogenins with the 2,10-dioxabicyclo[7.3.0]dodecene skeleton have been isolated. Examples include (+)-neolaurallene (**2**), which was isolated by Kurosawa and co-workers from the red alga *Laurencia okamurai* in 1984,[3] and (+)-itomanallene A, which was subsequently isolated by Suzuki et al. from the red alga *Laurencia intricata* collected at Itoman (Japan) in 2002.[4] The structure and absolute configuration of both isolaurallene (**1**) and neolaurallene (**2**) were firmly established on the basis of X-ray crystallographic studies.[2,3]



Two proposed structures of (+)-itomanallene A

Unlike isolaurallene and neolaurallene, itomanallene A possesses an α,α′-*cis*-tetrahydrofuran moiety. The relative stereochemistry of the bicyclic skeleton of itomanallene A was established by extensive spectroscopic studies. In particular, nOe interactions between the protons on C6 and C4 and between the protons on C6 and C7 were supportive of the assigned *cis* relative stereochemistry of the tetrahydrofuran ring. Judging from the strong positive rotation of itomanallene A, its bromoallene moiety would be assigned as *S* by application of Lowe's rule.[5] Since the relative stereochemistry between the bicyclic skeleton and the bromoallene unit could not be determined, **3a** and **3b** were proposed for the possible structures of itomanallene A.

Among these structurally exquisite dioxabicyclic oxonene marine natural products, only isolaurallene has succumbed to total synthesis to date, wherein Crimmins et al. exploited dual synergistic gauche effects to guide the course of their ring-closing metathesis (RCM) to form the nine-membered-ring ether.[6]

Reported herein are the first asymmetric total synthesis of (+)-itomanallene A and its structure revision. A highly stereoselective intermolecular α-alkoxy *N*,*N*-dimethylamide enolate alkylation is a key step in our approach. In the course of this work, we discovered a striking difference in the stereochemistry of the intramolecular alkylation involving either an *N*,*N*-dimethylamide enolate or a nitrile anion. We used this advantage to develop complementary routes for establishing the relative stereochemistry of the tetrahydrofuran oxymethine unit, and the synthesis of both isomers allowed us to propose the structure revision. Our substrate-controlled route should provide a general strategy for the synthesis of both α,α′-*cis*- and α,α′-*trans*-tetrahydrofurans in such dioxabicylic marine natural products and related structures.

Our first objective was to determine the relative stereochemistry between the dioxabicyclic core and the bromoallene appendage of itomanallene A. For simplicity, we initially opted to synthesize *ent*-**3a** and **3b** instead of the originally proposed structures **3a** and **3b**. As it turned out, this decision was a fortuitous one.

Our retrosynthetic plan for the substrate-controlled synthesis of *ent*-**3a** and **3b**, as shown in Scheme 1, hinges upon the versatility of the α-alkoxy *N*,*N*-dimethylamide functionality. We envisioned that bicyclic bromoaldehyde **4** could be elaborated to both *ent*-**3a** and **3b** by installation of the respective bromoallene units. The requisite bromoaldehyde **4** could be produced from **5** by bromination with inversion of

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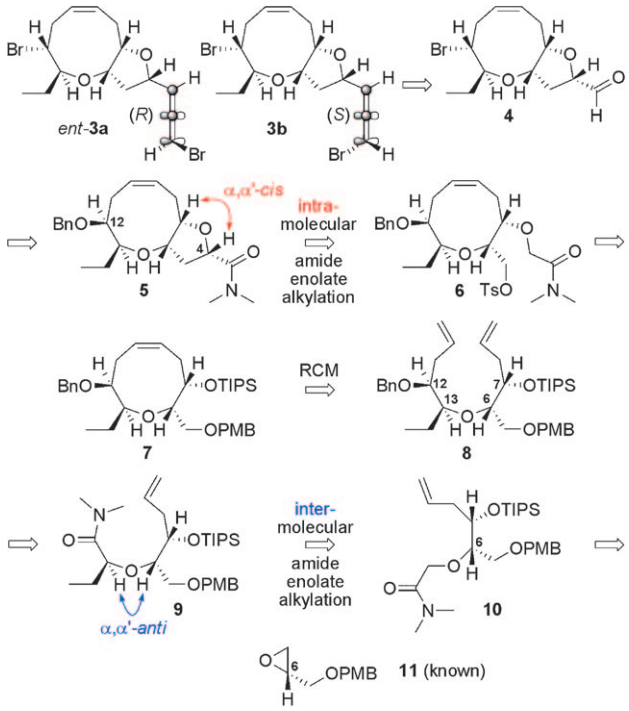


