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Concise Substrate-Controlled Asymmetric Total Syntheses of Dioxabicyclic Marine Natural Products with 2,10-Dioxabicyclo-[7.3.0]dodecene and 2,9-Dioxabicyclo[6.3.0]undecene Skeletons

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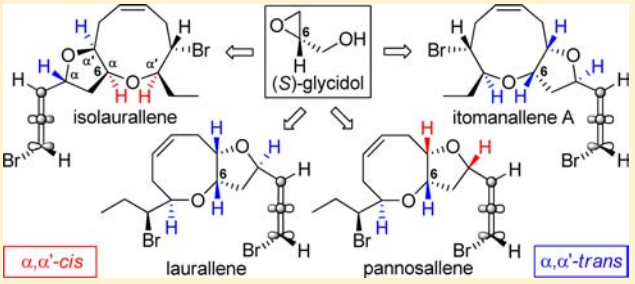
Supporting Information

ABSTRACT: We report a completely substrate-controlled approach to the asymmetric total synthesis of representative dioxabicyclic bromoallene marine natural products with either a 2,10-dioxabicyclo[7.3.0]dodecene or 2,9-dioxabicyclo[6.3.0]-undecene skeleton from commercially available glycidol as a common starting material. The former include (−)-isolaurallene (**1**), the enantiomeric form of natural (+)-neolaurallene (**2**), and (+)-itomanallene A (**3c**), and the latter are (+)-laurallene (**4**) and (+)-pannosallene (**5a**). In addition, our first syntheses of **3c** and **5a** established the structure and absolute stereochemistry of both natural products. Our general approach to establish the α,α'-relative stereochemistry of the medium-ring (oxonene or oxocene) and tetrahydrofuran, respectively, involved the judicious pairing of our protecting-group-dependent intermolecular amide enolate alkylation (either chemoselective chelation-controlled or dianion alkylation) with either our intramolecular amide enolate or nitrile anion alkylation. Remarkable selectivity was achieved through the use of the appropriate alkylation steps, and this approach offered us optional access to any of these dioxabicyclic bromoallene marine natural products. In addition, a computational analysis was performed to investigate conformational effects on the rate of oxonene formation via RCM, a key step in these approaches. The results suggested an alternative rationale for reactivity based on the avoidance of eclipsing torstional interactions in the **AS2**-type ring conformation.



INTRODUCTION

Species of the red algal genus *Laurencia* (Rhodomelaceae, Ceramiales) have been a prolific source of halogenated C_{15} acetogenins based on diverse skeletons such as 2,10-dioxabicyclo[7.3.0]dodecene and 2,9-dioxabicyclo[6.3.0]-undecene.[1] Since Kurata and co-workers first reported the isolation of isolaurallene (**1**) from the red alga *L. nipponica* in 1982,[2] new C_{15} acetogenins with the 2,10-dioxabicyclo[7.3.0]-dodecene skeleton have been isolated (Figure 1). Examples include (+)-neolaurallene (**2**), which was isolated by Kurosawa and co-workers from *L. okamurai* in 1984,[3] and (+)-itomanallene A that was subsequently isolated by the Suzuki group from *L. intricata* 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] Unlike isolaurallene and neolaurallene, itomanallene A was initially presumed to possess an α,α'-*cis*-tetrahydrofuran moiety. The relative stereochemistry of the bicyclic skeleton in itomanallene A was established by extensive spectroscopic studies.[4] Judging from the strongly positive rotation of itomanallene A $\{[\alpha]^{22}_{D}$ +99 (*c* 0.44, $CHCl_3)\}$, 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.

On the other hand, (+)-laurallene (**4**) and (+)-pannosallene (**5**) are representative members of the *Laurencia* C_{15} acetogenins with a 2,9-dioxabicyclo[6.3.0]undecene skeleton (Figure 1). (+)-Laurallene (**4**) was isolated from *L. nipponica* by Fukuzawa and Kurosawa in 1979,[6] and Suzuki and co-workers isolated **5** from *L. pannosa* in 1996.[7] The structure of **4** was determined from its physical and chemical properties.[6] The relative stereochemistry of the pannosallene bicyclic skeleton was defined by NOESY correlations, including the α,α'-*cis* relative stereochemistry in the tetrahydrofuran ring. The stereochemistry of the bromine on the C(12) side-chain was deduced from biosynthetic considerations.[7] Furthermore, as above,[5] the strongly positive optical rotation $\{[\alpha]^{26}_{D}$ +64.3 (*c* 0.070, $CHCl_3)\}$ led to the bromoallene moiety in pannosallene being assigned as *S*. However, because the relative stereochemistry of C(3) and C(4) was yet undetermined, **5a** and **5b** were proposed as potential structures for (+)-pannosallene.

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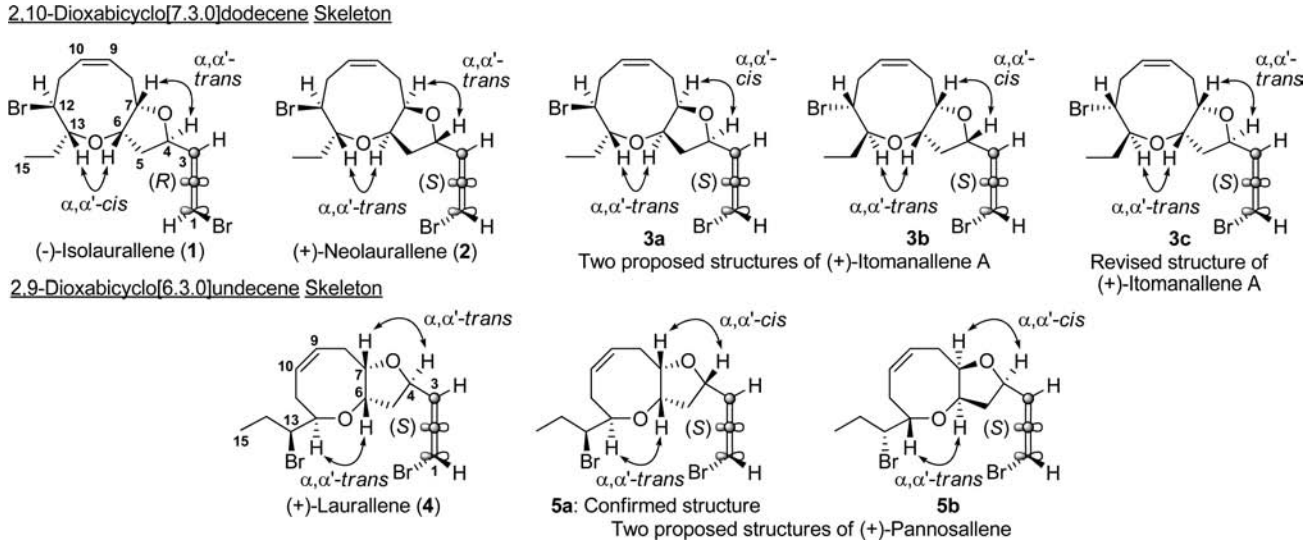
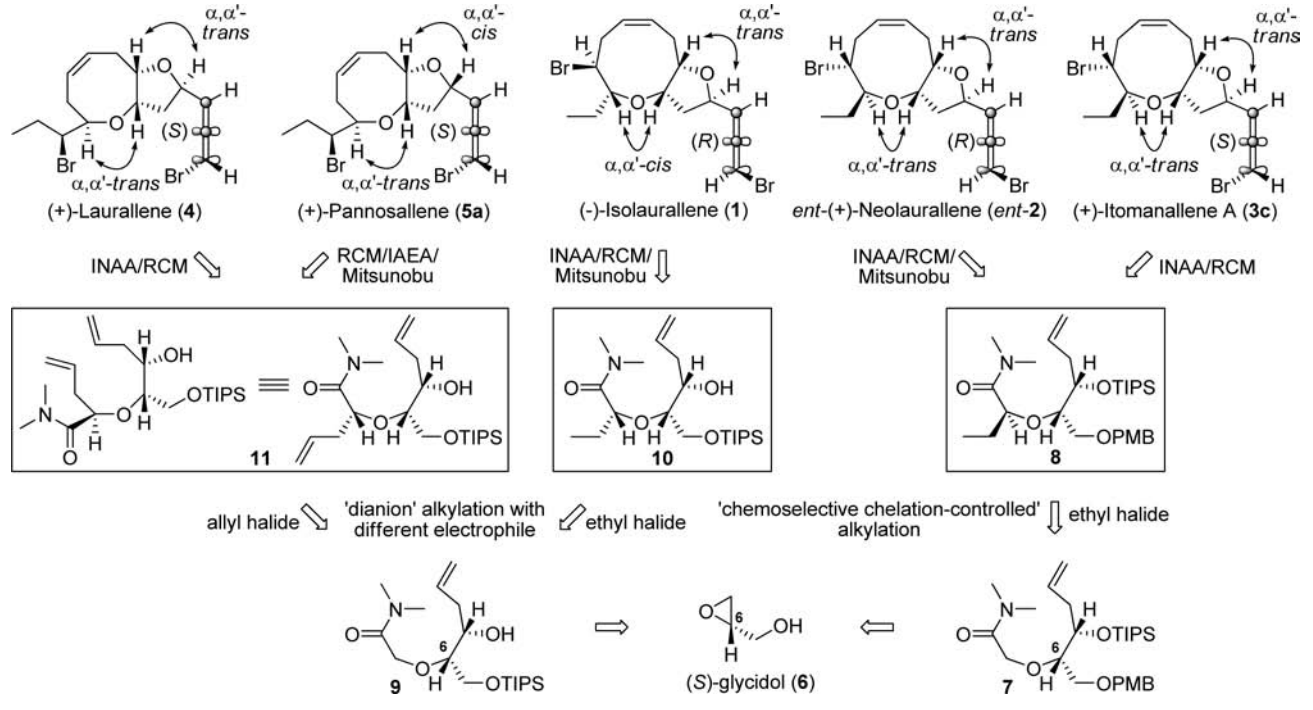


