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Enantioselective Total Synthesis of Isoedunol and β-Araneosene Featuring Unconventional Strategy and Methodology

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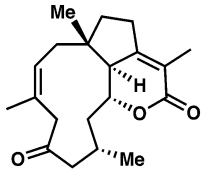
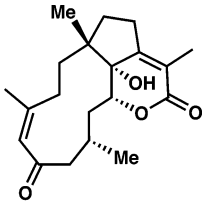
Three decades ago, Borschberg reported the discovery of β-araneosene (**1**, Scheme 1), a new metabolite of the terrestrial mold *Sordaria araneosa*.[1,2] The same skeleton was later termed "dolabellane" by Faulkner, Clardy, and co-workers who isolated a series of related diterpenoids from the sea hare *Dolabella californica*.[3] Many biologically active natural products bearing this ring system are now known, some of which incorporate additional complexity elements.[4] Outstanding among these are the potent cytotoxic agents clavulactone (**3**) and clavirolide (**4**).[5] As part of a program targeting these natural products for synthesis, we set out to identify efficient strategies for simultaneous construction of the *trans*-fused 5- and 11-membered rings. We report herein the first phase of this project that has led to total syntheses[6] of isoedunol (**2**)[7] and β-araneosene (**1**)[8] by a route that is notable for its brevity, stereocontrol, and reliance on an unusual strategy (Scheme 1).



clavulactone (3)



clavirolide (4)

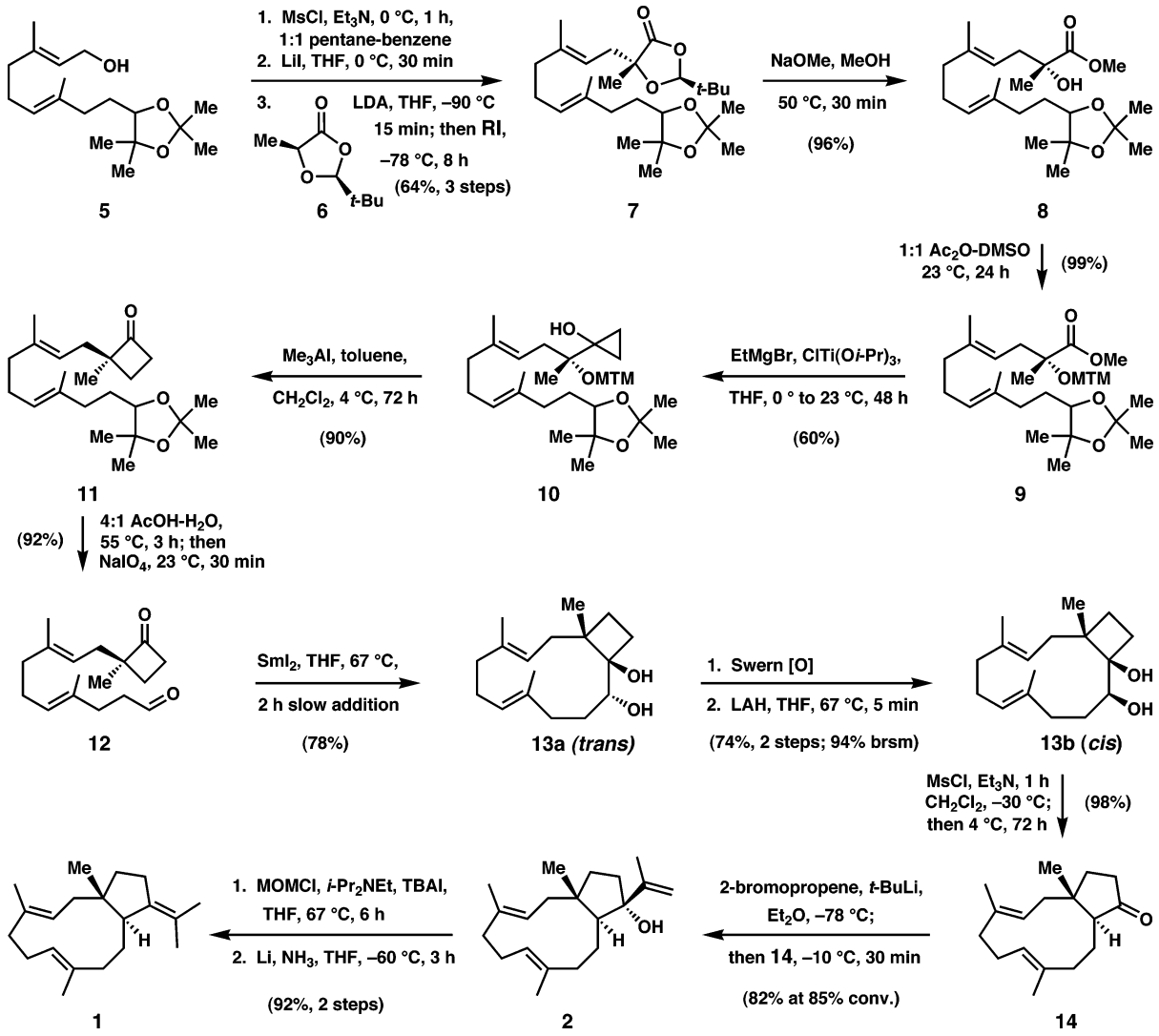
Racemic farnesol acetonide (**5**)[9] was transformed in 64% overall yield to the protected tertiary hydroxyester derivative **7** by the sequence: (1) mesylate formation with 1.2 equiv of MsCl and 1.25 equiv of Et_3N at 0 °C over 1 h, (2) mesylate displacement with LiI at 0 °C in THF, and (3) diastereoselective alkylation (at −78 °C for 8 h) with the lithium enolate generated by slow addition of Seebach's (*S*)-lactic acid-derived dioxolanone **6** to a solution of LDA in THF at −90 °C. The diastereomer that would result from electrophilic attack at the more screened face of the chiral metal enolate could not be detected in the unpurified reaction mixture (TLC, ^{1}H NMR analysis). Methanolysis (NaOMe in MeOH, 50 °C, 30 min, 96%) gave a tertiary alcohol (**8**) that was protected as the methylthiomethyl (MTM) ether in nearly quantitative yield (1:1 DMSO−Ac_2O, 23 °C, 24 h). Dropwise addition of EtMgBr (5 equiv) to a THF solution containing **9** and $ClTi(O\textit{i}\text{-}Pr)_3$ (2.5 equiv) at 0 °C, followed by warming and additional stirring at 23 °C for 48 h, afforded 60% of the Kulinkovich reaction product,[11] cyclopropyl carbinol **10**, after extractive workup and column chromatography on silica gel. The sole byproduct (35%) under these conditions is the ethyl ketone corresponding to **9**. Treatment of a dilute solution of **10** in CH_2Cl_2 with 1.0 equiv of Me_3Al, first at −10 °C (until gas evolution had subsided) then at 4 °C for 72 h, gave cyclobutanone **11** in 90% yield.