Scheme 1. Retrosynthetic plan for *ent*-**3a** and **3b**. PMB = *para*-methoxybenzyl, TIPS = triisopropylsilyl.

the configuration at C12, and reduction of the α-alkoxy *N*,*N*-dimethylamide functionality. Furthermore, we envisioned that the α,α′-*cis*-tetrahydrofuran ring in bicyclic α-alkoxy amide **5** could be constructed in a stereoselective manner through an intramolecular amide enolate alkylation (IAEA) of tosylate **6**, which in turn could be readily prepared from oxonene intermediate **7**. It is worthwhile mentioning at this point that carbon–oxygen bond formation at C4 by a 5-*exo*-trigonal ring closure leads to an α,α′-*trans*-tetrahydrofuran.[7]

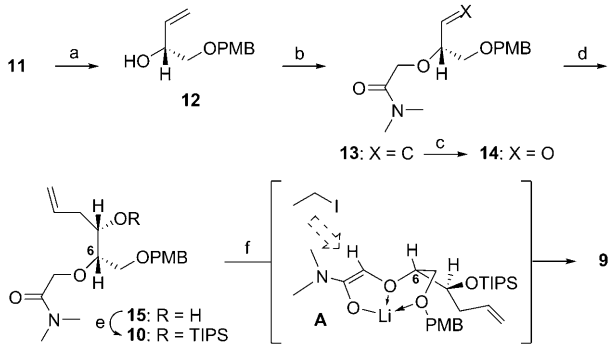
We reasoned that the nine-membered ether **7** could be constructed by RCM of bis-alkene **8**. However, the efficiency of the hitherto uninvestigated RCM of bis-alkene **8** (*syn*-C6/C7, *anti*-α,α′, *syn*-C12/C13) caused some concern since it was known that the relative stereochemistry of the incipient cyclic ether oxygen atom with respect to each of the adjacent oxygen substituents, as well as the α,α′ relative stereochemistry, can exert a subtle conformational effect on the rate of RCM reactions to give oxonenes.[8–10] Specifically, the *anti* isomer places one side chain in a pseudo-axial orientation in the transition state for ring closure, which would be unfavorable for the desired outcome.

In this plan, the *syn* stereochemical relationship between C12 and C13 in the RCM substrate **8** could be established by manipulation of the α-alkoxy *N*,*N*-dimethylamide group in **9** by using our direct ketone synthesis/L-Selectride reduction protocol.[11] For the greater challenge of the pivotal α,α′-*anti* stereochemistry in **9**, we envisaged that this would be established through a chemoselective chelation-controlled intermolecular amide enolate alkylation of **10**. Furthermore, analysis suggested that the alkylation substrate **10** would be readily accessible from known PMB-protected (*S*)-glycidol **11**[12] by addressing the C6/C7-*syn* stereochemistry through a chelation-controlled nucleophilic addition.

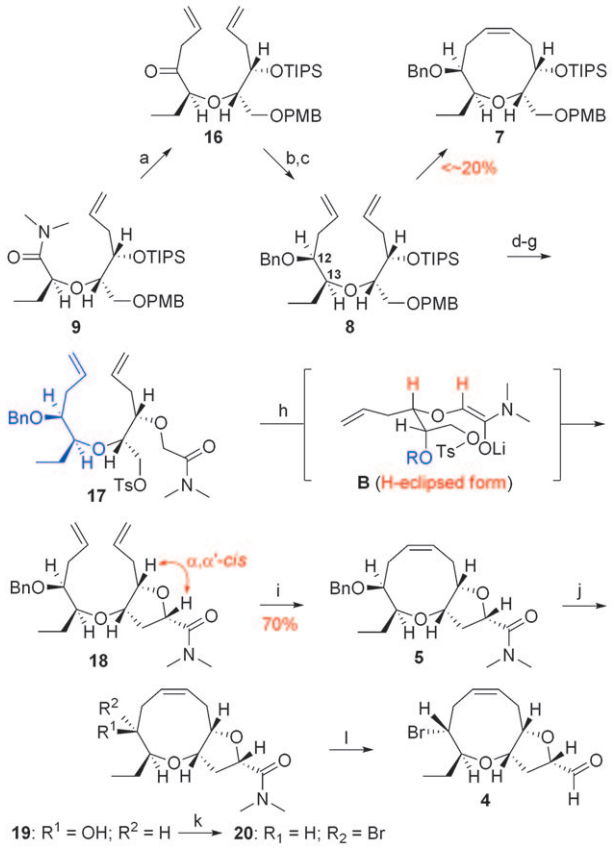
A significant feature of this approach is that it showcases the versatility of the α-alkoxy amide enolate alkylation in establishing both sets of α,α′-oxymethine relative configurations without recourse to using additional chiral auxiliaries.