Figure 1. Representative dioxabicyclic bromoallene marine natural products with 2,10-dioxabicyclo[7.3.0]dodecene and 2,9-dioxabicyclo[6.3.0]-undecene skeletons.

Scheme 1. General Synthetic Strategy



Owing to their exquisite structures, these medium-ring dioxabicyclic bromoallene marine natural products have received considerable attention from synthetic chemists. Among the marine natural products with a 2,10-dioxabicyclo[7.3.0]dodecene skeleton, only isolaurallene with an *α,α′-cis*-oxonene skeleton had yielded to total synthesis prior to our work, wherein the Crimmins group exploited dual synergistic gauche effects to guide the course of their nine-membered ether ring-closing metathesis.[8] We recently disclosed the first asymmetric total synthesis of (+)-itomanallene A,[9] in which the structure of this compound was revised to **3c** with an *α,α′-trans*-tetrahydrofuran instead of the initially presumed *α,α′-cis*. In addition, we have also achieved an asymmetric synthesis of *ent*-neolaurallene (*ent*-**2**). Likewise, synthetic efforts toward marine natural products with a 2,9-dioxabicyclo[6.3.0]undecene skeleton have culminated in several total and formal syntheses of laurallene (**4**).[10] However, (+)-pannosallene has not been synthesized to date.

This article gives a detailed account of our completely substrate-controlled approach to these medium-ring bromoallene marine natural products using the commercially available glycidol as a common starting material. This sequence features our protecting-group-dependent intermolecular amide enolate alkylation and either our intramolecular amide enolate (IAEA) or nitrile anion alkylation (INAA) to establish both sets of relative *α,α′*-oxymethine configurations in the natural products. Application of this approach offers optional access to any of these dioxabicyclic bromoallene marine natural products.

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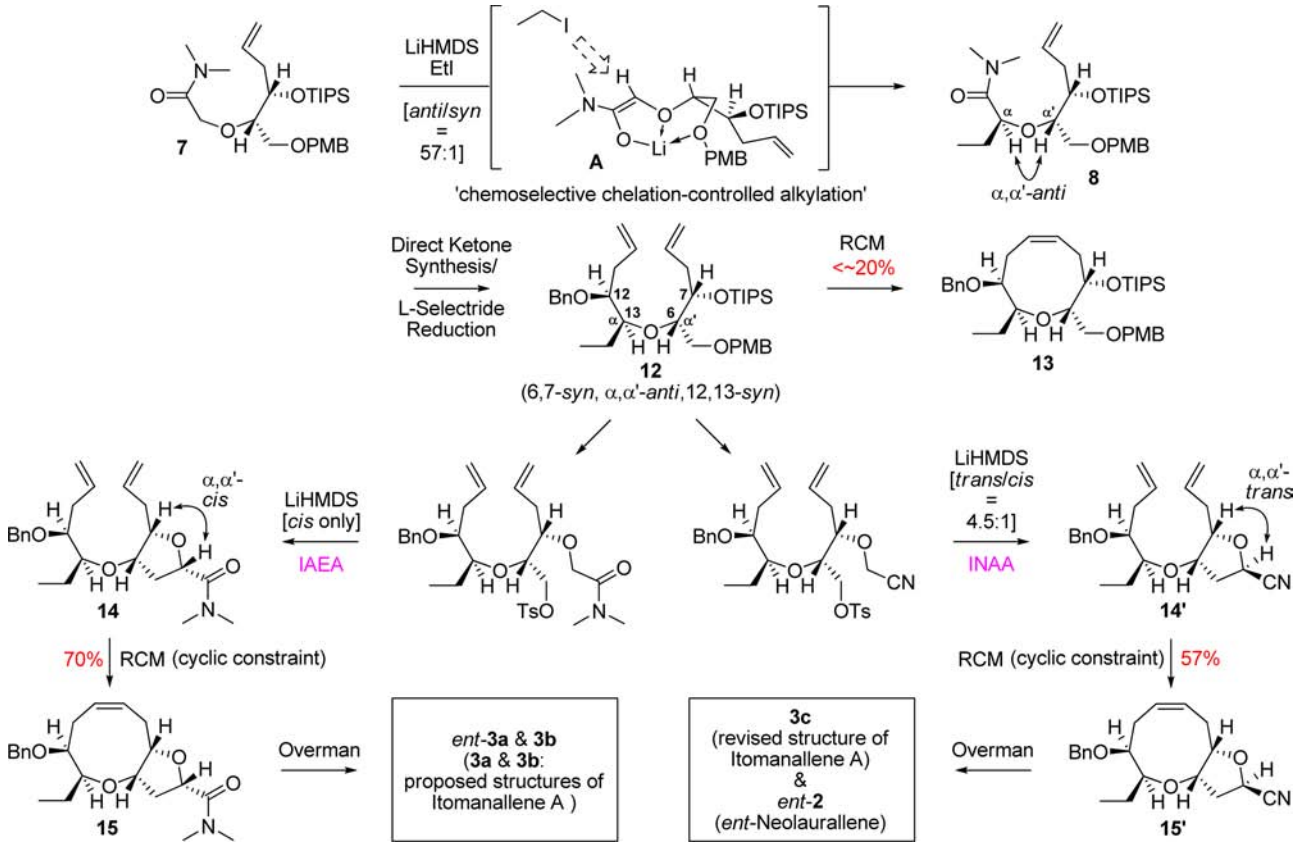
Scheme 2. Synthesis and Structure Revision of Itomanallene A, and Synthesis of *ent*-Neolaurallene



RESULTS AND DISCUSSION

As shown in Scheme 1, our general synthetic strategy was designed to encompass any arbitrary relative α,α'-oxymethine configurations in any of these dioxabicyclic bromoallene marine natural products without recourse to the use of any chiral auxiliary. Our entirely substrate-controlled sequence employs the commercially available glycidol (**6**) (or its enantiomer) as a common starting material. Our general approach to establish the α,α'-relative stereochemistry of the medium-ring (oxonene or oxocene) and tetrahydrofuran, respectively, involved the judicious pairing of our protecting-group-dependent intermolecular amide enolate alkylation (either chemoselective chelation-controlled or dianion alkylation) with either our intramolecular amide enolate or nitrile anion alkylation. Application of this approach would offer us optional access to any of these dioxabicyclic bromoallene marine natural products. In addition to our approach for installing the proper relative stereochemistry, our plan takes advantage of the versatility of the α-alkoxy *N*,*N*-dimethylamide functionality. Addition of organometallics such as Grignard or alkyllithium reagents to the α-alkoxydimethylamide gave the corresponding ketone directly in a highly reliable manner. The L-selectride reduction of this type of ketone is known to proceed in a highly stereoselective fashion, as rationalized by a Felkin−Ahn model. In addition, the dimethyl amide could be converted to the corresponding aldehyde or primary alcohol by addition of an ate complex or superhydride, respectively. The requisite bromoallene could be elaborated via the stereoselective Overman protocol, which would be applied to either a propargylic alcohol or its diastereomer obtained via a Mitsunobu inversion.

