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Concise Total Syntheses of Palominol, Dolabellatrienone, β-Araneosene, and Isoedunol via an Enantioselective Diels−Alder Macrobicyclization

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Although 75 years of study have proven that the Diels−Alder reaction is one of the most powerful tools for the construction of complex molecules, particularly natural products, its full potential has not yet been reached.[1] For instance, no chiral, small molecule catalyst has yet proven capable of coaxing an achiral precursor to undergo an enantioselective Type I Diels−Alder-based macrobicyclization. In this Communication, we report the first solution to this problem as part of a broader research program to develop effective synthetic pathways to bioactive dolabellane-type marine natural products,[2,3] including the parents β-araneosene (**1**, Figure 1),[4] dolabellatrienone (**2**),[5] and palominol (**3**).[6]

The overall approach to these targets is summarized retrosynthetically in Figure 1, for the case of dolabellatrienone (**2**). Retrosynthetic 5 → 6 ring expansion and functional group introduction serve to convert this structure to one suitable for retrosynthetic Diels−Alder disconnection. Since this disconnection would produce an achiral precursor, any enantioselective synthesis would require the application of a chiral catalyst. We surmised that this key step could proceed asymmetrically with the chiral *cis*-fused oxazaborolidinium cation **4**[7] by way of *endo*-transition state assembly **5**, whose organization involves a formyl hydrogen bond and π−π stacking between the dienophile and the catalyst. Such a reaction course would result in the required macrocyclic enantiomer.[1a]

The manner in which this general plan was reduced to practice is shown in Scheme 1. Synthetic efforts began with the stereospecific coupling of building blocks **6**[8] and **7**[9] through a π-allyl Stille reaction induced by catalytic Pd_2dba_3, to form **8** in 96% yield. Although this type of reaction has been employed on a number of occasions to fashion similar diene systems with high stereospecificity,[10] to our knowledge, this example represents the first case in which a farnesyl-derived fragment has been utilized successfully.[11] Subsequent exposure of this intermediate to HIO_4 (1.1 equiv) and $NaIO_4$ (0.6 equiv) in aqueous THF at 25 °C for 1 h generated an aldehyde that was then combined with the anion derived from the reaction of phosphonate **9** (3.0 equiv) with KO*t*-Bu (2.5 equiv), to provide methyl ketone **10** in 92% overall yield. This product was then converted into Diels−Alder precursor **11** in 78% overall yield via (1) TBAF-mediated deprotection of the *tert*-butyldiphenylsilyl (TBDPS) ether, (2) MnO_2 oxidation of the resultant alcohol, and (3) triisopropylsilyl (TIPS) enol ether formation by brief exposure of the intermediate methyl ketone to TIPSOTf (1.1 equiv) and *i*-Pr_2NEt (4.0 equiv) in CH_2Cl_2 at −78 °C for only 3 min.

With the key Diels−Alder substrate in hand, we next undertook the study of Diels−Alder macrocyclization. To our delight, effecting this reaction required little scouting since in the first experiment we found that the slow addition of a solution of 20 mol % of the (*S*)-catalyst **4** in toluene to a stirred solution of the highly acid sensitive **11** in toluene at −93 °C, followed by 3 h at −93 °C and 10 h at −78 °C, resulted in the formation of macrocycle **12** in 74% yield and 90% enantiomeric excess (ee). The structure and absolute configuration of **12** were verified by X-ray crystallographic analysis