Our synthesis commenced with preparation of the key intermolecular amide enolate alkylation substrate **10** (Scheme 2). Therefore, one-carbon homologation of (*S*)-glycidol **11** by treatment with dimethylsulfonium methylide,[13] and subsequent O-alkylation of the resulting allylic alcohol **12** with *N*,*N*-dimethyl chloroacetamide, produced α-alkoxy amide **13** in excellent overall yield (95%, two steps). Cleavage of alkene **13** by a modified Lemieux–Johnson oxidation then afforded aldehyde **14**.[14] Chemoselective chelation-controlled nucleophilic addition of allyltributylstannane to aldehyde **14**[15] in the presence of the α-alkoxy amide and subsequent protection of the resulting *syn*-diol derivative **15** as a TIPS ether furnished the requisite substrate **10** (67% for three steps from **13**), setting the stage for the crucial intermolecular amide enolate alkylation. Therefore, treatment of **10** with LiHMDS in the presence of ethyl iodide produced the desired α,α′-*anti*-alkoxy amide **9** in 91% yield as essentially a single isomer. The stereochemical outcome of the chemoselective chelation-controlled alkylation can be rationalized by considering that the alkylating agent approaches from the less hindered convex face of the cup-shaped, chelated enolate intermediate **A** where the bulky group at C6 prefers to be located.[16] Notably, the PMB-protected alkoxy group participates in the chelation in preference to the TIPS-protected alkoxy group, which is known to be a poor coordinating group.[17]

Having established the pivotal α,α′-*anti* stereochemistry in **9**, we proceeded to address construction of the dioxabicyclic skeleton using the projected RCM/IAEA strategy (Scheme 3). The C12/C13-*syn* stereochemistry in the RCM



Scheme 2. Intermolecular amide enolate alkylation: a) $(CH_3)_3SI$, *n*BnLi, THF, −10°C to RT, 2 h, 98%; b) $ClCH_2CONMe_2$, NaH, DMF, 0°C to RT, 3 h, 97%; c) 1. OsO_4, NMO, H_2O/acetone (2:1), RT, 4 h; 2. $NaIO_4$, RT, 2 h, 85%; d) allyltributyltin, $MgBr_2{\cdot}Et_2O$, CH_2Cl_2, −78°C to RT, 18 h, 85%, *syn*/*anti* = 15:1; e) TIPSOTf, Et_3N, CH_2Cl_2, 0°C to RT, 3 h, 93%; f) LiHMDS, EtI, THF, −78 to −40°C, 2 h, 91%, *anti*/*syn* = 57:1. DMF = *N*,*N*-dimethylformamide, LiHMDS = lithium hexamethyldisilazide, NMO = *N*-methylmorpholine-*N*-oxide.