More specifically, our "chemoselective chelation-controlled" intermolecular amide enolate alkylation [**7** → **8**] and intramolecular nitrile anion alkylation were utilized to establish the α,α'-*trans*-oxonene and α,α'-*trans*-tetrahydrofuran stereochemistry in itomanallene A and *ent*-neolaurallene, respectively. On the other hand, the intermolecular dianion alkylation strategy [**9** → **10**] and intramolecular nitrile anion alkylation provided access to the respective α,α'-*cis*-oxonene skeleton and α,α'-*trans*-tetrahydrofuran for the synthesis of isolaurallene. In addition, the use of an allyl halide electrophile in place of ethyl halide for the intermolecular dianion alkylation [**9** → **11**] enabled us to construct the α,α'-*trans*-oxocene skeleton in laurallene and pannosallene. The α,α'-*trans*- and α,α'-*cis*-tetrahydrofuran stereochemistry in laurallene and pannosallene were established through INAA and IAEA, respectively.

Asymmetric Total Synthesis and Structure Revision of Itomanallene A, and Synthesis of *ent*-Neolaurallene. Scheme 2 presents a summary of our recently published[9] synthesis and structure revision of (+)-itomanallene A and synthesis of *ent*-neolaurallene, with particular emphasis on the most salient stereo-, regio-, and chemoselective steps. The critical α,α'-anti stereochemistry in α-alkoxyamide **8** was successfully addressed via the chemoselective chelation-controlled intermolecular amide enolate alkylation of **7** with ethyl iodide, probably via attack on the convex face of the cup-shaped chelated enolate intermediate **A**.[9,11] Here, 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. The inefficiency in the ring-closure metathesis reaction of the C(6)/C(7)-*syn*, α,α'-*anti*, C(12)/C(13)-*syn* bis-alkene **12**, which produced the

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corresponding oxonene **13** in less than 20% yield, was overcome by modifying the synthetic route to incorporate the tetrahydrofuran ring earlier on to benefit from the associated conformational bias. Gratifyingly, tetrahydrofuranyl dienes **14** and **14′** underwent ring-closing metathesis with Grubbs' second generation catalyst to produce key bicyclic oxonenes **15** and **15′**, respectively, in reasonably good yield; this selectivity is rationalized on the basis of computational studies described below. Most importantly, the first asymmetric total synthesis and consequent structure revision of (+)-itomanallene A provides a versatile strategy for the synthesis of both *α,α′-cis*- and *α,α′-trans*-tetrahydrofurans in such dioxabicyclic marine natural products and related structures through the judicious choice between an amide enolate and nitrile anion, respectively, for the intramolecular alkylation. A rationale for the stereoselectivity observed during the INAA is provided in our synthesis of isolaurallene (vide infra).

Computational Studies on Oxonene Formation via RCM. 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 ring-closing metathesis to give oxonenes.[8,9,12] To gain insight into these conformational effects, we embarked on computational studies on RCM of the eight possible diastereomers of **12**.[13]

We located low-lying conformations of (*Z*)-2,3,4,7,8,9-hexahydrooxonin with a 10 000 step Monte Carlo conformational search and MMFF force-field; all conformers within 5 kcal/mol of the global minimum were then reoptimized at the wB97XD/6-31G(d) level of DFT (Figure 2). Following on the work of Favini and Furusaki,[14] conformers are classified as either asymmetric, boat−chair, or chair−chair. The relative conformer stabilities show good agreement across both levels of theory studied.

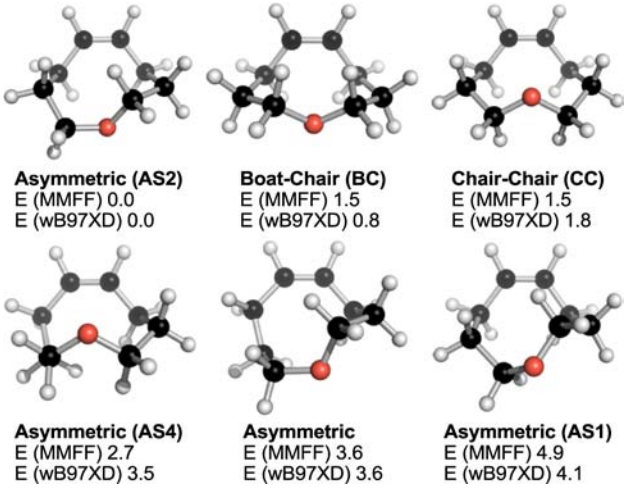

Figure 2. Lowest energy conformations for (*Z*)-2,3,4,7,8,9-hexahydrooxonin. Energetics with MMFF and wB97XD/6-31G(d) optimizations in kilocalories per mole.

Stabilities of open chain (i.e., with terminal alkenes) and ring-closed forms (following RCM) of the eight possible diastereomers of **12** (modeling protecting groups as Me groups) were calculated in an attempt to gauge the effect of stereochemistry on the energetics of RCM. The mechanism of ring closure involves Ru-alkylidene and metallocycle intermediates and transition states, but the quantum-chemical calculations required to study these species for such flexible systems are computationally intractable. Thus, we focused instead on the relative stabilities of diastereomeric reactants and cyclized products to give values for $\Delta\Delta E_{rxn}$: this enables us to rank the systems in terms of thermodynamic favorability. This energetic driving force provides quantitative insight into reactivity.

A 10 000 step Monte Carlo conformational search was performed, and energies were evaluated separately with MMFF and OPLSAA force fields, as shown in Figure 3. Open chain reactant energies all lie within 0.5 kcal/mol of each other, since the reactants are flexible and may adopt a number of conformations. Following RCM, the cyclized product stability, however, is more variable, and it is this energy that dictates $\Delta\Delta E_{rxn}$. With the exception of **I**, all the systems (i.e., **II**−**VIII**) show a preference for the asymmetric **AS2** conformation. Values of $\Delta\Delta E_{rxn}$ are shown relative to **II**, which is predicted to have the most favorable $\Delta\Delta E_{rxn}$. Diastereomer **VII**, which corresponds to the stereochemistry of **12**, has less favorable reaction energy in comparison with other diasteromers, and this analysis is consistent with the fact that the attempted RCM on **12** proceeded in <20% yield. However, we also modeled the furanyl-containing **14′** (which has the same stereochemistry as **12**) in which the alkoxy side chains are tethered together. This tethered form is computed to cyclize with a more favorable reaction energy by 3−4 kcal/mol than is the case for **12**. This is in agreement with experiment where RCM of **14** and **14′** proceeded in 70% and 57% yield, respectively, after tethering the side chain.

In the **AS2** conformation preferentially adopted by the ring, one of the dihedral angles is partially eclipsing, as shown in Figure 3. In nearly all of these, a *β*-alkoxy group points away from the ring, presumably to avoid destabilization from an eclipsing CCCO interaction. In the one diastereomer that this is not possible, *α,α′-cis*-disubstituted **I**, the ring adopts a less stable boat−chair conformation to avoid this clash. In *α,α′-trans*-disubstituted **VII**, the eclipsing CCCO interaction is present and results in the destabilization of this structure and retardation of ring closure. It is notable that the most stable diastereomers do not benefit from the double gauche C−O alignment. In fact, these bonds are *trans*-aligned in the most stable diastereomer **II**, so that evidently torsional strain in these cyclic systems overrides stereoelectronic effects. Synthetic intermediates with a stereochemistry corresponding to that of diastereomer **IV** have been observed experimentally to undergo RCM with good yields.[8] This has previously been attributed to a reinforcing double gauche effect. The reaction energy is computed to be the second most favorable, however, and this is predominantly due to the minimization of torisonal strain, as discussed previously, while benefitting from a single gauche effect. In fact, although diastereomer **II** does not benefit from any gauche C−O interactions, it was computed to be the most stable ring-closed product. We have synthesized **19′**, with the same stereochemistry as in model **II** and found that it readily underwent RCM [$(Cy_3P)_2Cl_2Ru$=CHPh, CH_2Cl_2, reflux, 6.5 h, 80%; unoptimized]. More importantly, diene **19′** reacted faster than **19** (corresponding to **IV**) in a parallel RCM experiment [$(Cy_3P)_2Cl_2Ru$=CHPh (10 mol %), CH_2Cl_2 (0.003 M), reflux, 1.5 h: product/starting material = 2.7:1, 73% conversion for **19′** by 600 MHz ^{1}H NMR; product/starting material =1:1.1, 48% conversion for **19**]. This experimental result thus supports our computational prediction of greater stability of diastereomer **II** and our new rationalization of reactivity based on the