Though hindered, this strained ketone readily took part in additional C−C bond-forming and ring-expanding processes. Acidic hydrolysis of **11** (4:1 AcOH−H_2O, 55 °C, 3 h) and periodate cleavage of the resulting diol (3.0 equiv of $NaIO_4$, 23 °C, 30 min) gave in 92% yield a keto aldehyde (**12**) suitable for reductive macrocyclization. Surprisingly, a number of low-valent Ti-based reagents[12] failed to effect the desired transformation, giving rise exclusively to a diastereomeric mixture of reduced but uncyclized diols. However, slow addition (2 h, syringe pump) of **12** to a refluxing solution of SmI_2 [13] (8 equiv) in THF smoothly delivered the *trans* pinacol **13a** (mp 129−130 °C) as a single diastereomer in 78% yield after basic aqueous workup and flash silica gel chromatography. An oxidation/reduction sequence was accomplished next since the alternative *cis* relative configuration in the macrocyclic diol was required for bond-selective expansion of the four-carbon ring (see below). Successive addition of **13a** and Et_3N (7 equiv) at −78 °C to a CH_2Cl_2 solution of the Swern reagent (prepared at −78 °C from 2 equiv of oxalyl chloride and 2.3 equiv of DMSO) gave the expected hydroxy ketone, which, without purification, was added to a refluxing solution of excess LAH in THF. After an aqueous quench of the reductant and filtration, a 4:1 mixture (by ^{1}H NMR analysis) of *cis*:*trans*-**13** was recovered and separated by column chromatography (74% isolated yield of **13b**, mp 82 °C; 20% recovered **13a**). Slow addition of Et_3N (4 equiv) to a solution of **13b** and MsCl (1.1 equiv) in CH_2Cl_2 at −30 °C (bromobenzene−dry ice bath), followed by slow warming to 4 °C and additional stirring for 72 h (optimized conditions) afforded pure *trans*-fused 5,11-bicyclic ketone **14** in 98% yield.

Completion of the synthesis required introduction of the remaining three-carbon fragment in the target diterpenes and a reductive deoxygenation with allylic transposition. Reverse addition of **14** to a solution of 2-lithiopropene (generated at −78 °C by treatment of 2-bromopropene with 2 equiv of *t*-BuLi) at −10 °C in Et_2O gave isoedunol (**2**) diastereoselectively (82% yield)[7] along with a minor amount (15%) of **14** (from substrate deprotonation). A preferred crown-like conformation in the medium ring is likely responsible for the high degree of stereocontrol. Formation of the methoxymethyl (MOM) ether of **2** (6 equiv of chloromethyl methyl ether and 6 equiv of $\textit{i}\text{-}Pr_2NEt$ in two portions, 1 equiv of TBAI, THF, 67 °C, 6 h, 92%), followed by dissolving metal reduction (excess Li in NH_3, THF, −60 °C for 3 h) afforded β-araneosene (**1**) in quantitative yield after filtration through silica gel in hexanes. The identity of synthetic and naturally derived **1** and **2** was confirmed by comparison of IR, ^{1}H NMR, ^{13}C NMR, optical rotation, and mass spectral data with data reported in the literature.[7,8]