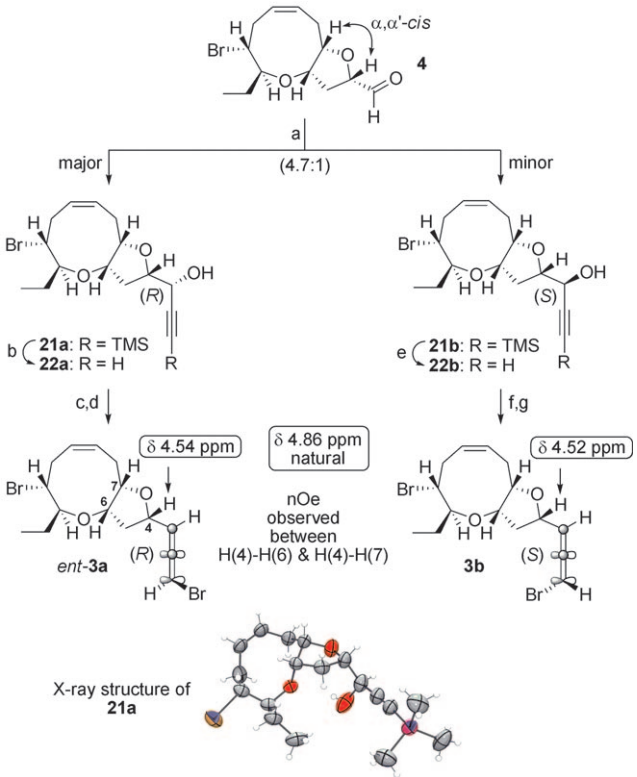
Scheme 3. Intramolecular amide enolate alkylation and RCM: a) $CH_2=CHCH_2MgCl$, THF, −78 °C, 2 h; b) L-Selectride, THF, −78 °C, 2 h, 85 % (2 steps), *syn*/*anti* = 17:1; c) NaH, BnBr, DMF, 0 °C to RT, 3 h, 95 %; d) TBAF, THF, RT, 2 h, 99 %; e) $ClCH_2CONMe_2$, NaH, DMF, 0 °C to RT, 3 h, 96 %; f) DDQ, CH_2Cl_2/buffer solution (pH 7.4; 9:1), 0 °C to 15 °C, 3 h, 94 %; g) TsCl, DMAP, Et_3N, CH_2Cl_2, 0 °C to RT, 8 h, 95 %; h) LiHMDS, THF, −78 to −40 °C, 2 h, 96 %; i) $(H_2IMes)(Cy_3P)Cl_2Ru{=}CHPh$, CH_2Cl_2, 70 °C, 5 h, then DMSO, RT, 12 h, 70 %; j) DDQ, CH_2Cl_2/buffer solution (pH 7.4; 9:1), RT, 12 h, 91 %; k) CBr_4, Oct_3P, 1-methylcyclohexene, toluene, 70 °C, 12 h, 65 %; l) *n*BuLi/DIBAL-H (1:1), THF, 0 °C, 30 min, 85 %. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DIBAL-H = diisobutylaluminum hydride, DMAP = 4-dimethylaminopyridine, DMSO = dimethyl sulfoxide, TBAF = tetra-*n*-butylammonium fluoride, Ts = toluenesulfonyl.

substrate **8** was introduced as follows: addition of allylmagnesium chloride to **9**, and subsequent L-Selectride reduction of the resulting ketone **16** (in the crude reaction mixture) according to Felkin–Ahn control;[18] then protection as a benzyl ether yielded the desired RCM substrate **8** in good overall yield (81 %, three steps) with 17:1 *syn*/*anti* selectivity.

Our initial concerns regarding the RCM of **8** were borne out, as only a low yield of the desired oxonene (ca. 20 %) was obtained despite a considerable amount of effort. The rationale that a cyclic constraint might facilitate the RCM prompted us to construct the five-membered ring first.[19] To this end, **8** was transformed into the key intramolecular alkylation substrate **17** by a straightforward four-step sequence [1) removal of TIPS group; 2) O-alkylation with *N*,*N*-dimethyl chloroacetamide; 3) chemoselective removal of the PMB group with wet DDQ;[20] 4) tosylation] in excellent overall yield (85 %). As anticipated, intramolecular amide enolate alkylation of **17** afforded the desired α,α′-*cis*-tetrahydrofuran **18** exclusively in 96 % yield, probably through the H-eclipsed transition-state geometry **B**.

Gratifyingly, subjection of tetrahydrofuranyl diene **18** to RCM using Grubbs' second-generation catalyst produced a 70 % yield of key bicyclic oxonene **5**. Removal of the benzyl group in **5** under the reaction conditions reported by Yonemitsu and co-workers[20] and subsequent bromination[21] of the resulting secondary alcohol **19**, with inversion of configuration, furnished α-bromide **20** (59 %, two steps). Finally, reduction of **20** using the ate complex[22] derived from DIBAL-H and *n*BuLi gave rise to the key bromoaldehyde **4** (85 %).