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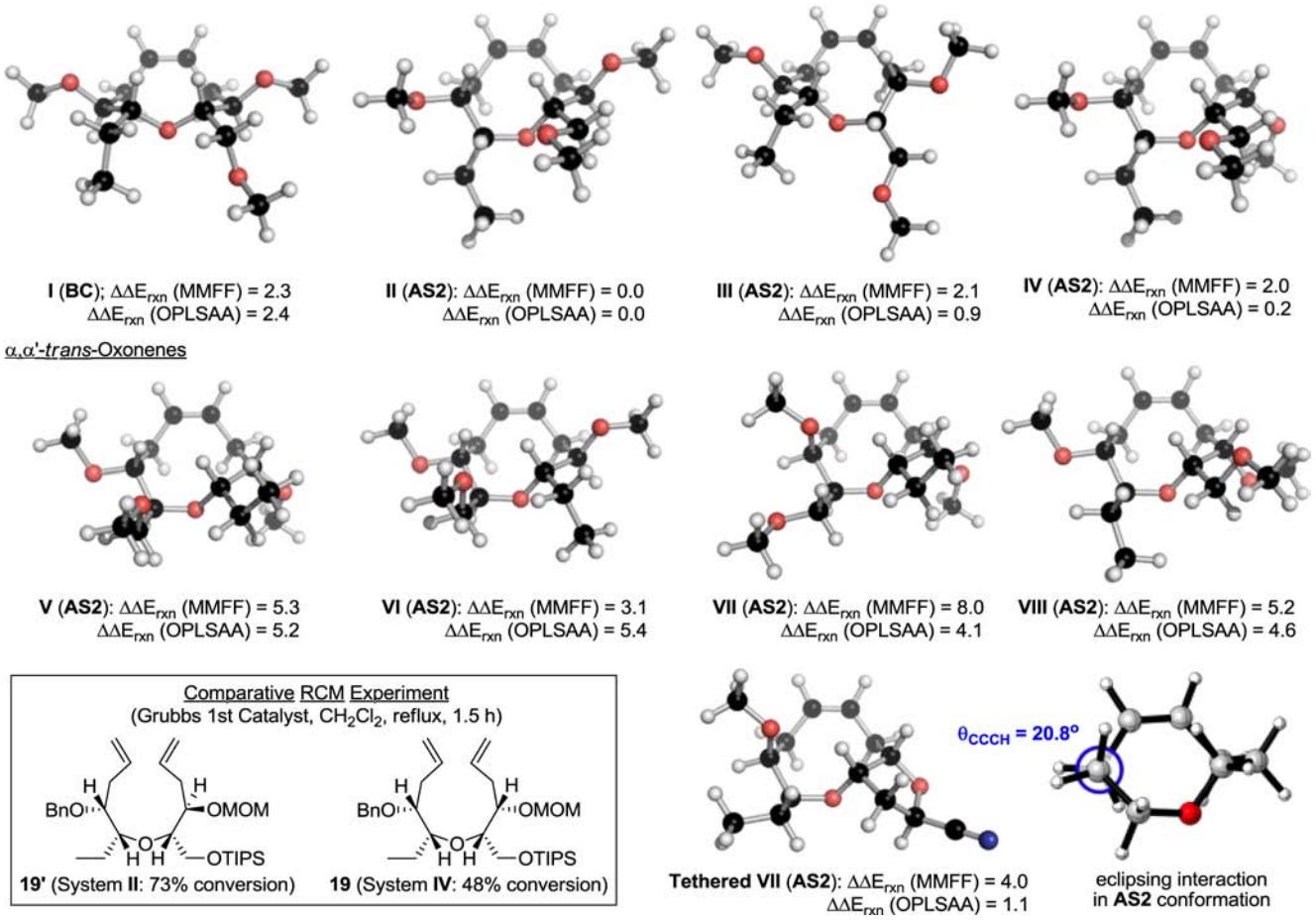


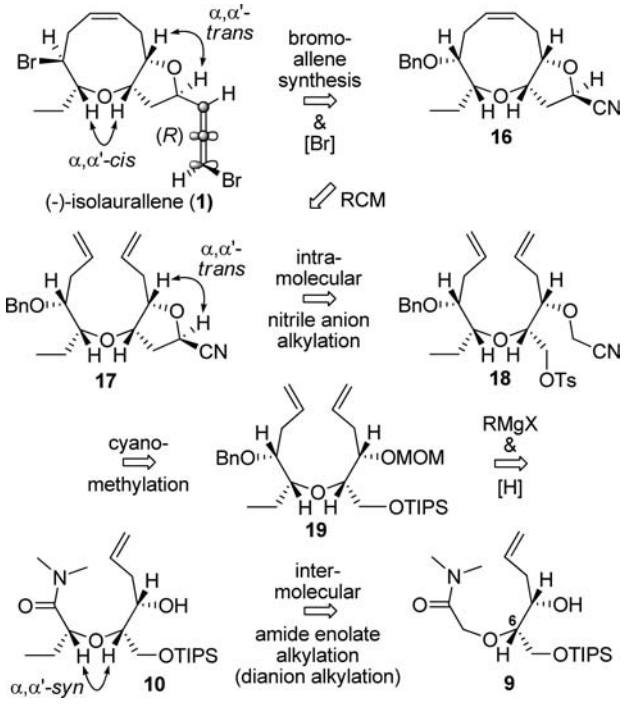
Figure 3. Global minimum energy conformations for the eight possible diastereomers (plus ring-tethered form of diastereomer XII) following RCM. MMFF and OPLSAA energies in kilocalories per mole.

minimization of torsional strain in the preferred **AS2** ring conformation.

Asymmetric Total Synthesis of (−)-Isolaurallene (1). As shown in our retrosynthetic plan (Scheme 3), we envisioned that isolaurallene (**1**) could be synthesized from key bicyclic nitrile **16** through installation of the requisite bromoallene unit. Unlike its congeners **2** and **3c**, **1** possesses an *α,α′-cis*-disubstituted oxonene skeleton. Our previous experiences led to initial confidence that the critical *α,α′-cis*-oxonene stereochemistry could be established by applying our dianion alkylation protocol to hydroxy *N,N*-dimethyl amides with any protected hydroxymethyl group at C(6), such as in **9** (vide infra).[15] The other crucial stereochemical problem, preparation of the *α,α′-trans*-tetrahydrofuran **17**, was to be solved by an intramolecular nitrile anion alkylation of tosyl nitrile **18**. This tactic was based on the insights acquired during our itomanallene A synthesis, which drew inspiration from the pioneering work by Stork and co-workers[16] and subsequent investigations by Fleming et al.[17] Notably, the MOM group in **19** serves a dual function as a protecting group and as a highly efficient precursor for cyanomethylation to prepare the INAA substrate.

This sequence began with the preparation of key intermolecular dianion alkylation substrate **9** from known TIPS-protected (*S*)-glycidol (**20**)[18] by the four-step sequence shown in Scheme 4. In this scheme, we were concerned that the TIPS group, which is essential for high stereoselectivity in the planned intermolecular dianion alkylation (vide infra), might

Scheme 3. Retrosynthetic Plan for (−)-Isolaurallene



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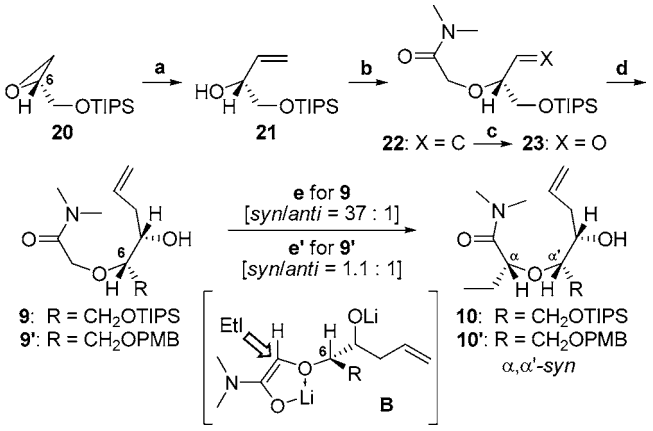
Scheme 4. Intermolecular Dianion Alkylation[a]