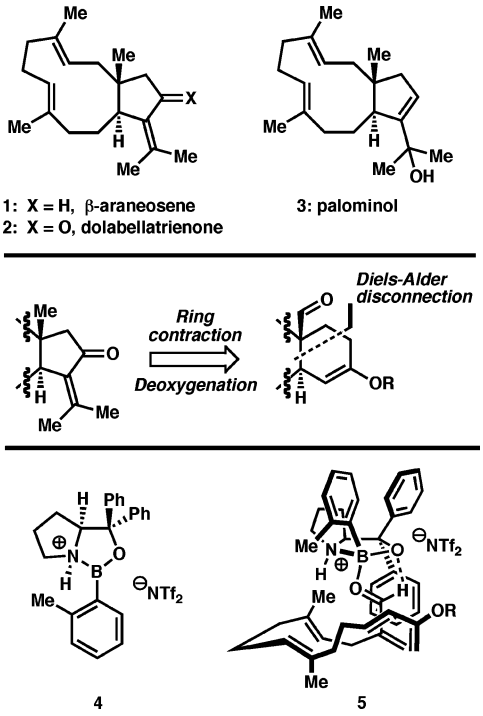


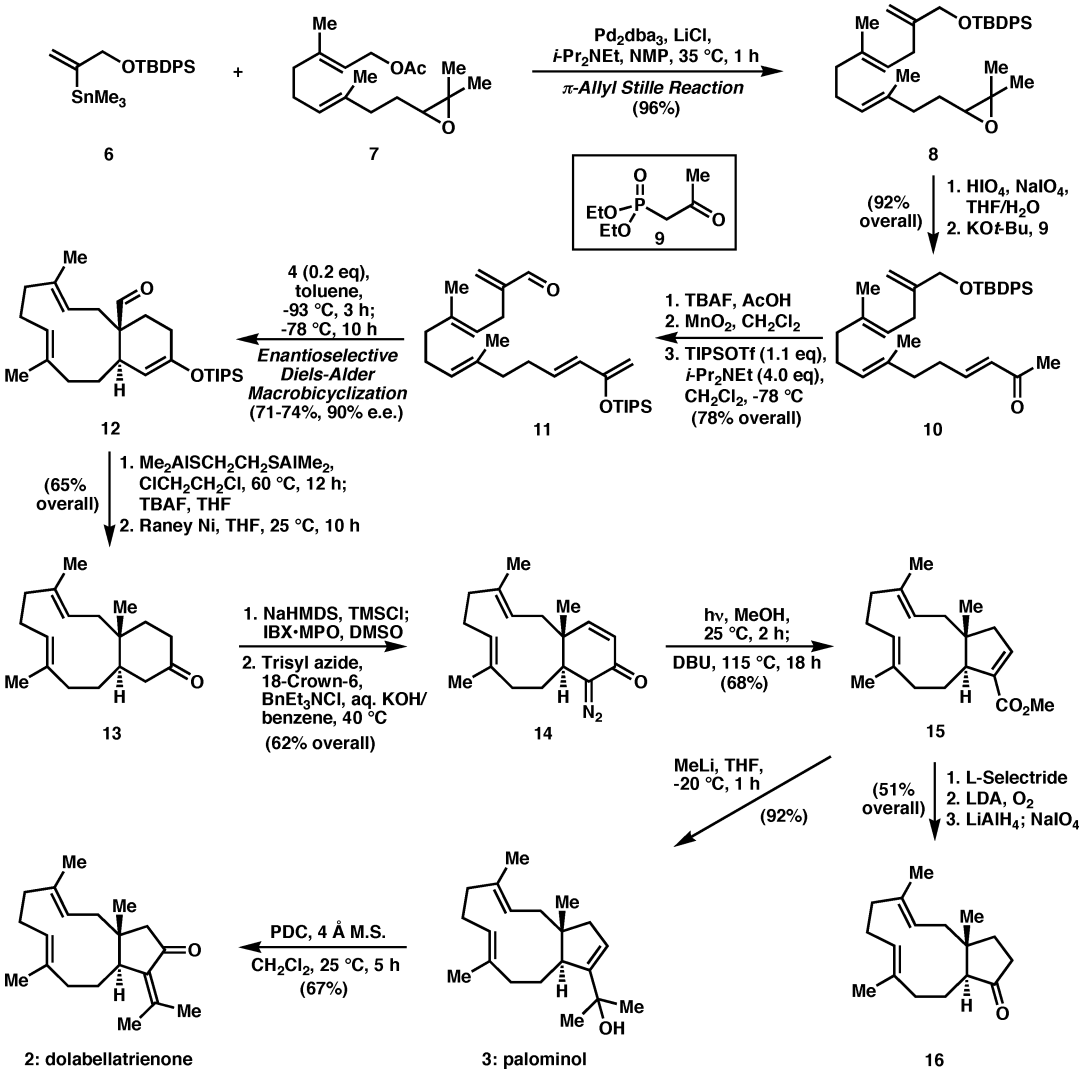
Figure 1.

of the tosylhydrazone derivative. Both the structure and absolute configuration of **12** are as predicted by the transition state model **5**.[12] Remarkably, catalyst **4** was unique in its ability to effect this [4 + 2]-cycloaddition. Exposure of **11** to standard achiral initiators, such as Me_2AlCl, $MeAlCl_2$, $EtAlCl_2$, or heat deprotected and/or polymerized **11**, without detectable conversion to **12** or any other Diels−Alder-type product.