With the key bromoaldehyde **4** in hand, we turned our attention to installation of the bromoallene unit on the basis of the well-established protocol described by Overman and co-workers.[23] Therefore, addition of titanium TMS-acetylide to aldehyde **4** with Felkin–Ahn-type stereoselectivity produced a 4.7:1 mixture of TMS-propargylic alcohols **21a** and **21b** in 82 % total yield. The structure and absolute configuration of the major (*R*)-TMS-propargylic alcohol **21a** were confirmed by X-ray crystallography.[24] Removal of the TMS groups in **21a** and **21b** by exposure to TBAF then afforded **22a** and **22b**, respectively. Finally, trisylation of propargylic

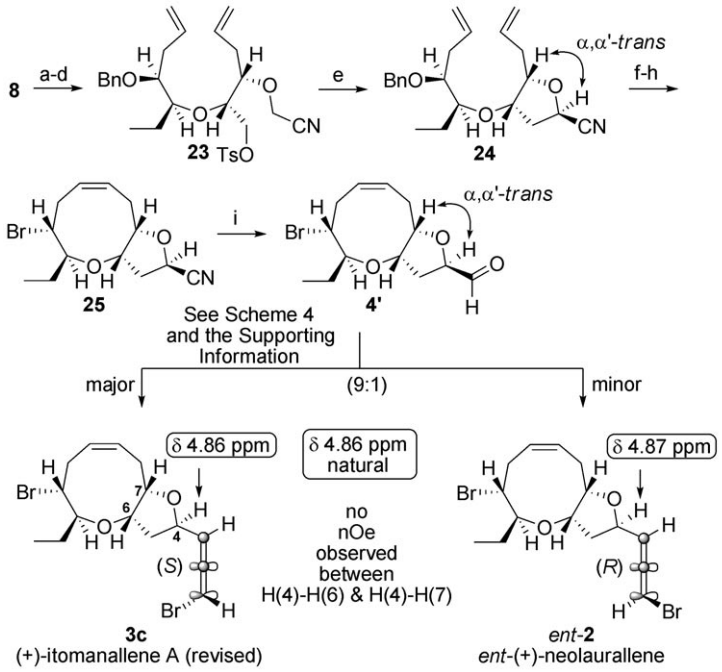


Scheme 4. Completion of the synthesis of *ent*-**3a** and **3b**: a) TMS-acetylene, *n*BuLi, $ClTi(OiPr)_3$, Et_2O, −78 °C to RT, 12 h, 82 %, *R*/*S* = 4.7:1; b) TBAF, THF, RT, 2 h, 96 %; c) TrisCl, DMAP, CH_2Cl_2, 0 °C to RT, 12 h, 99 %; d) $LiCuBr_2$, THF, reflux, 14 h, 80 %; e) TBAF, THF, RT, 3 h, 89 %; f) TrisCl, DMAP, CH_2Cl_2, 0 °C to RT, 16 h, 83 %; g) $LiCuBr_2$, THF, reflux, 48 h, 73 %. TMS = trimethylsilyl, Tris = 2,4,6-triisopropyl benzenesulfonyl.

alcohols **22a** and **22b**, and then the copper-catalyzed *anti*-S_N2' reaction of the corresponding trisylates gave rise to *ent*-**3a** and **3b**, respectively. Unfortunately, the ^{1}H NMR spectra of both compounds differ from that of natural itomanallene A. In particular, the chemical shift values of the C4 protons were significantly different as indicated in Scheme 4.

Careful examination of NMR data of structurally related natural products that possess a bromoallene led to the conclusion that itomanallene A might possess an α,α′-*trans*-tetrahydrofuran despite the aforementioned reported observation of an nOe interaction between the protons on C4 and C6. On the basis of this assumption, we set out to synthesize the C4 epimers of *ent*-**3a** and **3b**. Incidentally, the C4 epimer of *ent*-**3a** corresponds to the enantiomeric form of neolaurallene (*ent*-**2**; Scheme 5).

For this purpose, we were intrigued by the possibility that the requisite α,α′-*trans*-tetrahydrofuranyl aldehyde **4'** might be secured by intramolecular nitrile anion alkylation methodology based on the pioneering work by Stork et al.[25] and ensuing investigations by Fleming et al.[26,27] To this end, the key intramolecular nitrile anion cyclization substrate **23** was synthesized uneventfully in four steps starting from **8** [1) removal of TIPS group (99%); 2) O-alkylation with bromoacetonitrile (69%, 91% brsm); 3) removal of the PMB group with DDQ (92%); 4) tosylation (97%)].[28] We were delighted to find that upon exposure to LiHMDS in benzene, nitrile tosylate **23** gave rise to the desired α,α′-*trans* isomer **24** as the major isomer (87% total yield; *trans*/*cis* = 4.5:1).