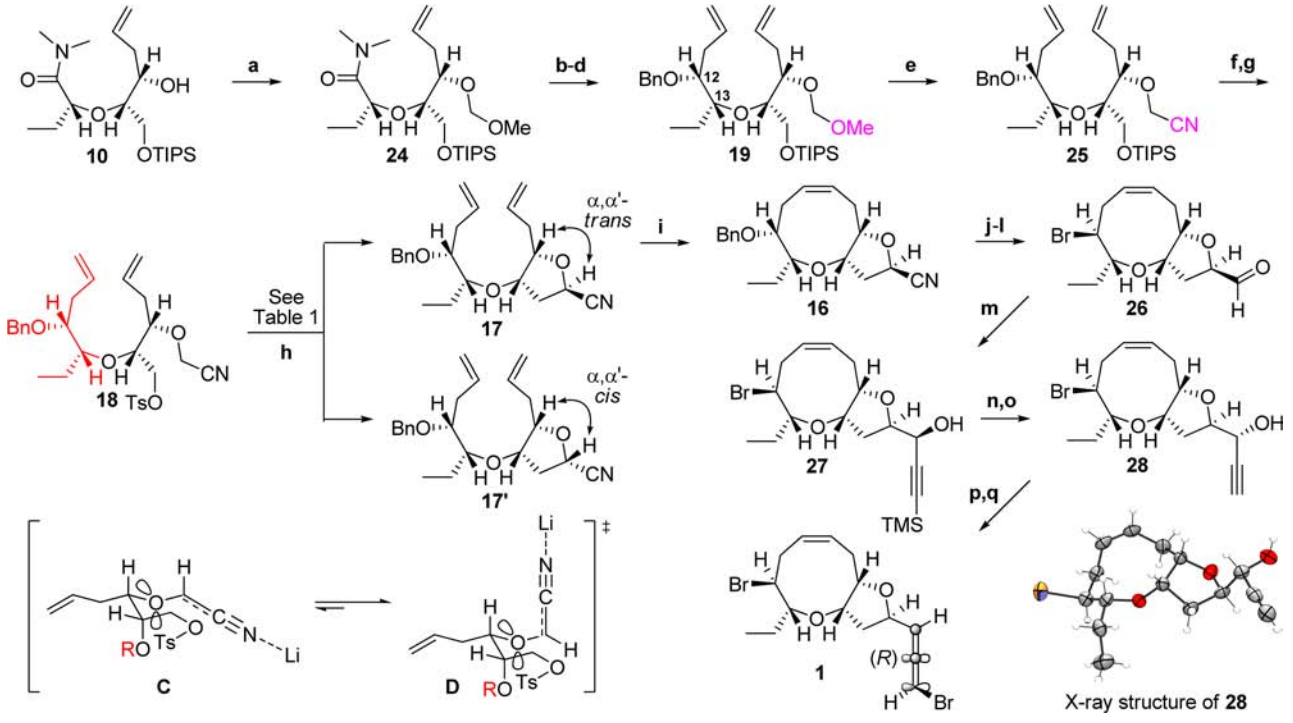
[a]Reagents and conditions: (a) $(CH_3)_3SI$, *n*-BuLi, THF, −10 °C to rt, 2 h, 95%; (b) NaH, ICH_2CONMe_2, CH_2Cl_2, rt, 40 min, 96%; (c) OsO_4, NMO, H_2O/acetone (2:1), rt, 3 h, then $NaIO_4$, rt, 30 min; (d) allyltributyltin, $MgBr_2{\cdot}Et_2O$, CH_2Cl_2, −78 °C to rt, 3 h, 77% total yield for two steps, syn/anti = 7:1; (e) LiHMDS, ethyl iodide, THF, −40 °C, 30 min, 91% total yield, syn/anti = 37:1; (e′) LiHMDS, ethyl iodide, THF, −40 °C, 2 h, 54% total yield, syn/anti = 1.1:1.

migrate at some stage of the synthesis. In the event, TIPS-(*S*)-glycidol (**20**) was converted to allylic alcohol **21** in excellent yield (95%) by methylenation of the epoxide according to the Falck−Mioskowski protocol.[19] Our initial concerns regarding silyl group migration were borne out in the Williamson ether synthesis [**21** → **22**] under the usual conditions (NaH, *N*,*N*-dimethyl chloro- or bromoacetamide, THF or DMF) because the desired product was accompanied by an inseparable TIPS-migrated alkylation product (ca. 15−20%). After some experimentation, we were pleased to find that O-alkylation of allylic alcohol **21** could be accomplished without migration of the TIPS group by treatment with NaH and *N*,*N*-dimethyl iodoacetamide in CH_2Cl_2 to produce the desired α-alkoxyamide **22** in nearly quantitative yield (96%). One-pot cleavage of alkene **22** by a modified Lemieux−Johnson oxidation,[20] followed by Keck allylation[21] of the resultant α-alkoxyaldehyde **23**, gave the desired *syn*-homoallylic alcohol **9** (77% yield for the two steps, syn/anti = 7:1) and set the stage for the pivotal dianion alkylation.

Dianion alkylation of hydroxy α-alkoxy amides with various substituents {R = CH_2CH_3, CH_2CH_2OBn, $CH_2CH_2CH_2OBn$, or $CH_2CH(OCH_2CH_2O)$} at C(6) in intermediate **9** offers serviceable syn/anti stereoselectivity (ca. 6−9 to 1), and has been utilized as a key step for our substrate-controlled total synthesis of medium-ring oxacyclic natural products.[15a,c] The observed stereoselectivity could be rationalized by invoking our empirical model **B** with the electrophile approaching from the least hindered side in the H,H-eclipsed conformation, as depicted in the scheme.

However, dianion alkylation of **9′** (R = CH_2OPMB), an intermediate for our synthesis of (+)-itomanallene A,[9] gave very disappointing stereoselectivity (syn/anti = 1.1:1) and chemical

Scheme 5. Cyanomethylation, INAA, and Completion of the Synthesis[a]



[a]Reagents and conditions: (a) MOMCl, *N*,*N*-diisopropylethylamine, CH_2Cl_2, 0 °C to rt, 5 h, 98%; (b) $CH_2{=}CHCH_2MgCl$, THF, −78 °C, 30 min; (c) L-Selectride, THF, −78 °C, 2 h, 80% total yield for two steps, syn/anti = 7:1; (d) NaH, BnBr, DMF, 0 °C to rt, 2 h, 95%; (e) Me_2BBr, *n*-Bu_4NCN, CH_2Cl_2, −78 °C, 20 min, 88%; (f) TBAF, THF, rt, 30 min, 98%; (g) TsCl, DMAP, Et_3N, CH_2Cl_2, 0 °C to rt, 3 h, 97%; (h) see Table 1; (i) $(H_2IMes)(Cy_3P)Cl_2Ru{=}CHPh$, CH_2Cl_2, reflux, 2 h, then DMSO, rt, 12 h, 96%; (j) DDQ, CH_2Cl_2/pH 7.4 buffer solution (9:1), 40 °C, 12 h, 93%; (k) CBr_4, *n*-Oct_3P, 1-methylcyclohexene, toluene, 70 °C, 7 h, 68%; (l) DIBAL-H, toluene, −78 °C, 30 min; (m) TMS−acetylene, *n*-BuLi, $ClTi(O\textit{i}\text{-}Pr)_3$, Et_2O, −78 °C to rt, 12 h, 76% total yield for two steps, *S*/*R* = 7.4:1; (n) *p*-bromobenzoic acid, PPh_3, DIAD, THF, 0 °C to rt, 2 h, 79%; (o) K_2CO_3, MeOH, rt, 20 min, 98%; (p) TrisCl, DMAP, CH_2Cl_2, reflux, 1 h, 98%; (q) $LiCuBr_2$, THF, reflux, 19 h, 71% total yield, *R*/*S* = 5.6:1.

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yield (54%). Although the use of **9′** in this sequence would simplify our general approach to these targets, the virtual absence of stereoselectivity forced us to employ an alternative protecting group at the C(6) hydroxymethyl group, even though this required an earlier divergence in our overall scheme. We reasoned that use of the corresponding TIPS-protected alkoxy group might avoid any potential interference by the PMB-alkoxy group in **9′** due to chelation, since TIPS ethers are known to be poor coordinating groups. We were delighted to find that the application of our protocol to TIPS-protected hydroxy α-alkoxy amide **9** (R = CH_2OTIPS) proved successful, and treatment with LiHMDS in the presence of ethyl iodide furnished the desired α,α′-*syn*-hydroxyamide **10** with excellent stereoselectivity (91% total yield; syn/anti = 37:1). We are still developing a rationale to explain this relatively high degree of stereoselectivity.