With this critical operation complete, the task of deoxygenating the aldehyde function that had enabled the enantioselective Diels−Alder reaction was undertaken. After numerous unsuccessful attempts, for example, involving reduction of arylsulfonylhydrazones, the required reduction was accomplished in two steps using novel methodology that depended on dithiolane formation using **12** and the reagent $Me_2AlSCH_2CH_2SAlMe_2$[13] (3 equiv, prepared in situ from ethanedithiol and Me_3Al) at 60 °C in dichloroethane solution for 12 h. After silyl ether cleavage, the dithiolane was treated with deactivated Raney Ni (formed by stirring Raney Ni in acetone for 30 min at 25 °C prior to reaction) in THF at 25 °C for 10 h to afford the required product **13** in 65% overall yield from **12**.[15] Many other reagents and methods were screened for thioacetal formation, but all failed because of vinyl ether cleavage and further reaction. As indicated by the additional examples in Table 1, this method of nonacidic thioacetalization is quite general and mild as ketones (**17**), aryl aldehydes (**19**), and hindered aldehydes containing *tert*-butyldimethylsilyl (TBS) ether subunits (**25**) are all smoothly

10.1021/ja0576379 CCC: $33.50

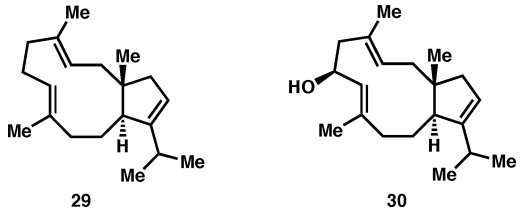
Scheme 1



converted into the thioacetals in good yields. Additionally, it should be noted that alternative protocols, such as Wolff−Kishner reduction and Barton−McCombie deoxygenation, failed to convert **12** into **13**.

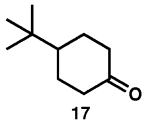
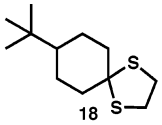
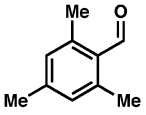
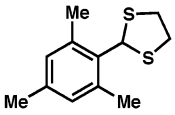
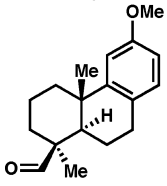
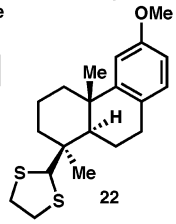
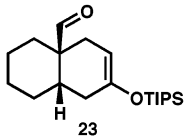
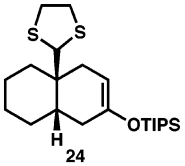
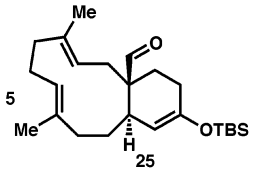
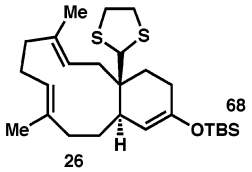
The next strategic operation, ring contraction,[14] was achieved in a single step by an unusual application of the Wolff rearrangement.[16] In the first stage, the synthesis of α,β-unsaturated diazoketone **14** was carried out in 62% overall yield by the following sequence: (1) α,β-desaturation using the oxidation conditions developed by Nicolaou;[17] and (2) a phase-transfer-induced diazo transfer reaction as described by the Mander group.[18] Photoirradiation of **14** in MeOH for 2 h at 25 °C, followed by solvent removal and heating in neat 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at 115 °C for 18 h, generated the required ring-contracted ester **15** in 68% yield.[19] The success of this ring-contraction process, given the number of potential side reactions of an intermediate carbene generated so close to a neighboring olefinic linkage and ring junction, is noteworthy; an additional example, **27** → **28**, is shown in Scheme 2.[20]