Scheme 5. Intramolecular nitrile anion alkylation and structure revision: a) TBAF, THF, RT, 2 h, 99%; b) NaH, $BrCH_2CN$, MeCN, RT, 20 min, then −20°C, 72 h, 69% (brsm 91%); c) DDQ, CH_2Cl_2/buffer solution (pH 7.4; 9:1), 15°C, 4 h, 92%; d) TsCl, DMAP, Et_3N, CH_2Cl_2, 0°C to RT, 5 h, 97%; e) LiHMDS, benzene, 7°C, 30 min, 87%, *trans*/*cis* = 4.5:1; f) $(H_2IMes)(Cy_3P)Cl_2Ru{=}CHPh$, CH_2Cl_2, 70°C, 4 h, then DMSO, RT, 12 h, 57%; g) DDQ, CH_2Cl_2/buffer solution (pH 7.4; 9:1), RT to 40°C, 27 h, 87%; h) CBr_4, Oct_3P, 1-methylcyclohexene, toluene, 70°C, 4 h, 60%; i) DIBAL-H, toluene, −78°C, 1 h. brsm = based on recovered starting material.

To the best of our knowledge, this constitutes the first example of the construction of a tetrahydrofuran through an intramolecular alkylation of an α-alkoxy nitrile.[29] It is also highly significant that in this tetrahydrofuran construction, the α-alkoxy nitrile affords stereoselection that is complementary to that obtained with the corresponding α-alkoxy *N*,*N*-dimethylamide. The origin of this stereodifferentiation is unclear at the present time; although not unprecedented,[25–27] it is not clear that comparable parameters determine the outcome. The exact nature of the nitrile anion involved is elusive factor, and the underlying reasons for this selectivity along with its use in synthesis are the subject of further investigation.[30]

To complete the synthesis, tetrahydrofuranyl nitrile **24** was converted into the desired α,α′-*trans*-bicyclic nitrile **25** by a three-step sequence analogous to that employed for synthesis of **20** [1) RCM; 2) removal of benzyl group; 3) bromination with inversion of configuration]. The α,α′-*trans*-aldehyde **4′**, prepared by DIBAL-H reduction of nitrile **25**, was converted into **3c** and *ent*-**2** by a four-step sequence identical to that employed for syntheses of *ent*-**3a** and **3b**.[31] The spectral characteristics and optical rotation of our synthetic material **3c**, which corresponds to the C4 epimer of one of the proposed structures (**3b**), were in good agreement with those reported for the natural itomanallene A: $[\alpha]_D^{22} = +122.1\ \mathrm{deg\,cm^3\,g^{-1}\,dm^{-1}}$ ($c = 0.25\ \mathrm{g\,cm^{-3}}$, $CHCl_3$) [Ref. [3] $[\alpha]_D^{22} = +99\ \mathrm{deg\,cm^3\,g^{-1}\,dm^{-1}}$ ($c = 0.44\ \mathrm{g\,cm^{-3}}$, $CHCl_3$)]. On the basis of the synthesis, the structure of itomanallene A should be revised to that shown in Scheme 5. In addition, the spectral and optical rotation data of our synthetic *ent*-**2** were in close agreement with those of the natural product except for the sign of the optical rotation.[32] It is worth mentioning that we were unable to observe nOe interactions between the protons on C4 and C6 in **3c** as well as *ent*-**2**.

In summary, the first asymmetric total synthesis, and consequent structure revision of (+)-itomanallene A, has been achieved starting from the readily available PMB-protected (*S*)-glycidol **11**. Our substrate-controlled synthesis provides a versatile strategy for the synthesis of both α,α′-*cis*- and α,α′-*trans*-tetrahydrofurans in such dioxabicylic marine natural products and related structures through the judicious choice of an amide enolate versus nitrile anion, respectively, for the intramolecular alkylation. Problems with an inefficient ring-closing metathesis reaction were overcome by modifying the synthetic route to incorporate the tetrahydrofuran ring earlier and benefit from its conformational bias. An asymmetric synthesis of *ent*-neolaurallene has also been achieved.

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[31] The α,α′-*trans*-THF-aldehyde **4′** was identical to that produced by epimerization of α,α′-*cis*-THF-aldehyde **4** by treatment with base [KOH, THF/MeOH/H_2O (3:2:1), 78%, *cis*/*trans* = 1:1].
[32] In addition, the major (*S*)-propargylic alcohol derived from **4′** could be converted cleanly into the corresponding *R* isomer by a Mitsunobu inversion–saponification sequence for the synthesis of *ent*-neolaurallene: O. Mitsunobu, M. Yamada, *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380 – 2382; see the Supporting Information.