With the critical α,α′-syn stereochemistry installed, attention turned to the preparation of key INAA substrate **18** for the construction of the desired α,α′-*trans*-tetrahydrofuranyl nitrile **17**, as outlined in Scheme 5. MOM protection of **10** (98%), followed by elaboration of the α-alkoxydimethylamide moiety in the resultant **24** via our direct ketone synthesis/L-Selectride reduction sequence,[22] furnished diene **19** with the desired C(12)/C(13)-*syn* relative stereochemistry in 67% overall yield for the three steps after benzylation. The chemoselective cyanomethylation of MOM ether **19** was readily accomplished in good yield (88%) upon exposure to *n*-Bu_4NCN in the presence of Me_2BBr according to Morton and Guindon,[23] which made gram quantities of cyanomethyl ether **25** available with relative ease. With an efficient cyanomethylation protocol established, removal of the TIPS group and tosylation led to key INAA substrate **18**, setting the stage for the intramolecular nitrile anion alkylation.

Many of the extant applications of this intramolecular nitrile anion alkylation methodology have involved the stereoselective construction of a quaternary center by taking advantage of the relatively small size and powerful nucleophilicity of the nitrile function.[16,17] The presence of an acidic proton in α-unsubstituted cases, such as the present one, raises a concern regarding a potential loss of stereochemical integrity of the cyclization.

Given the relevance to defining a broader scope for this methodology, we investigated the stereochemical effects in the intramolecular nitrile anion alkylation of **18** by varying the solvent, base, leaving group, and temperature. Ideally, we sought to identify parallel routes to obtain either the α,α′-*trans* or α,α′-*cis* isomer, analogous to what has been demonstrated by Stork and co-workers.[16] Unfortunately, our system did not prove amenable to this sort of dramatic stereochemical dichotomy based on reaction conditions. However, we were able to secure the desired α,α′-*trans*-tetrahydrofuran **17** as the major isomer upon exposure of nitrile tosylate **18** to LiHMDS. As is evident from Table 1, the lower the polarity of the solvent, from tetrahydrofuran through diethyl ether to toluene, the slower the reaction proceeded. The best conditions for optimal yield, stereoselectivity, and procedural ease were 40 min at −30 °C in ether. An equilibration experiment to probe the relative stability of the isomers showed that the α,α′-*trans* isomer is more stable than the corresponding *cis* by a 2 to 1 margin, which is in good agreement with the computed energy difference (0.4 kcal/mol) between these isomers.[13] Furthermore, from a deuterium incorporation study as well as resubjection of the isolated isomers separately to the reaction conditions, we were able to establish that this 5.8:1 selectivity ratio (entry 5) arises from a kinetically controlled process under the cyclization conditions. The internal alkylation of the linear, N-metalated nitrile anion generated under the reaction conditions furnishes the desired α,α′-*trans*-tetrahydrofuran as the major product.[17] We reason that the intermediate passes through transition state geometry **D** (Scheme 5), which benefits from stereoelectronic stabilization by placing the C−CN bond anti-periplanar to the oxygen lone pair on the ether oxygen.[24,25b] To the best of our knowledge, the examples that appear in the present study constitute the first construction of a tetrahydrofuran via an intramolecular α-alkoxynitrile alkylation.[25] It is both highly significant and fortunate that the α-alkoxynitrile affords stereoselection that is complementary to that obtained with the corresponding α-alkoxy *N*,*N*-dimethylamide (vide infra).

Table 1. Intramolecular Nitrile Anion Alkylation

entry no.	solvent[a]	base[b]	temp[c] (°C)	time (min)	yield % (total)	ratio[d] (*trans*/*cis*)
1	THF	LiHMDS in THF	−10	5	75	2.4:1
2	THF	LiHMDS in THF	−30	13	93	3.1:1
3	THF	LiHMDS in THF	−78	40	88	4.0:1
4	Et_2O	LiHMDS in THF	−10	10	85	5.6:1
5	Et_2O	LiHMDS in THF	−30	40	83	5.8:1
6	toluene	LiHMDS in THF	−10	40	89	4.3:1
7	toluene	LiHMDS in THF	−20	75	81	4.9:1

[a]0.005 M. [b]1.0 M sol. (3 equiv). [c]Bath temp. [d]By ^1H NMR.

To complete the synthesis, tetrahydrofuranyl nitrile **17** was converted to the desired bicyclic bromoaldehyde **26** by a four-step sequence (1. ring-closing metathesis; 2. deprotection of benzyl group; 3. bromination with inversion of configuration; 4. DIBAL-H reduction of nitrile). With key bromoaldehyde **26** in hand, we turned our attention to installation of the bromoallene unit on the basis of the well-established Overman protocol.[26] Thus, addition of titanium TMS-acetylide to aldehyde **26** with Felkin−Ahn-type stereoselectivity,[26,27] followed by adjustment of the propargylic alcohol configuration of the resultant TMS-propargylic alcohols **27** via a Mitsunobu-saponification sequence,[28] led to (*R*)-propargylic alcohol **28**, the structure of which was confirmed by X-ray crystallography.[29] Finally, trisylation of (*R*)-propargylic alcohol **28**, followed by copper-catalyzed anti-S_N2' reaction of the corresponding trisylate,[26,30] gave rise to give a 5.6:1 mixture of (−)-isolaurallene (**1**) and *epi*-isolaurallene in 71% total yield. Of note here is that ring-closing metathesis of bis-alkene **17**, which has the same stereochemistry as that of **IV** in Figure 3, proceeded with the anticipated high efficiency (96%). The spectral characteristics and optical rotation of our synthetic material **1** were in good agreement with those reported for both the natural and synthetic isolaurallene: $[\alpha]^{25}_D$ −107.2 (*c* 0.38, $CHCl_3$) [natural: lit.[2] $[\alpha]_D$ −113.9 (*c* 1.00, $CHCl_3$); synthetic: lit.[8a] $[\alpha]^{24}_D$ −117.8 (*c* 0.09, $CHCl_3$)].

In summary, an asymmetric total synthesis of (−)-isolaurallene (**1**) was accomplished in 22 steps from readily available TIPS-protected (*S*)-glycidol (**20**). In our completely substrate-controlled synthesis, an intermolecular dianion alkylation or

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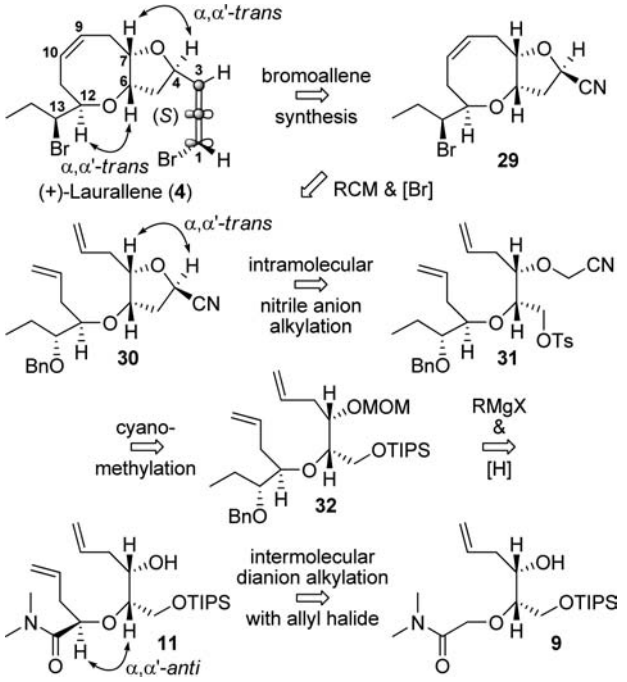
intramolecular nitrile anion alkylation sequence provided access to the α,α′-*cis*-oxonene skeleton or α,α′-*trans*-tetrahydrofuran, respectively. In addition, we have developed a highly efficient protocol where the MOM group serves a dual function, alternately as a protecting group and as a precursor for the cyanomethylation to prepare the INAA substrate.