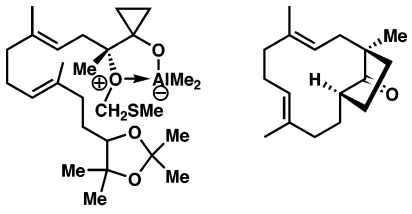
An enabling feature of the above-described synthesis is the reaction sequence **9** → **10** → **11**, which effectively installs the angular methyl-bearing quaternary carbon atom in **1** and **2** with stereochemical control. It is noteworthy that preliminary attempts to effect the cyclopropanol → cyclobutanone conversion by mild protic catalysis resulted in partial racemization. Thus, treatment of **10** with 1 equiv of PPTS in warm CH_2Cl_2 (35−38 °C, 2 h) afforded the product (**11**) in only 60% ee. The success achieved with Me_3-Al is likely due to its bifunctional role in inducing a concerted

Scheme 1



rearrangement pathway via the intermediacy of chelate **15**. Nonetheless, care must taken in this transformation as well, since the use of higher temperatures (40 °C) or excess reagent resulted in 5−8% loss of enantiopurity. With regard to the Kulinkovich synthesis of **10**, protected α-hydroxy alkanoate **9** appears to be the most hindered substrate successfully used to date with diisopropoxytitanacyclopropane.[14] Given the diversity of tertiary α-hydroxy carboxylic esters available in enantiomerically pure form, we believe that this reaction, together with the simple procedure for ring enlargement, may be a general and useful method for the asymmetric synthesis of cyclobutanones with an all-carbon-substituted α-quaternary center.[15]

During this study of the 4 → 5 ring expansion, important conformational information was obtained regarding the 12-membered ring system. Although the *trans* diol **13a** might serve as a direct precursor to key intermediate **14**, it transpired that the exclusive pinacol rearrangement product formed upon activation of the secondary hydroxyl is the *bridged* 5,12-bicyclopentanone **16**. As shown in the X-ray crystal structure obtained for racemic[16] **13a** (Figure 1A), conformational rigidity enforced by the 12-membered ring results in a stereoelectronic preference for 1,2-migration of the less substituted, exocyclic cyclobutane bond (C4−C3, bond length 1.543(3) Å), even though the internal σ bond (C1−C4, 1.567(3) Å) is considerably weaker. By contrast, an X-ray structure of the racemic diol **13b** (Figure 1B), which also shows bond angle and length distortion in the cyclobutane ring, situates the longer C1−C4 linkage antiperiplanar to the secondary C−O bond. Thus, the two-step oxidation/reduction sequence reported in Scheme 1 is accompanied by a dramatic structural change in the medium ring that favors the pinacol rearrangement of **13b** → **14**.



This overriding importance of conformation is also evidenced by a very facile rearrangement of hydroxy ketone **17** (the Swern oxidation product from **13a**) to **18** (structure established by X-ray crystallography) by exposure to silica gel at 23 °C (Scheme 2). The facile ring expansion of **17** → **18** may be useful for the synthesis of other dolabellane structures, such as clavirolide F (**4**).

In summary, the first total enantioselective syntheses of β-araneosene (**1**) and isoedunol (**2**) have been demonstrated by a strategy involving two small ring expansions and a medium ring contrac-

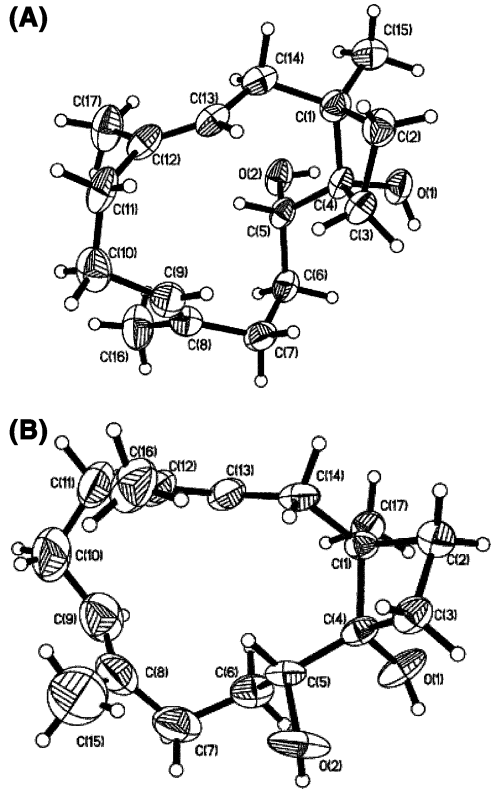
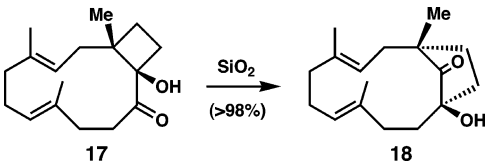


Figure 1. (A) ORTEP of (±)-**13a** and (B) (±)-**13b**.

Scheme 2



tion.[6] Further synthetic studies pertaining to more complex members of this class of diterpenoids are underway.[17]

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Supporting Information Available: Experimental procedures and characterization data for all new products and X-ray diffraction data (CIF) for **13a**, **13b**, and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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