The chiral dolabellane derivative **15** was readily converted to palominol (**3**) and dolabellatrienone (**2**) as indicated in Scheme 1.[2c,5c] In addition to these target molecules, synthetic routes to both β-araneosene (**1**) and isoedunol[2a] were established by the successful conversion of **15** into ketone **16** by a three-step sequence in 51% overall yield (following earlier studies):[21] (1) conjugate reduction of **15** using L-Selectride (4 equiv) in THF at 0 °C, (2) α-oxygenation, and (3) diol formation upon exposure to excess $LiAlH_4$ and subsequent cleavage using $NaIO_4$ on silica gel. Beyond accomplishing the enantioselective total syntheses of these four natural product targets, the developed sequence could also be employed to access the parent structures of several additional dolabellanes. For instance, the transformation of palominol (**3**) into the corresponding methoxymethyl ether (MOM) using MOMI (4 equiv) and *i*-Pr_2NEt (6 equiv) in refluxing THF for 12 h followed by Li−NH_3 reduction [excess Li in NH_3/THF (1:1), −40 °C, 2 h] provided triene **29** (95% yield),[22] a regioisomer of β-araneosene (**1**) and the core element of several more highly oxidized dolabellane diterpenoids, such as **30**.[3]



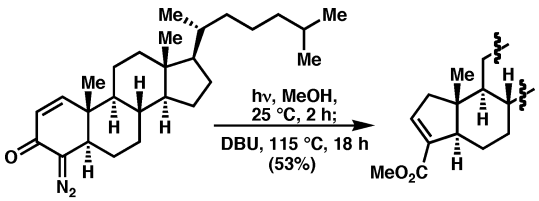
In summary, concise and stereoselective total syntheses of four members of the dolabellane family of diterpenoids, as well as the carbocyclic core of several more highly oxygenated natural products, have been achieved by an efficient synthetic strategy

Table 1. $Me_2AlSCH_2CH_2SAlMe_2$-Induced Dithiane Formation[a]

Entry	Starting material	Product	Yield (%)
1	 17	 18	83
2	 19	 20	87
3	 21	 22	79
4	 23	 24	72
5	 25	 26	68

[a] With 3 equiv of sulfide reagent at 60 °C in 1,2-dichloroethane for 2−12 h.

Scheme 2



27 28

featuring a highly enantioselective intramolecular Diels−Alder macrobicyclization of an achiral precursor in combination with several key reactions: (1) the first example of a stereoselective π-allyl Stille coupling reaction involving a farnesyl-derived intermediate, (2) a powerful new reagent for the formation of dithiolanes with acid-sensitive molecules, and (3) a unique and highly efficient ring-contraction sequence based on a modified Wolff photochemical rearrangement. Additional synthetic studies pertaining to more complex members of this class of diterpenoids, as well as studies into the general ability of chiral oxazaborolidinium cations to orchestrate enantioselective, intramolecular Diels−Alder macrocyclizations, are underway.

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Supporting Information Available: Experimental procedures and characterization data for all new products, list of abbreviations, selected ^{1}H NMR spectra of key intermediates and synthetic natural products, and X-ray diffraction data (CIF). This material is available free of charge via the Internet at http://pubs/acs.org.

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(20) The only side product in this conversion is that bearing a tetrasubstituted olefin adjoining the A and B rings; such a side product has been formed from **28** before through a thermal reaction: Fuchs, B.; Loewenthal, H. J. E. *Tetrahedron* **1960**, *11*, 199.

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(22) The selectivity in this event appears to be unique, as related model compounds derived from 5α-cholestan-3-one afforded products corresponding to β-araneosene (**1**). We ascribe the unique reactivity to destabilizing steric interactions between the isopropylidene methyl groups and the adjoining 11-membered ring that are relieved upon tertiary radical formation followed by rapid H-atom abstraction from THF. Use of the proton source *tert*-butyl alcohol afforded a 1:1 mixture of **29** and β-araneosene (**1**).

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