Asymmetric Total Synthesis of (+)-Laurallene (4). (+)-Laurallene (**4**) possesses a *cis*-fused 2,9-dioxabicyclo[6.3.0]-undecene skeleton that includes an α,α′-*trans*-oxocene and α,α′-*trans*-tetrahydrofuran. As shown in Scheme 6, we

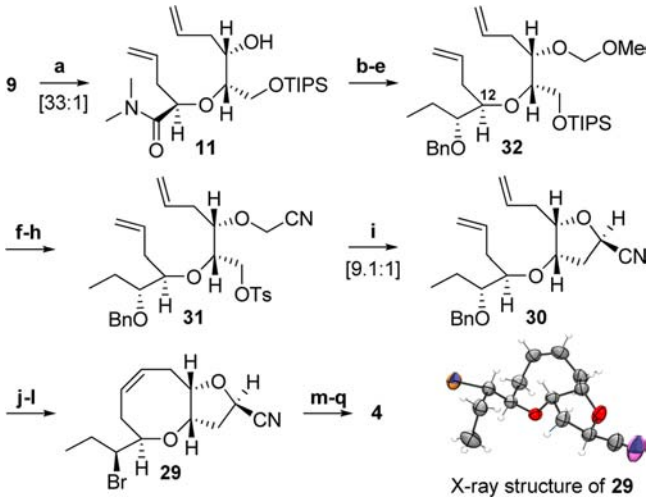
Scheme 6. Retrosynthetic Plan for (+)-Laurallene (4)



envisioned that the critical α,α′-anti stereochemistry in bis-alkene **11** could be established by an intermolecular dianion alkylation of α-alkoxyamide **9** with allyl halide in this case. By contrast, our earlier described synthesis of isolaurallene employed ethyl iodide as the electrophile in the dianion alkylation of α-alkoxyamide **9**. Our strategy is adaptable in that use of either ethyl or allyl halide as the electrophile for the dianion alkylation leads to an α,α′-*cis*-oxonene or α,α′-*trans*-oxocene product, respectively. We further envisioned that the intermolecular dianion allylation product **11** could be elaborated using a pathway parallel to the isolaurallene sequence up to key dioxabicyclic intermediate **29**.

Our synthesis began with the preparation of α,α′-*anti*-bis-alkene **11** (Scheme 7) using our dianion alkylation protocol. As anticipated, treatment of TIPS-protected α-alkoxyamide **9** with LiHMDS in the presence allyl bromide furnished the desired α,α′-*anti*-diene **11** with excellent stereoselectivity (90% total yield; anti/syn = 33:1).[31] After MOM protection of the secondary hydroxyl group in diene **11** (96%), the α-alkoxydimethylamide function in the resulting intermediate was elaborated to append the C(12) side chain without incident via a three-step sequence (direct ketone synthesis, L-Selectride reduction, benzylation) to furnish diene **32** in 87% overall yield. Conversion of MOM ether **32** to the corresponding cyanomethyl ether,[23] followed by removal of the TIPS group and subsequent tosylation, yielded the key

Scheme 7. Synthesis of (+)-Laurallene (4)[a]



[a]Reagents and conditions: (a) LiHMDS, allyl bromide, THF, −40 °C, 2 h, 90% total yield, anti/syn = 33:1; (b) MOMCl, *N*,*N*-diisopropylethylamine, CH_2Cl_2, 0 °C to rt, 3 h, 96%; (c) EtMgBr, THF, 0 °C, 1 h, 96%; (d) L-Selectride, THF, −78 °C, 1 h, 96% total yield, syn/anti = 28:1; (e) BnBr, NaH, DMF, 0 °C to rt, 5 h, 98%; (f) Me_2BBr, *n*-Bu_4NCN, CH_2Cl_2, −78 °C, 30 min; (g) TBAF, THF, rt, 20 min, 85% (2 steps); (h) TsCl, DMAP, Et_3N, CH_2Cl_2, 0 °C to rt, 2.5 h, 98%; (i) LiHMDS (1.0 M sol. in THF), Et_2O, −30 °C, 40 min, 80% total yield, *trans*/*cis* = 9.1:1; (j) $(H_2IMes)(Cy_3P)Cl_2Ru{=}CHPh$, CH_2Cl_2, reflux, 2 h, then DMSO, rt, 12 h, 84%; (k) DDQ, CH_2Cl_2/pH 7.4 buffer solution (9:1), 40 °C, 12 h, 93%; (l) CBr_4, *n*-Oct_3P, 1-methylcyclohexene, toluene, 70 °C, 2 h, 88%; (m) DIBAL-H, toluene, −78 °C, 30 min; (n) TMS−acetylene, *n*-BuLi, $ClTi(O\text{-}i\text{-}Pr)_3$, Et_2O, −78 °C to rt, 12 h, 64% total yield for two steps, *S*/*R* = 5.5:1; (o) TBAF, THF, rt, 10 min, 94%; (p) TrisCl, DMAP, CH_2Cl_2, reflux, 2.5 h, 97%; (q) $LiCuBr_2$, THF, reflux, 18 h, 76% total yield, *S*/*R* = 15:1.

INAA substrate **31** (83% over 3 steps). Tosylate **31** was subjected to INAA (LiHMDS/ether/−30 °C/40 min) to give the desired α,α′-*trans*-tetrahydrofuran **30** (80% total yield; α,α′-*trans*/*cis* = 9.1:1). Finally, α,α′-*anti*-bis-alkene **30** underwent RCM with the second-generation Grubbs' Ru catalyst, followed by debenzylation and introduction of the bromine atom at C(13) with inversion of configuration to give rise to key intermediate **29**, the structure of which was validated by X-ray crystallography.[29]

The completion of the (+)-laurallene synthesis employed a pathway analogous to that described earlier for isolaurallene (**1**) except that the step in which the propargylic alcohol configuration was adjusted was unnecessary. The spectral characteristics and optical rotation of our synthetic material **4** were in good agreement with those reported for both natural and synthetic laurallene: $[\alpha]^{26}_D$ +159.1 (*c* 0.24, $CHCl_3$) [natural: lit.[6] $[\alpha]_D$ +173.6 (*c* 1.13, $CHCl_3$); synthetic: lit.[10b] $[\alpha]^{24}_D$ +161.1 (*c* 0.28, $CHCl_3$)]. In addition, this work confirmed that the structure and absolute stereochemistry of (−)-*epi*-laurallene are identical to those of (−)-nipponallene, recently isolated from *L. nipponica*.[32]

In summary, a highly stereoselective and efficient 21-step synthesis of laurallene (**4**) has been accomplished in an entirely substrate-controlled fashion starting from the known TIPS-protected (*S*)-glycidol (**20**). Our strategy is highly adaptable in that either an α,α′-*cis*-oxonene or α,α′-*trans*-oxocene product can be accessed by employing either ethyl or allyl halide as the electrophile for the dianion alkylation, respectively.

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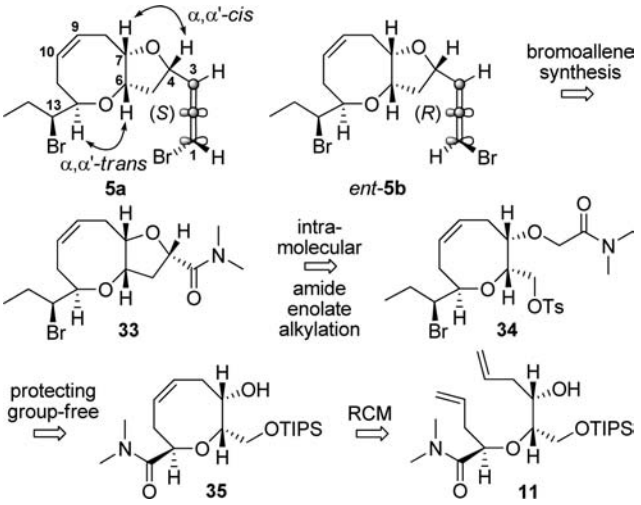
Asymmetric Total Synthesis and Structure Determination of (+)-Pannosallene. For the sake of simplicity in determining the relative stereochemistry of C(3) and C(4) in pannosallene, we set out to synthesize **5a** and *ent*-**5b** instead of the originally proposed structures **5a** and **5b** (Scheme 8), an

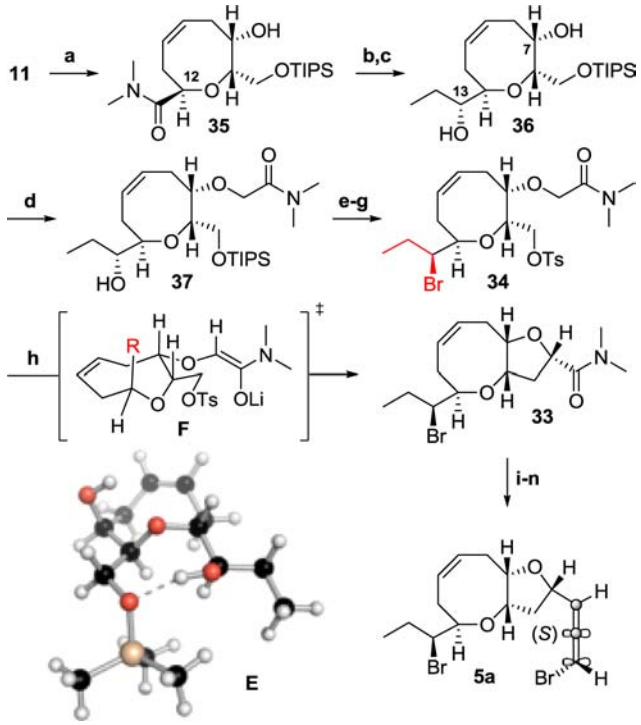
Scheme 8. Retrosynthetic Plan for 5a and *ent*-5b



arbitrary decision that turned out to be fortuitous. We were confident that the necessary *α,α′-cis*-tetrahydrofuran ring in **33** could be constructed in a stereoselective manner via IAEA on tosyl amide **34**,[9,33] which in turn could be elaborated from oxocene intermediate **35**. The eight-membered cyclic ether **35** could then be formed by RCM of bis-alkene **11**, a key common intermediate used earlier in the synthesis of laurallene (**4**). As we formulated a plan for this particular synthesis, a considerable amount of effort was directed to streamlining the sequence by minimizing the use of protecting groups, an effort that was well rewarded (vide infra).

Our synthesis began with preparation of oxocene **35** (Scheme 9), which was obtained in 75% yield via RCM of *α,α′-anti*-bis-alkene **11** with the second-generation Grubbs' Ru catalyst. The C(12) side chain appendage was elaborated as before (direct ketone synthesis/L-Selectride reduction),[22] with conversion of *α*-alkoxyamide **35** to diol **36** without protection of the C(7) hydroxyl group in a highly stereoselective fashion in 65% overall yield [73% BRSM] for the two steps. Gratifyingly, chemoselective monoalkylation at the C(7) hydroxyl group of diol **36** with *N,N*-dimethyl chloroacetamide produced an 83% yield of *α*-alkoxyamide **37** along with a small amount of the corresponding dialkylated product (8%). DFT calculations indicated that in the preferred conformation, **E**, of diol **36** (and in all other low-energy conformers), the C(13) alcohol in the side chain forms a weak interaction with the oxygen of the silyl protecting group. We posit that the C(7) hydroxyl in the ring is more exposed and, hence, is alkylated preferentially.[13] Bromination of secondary alcohol **37** with inversion of configuration, followed by removal of the TIPS group and subsequent tosylation, led to the key IAEA substrate **34** in 66% overall yield for the three steps. Treatment of tosyl amide **34** with LiHMDS in the presence of the C(13) bromide functionality gave rise to the desired *α,α′-cis*-tetrahydrofuran **33** (94% total yield; *α,α′-cis/trans* = 17:1), presumably via "H-eclipsed" transition-state geometry **F**.

Scheme 9. Protecting-Group-Free Sequence to 33 from 11 and Completion of the Synthesis[a]



[a]Reagents and conditions: (a) $(H_2IMes)(Cy_3P)Cl_2Ru{=}CHPh$, CH_2Cl_2, reflux, 12 h, then DMSO, rt, 6 h, 75%; (b) EtMgBr, THF, 0 °C to rt, 1.5 h, 70% [79% BRSM]; (c) L-Selectride, THF, −78 °C, 30 min, 93%; (d) $ClCH_2CONMe_2$, NaH, THF, 0 °C to rt, 2 h, 83%; (e) CBr_4, *n*-Oct_3P, pyridine, toluene, 60 °C, 3 h; (f) TBAF, THF, rt, 10 min, 78% for two steps; (g) TsCl, DMAP, Et_3N, CH_2Cl_2, reflux, 12 h, 84%; (h) LiHMDS, THF, −78 °C, 30 min, 94% total yield, *cis/trans* = 17:1; (i) DIBAL-H/*n*-BuLi (1/1), THF, 0 °C, 10 min, 89%; (j) TMS−acetylene, *n*-BuLi, $ClTi(O\text{-}i\text{-}Pr)_3$, Et_2O, −78 to −10 °C, 12 h, 83% total yield, *R/S* = 6.7:1; (k) *p*-bromobenzoic acid, PPh_3, DIAD, THF, rt, 1 h, 73%; (l) K_2CO_3, MeOH, rt, 30 min, 96%; (m) TrisCl, DMAP, CH_2Cl_2, reflux, 1.5 h, 92%; (n) $LiCuBr_2$, THF, reflux, 18 h, 91% total yield, *S/R* = 4:1.

A significant advantage in this approach is that the chemoselective Williamson ether synthesis of diol **36** as well as the highly efficient IAEA of bromo tosylate **34** enabled us to secure the dioxabicyclic compound **33** without additional protecting-group manipulations.

For the completion of the synthesis, the bromoallene endgame sequence was implemented as for the earlier described synthesis of isolaurallene (**1**), except that in this case, the aldehyde intermediate was derived from the dimethylamide function by reduction with the ate complex of DIBAL-H and *n*-BuLi,[34] to produce a 4:1 mixture of **5a** and *ent*-**5b** in 91% yield. The spectral and optical rotation data for our synthetic material **5a** were in good agreement with those of the natural product, which enabled us to confirm the structure and absolute configuration as depicted in **5a**: $[\alpha]^{25}_D$ +87.5 (*c* 0.20, $CHCl_3$) [natural: lit.[7] $[\alpha]^{26}_D$ +64.3 (*c* 0.070, $CHCl_3$)].[35]

In summary, this first asymmetric total synthesis and structure confirmation of (+)-pannosallene was accomplished in a substrate-controlled fashion in 19 steps from readily available TIPS-protected (*S*)-glycidol (**20**). Our concise synthesis of this C_{15} acetogenin containing the rare *α,α′-cis*-tetrahydrofuran moiety features highly stereoselective inter-

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molecular and intramolecular amide enolate alkylations as key steps to establish both sets of relative α,α'-oxymethine configurations in the natural product.

CONCLUSION

We have developed a completely substrate-controlled approach to the asymmetric total synthesis of representative dioxabicyclic bromoallene marine natural products with either a 2,10-dioxabicyclo[7.3.0]dodecene or 2,9-dioxabicyclo[6.3.0]-undecene skeleton from commercially available glycidol as a common starting material. The former include (−)-isolaurallene (**1**), the enantiomeric form of natural (+)-neolaurallene (**2**), and (+)-itomanallene A (**3c**), and the latter are (+)-laurallene (**4**) and (+)-pannosallene (**5a**). In addition, our first syntheses of (+)-itomanallene A (**3c**) and (+)-pannosallene (**5a**) have established the structure and absolute stereochemistry of both natural products. Furthermore, we report spectral data for the bromoallene diastereomers of the natural products for reference to aid in identification when they are isolated from natural sources in the future.

In addition, a computational analysis was performed to investigate conformational effects on the rate of oxonene formation via RCM, a key step in these approaches. The results suggested an alternative rationale for reactivity based on the avoidance of eclipsing torstional interactions in the **AS2**-type ring conformation. A prediction was made of the most reactive diastereomer, and this was subsequently verified experimentally.

We identify several useful contributions of this work that should be of keen interest in the field of organic synthesis. Our general approach to establish the α,α'-relative stereochemistry of the medium ring (oxonene or oxocene) and tetrahydrofuran, respectively, involved the judicious pairing of our protecting-group-dependent intermolecular amide enolate alkylation (either chemoselective chelation-controlled or dianion alkylation) with either our intramolecular amide enolate or nitrile anion alkylation. Remarkable selectivity was achieved through the use of the appropriate alkylation steps, and this approach offered us optional access to any of these dioxabicyclic bromoallene marine natural products. We note that our "protecting-group-dependent" alkylation−RCM strategy for medium ring construction is related to the Crimmins asymmetric alkylation−RCM strategy,[8,10b,12] but in our case is executed with complete substrate-based control. These syntheses feature a number of stereo-, regio-, and chemoselective transformations that enabled us to achieve concise and efficient syntheses, routes that are competitive with or surpass existing approaches in terms of brevity and selectivity.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures; spectroscopic and analytical data for all new compound including copies of NMR spectra; X-ray crystallographic data; computational details; full reference 13. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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