Natural Product Synthesis

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Total Synthesis of (+)-Asperolide C by Iridium-Catalyzed Enantioselective Polyene Cyclization**

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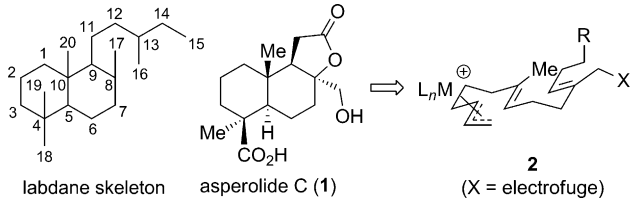
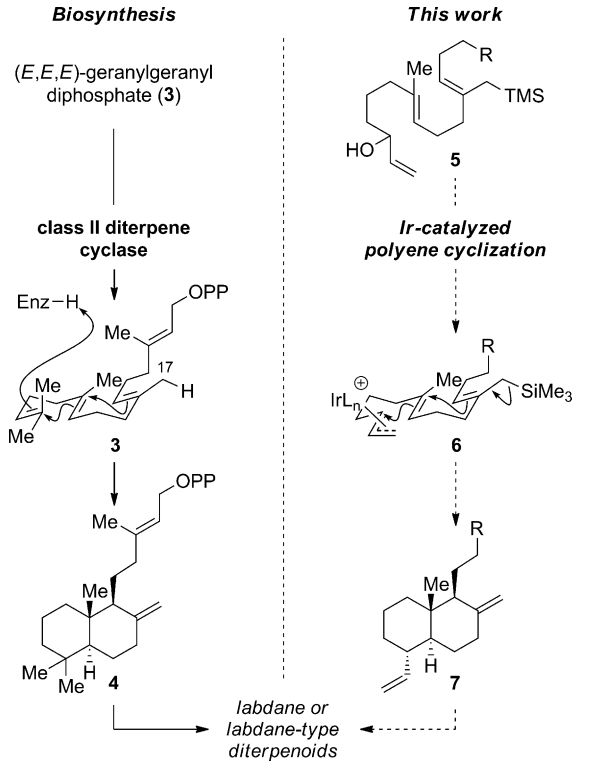
The labdane diterpenes encompass a structurally diverse class of natural products that are widely distributed in terrestrial and marine organisms.[1] Many of these compounds exhibit notable biological properties, such as antibacterial,[2] antimutagenic,[3] cytotoxic,[4] anti-inflammatory, and analgesic activities.[5] Various procedures have been developed for their preparation,[6] including isolation from natural sources and chemical or biological manipulation.[7] Herein we report the first total synthesis of asperolide C (**1**, Scheme 1), a tetranor-



Scheme 1. Labdane skeleton, structure of asperolide C (**1**) and asymmetric catalytic polycyclization.

labdane diterpenoid isolated from *Aspergillus wentii* EN-48,[8] through a unique asymmetric catalytic polycyclization cascade which is reminiscent of its biogenesis. A number of enantioselective polyolefin cyclizations have been reported in the literature.[9] It is interesting to note, however, that applications of these processes in natural product synthesis are scarce, with only two reports emanating from the Yamamoto research group.[10]

The carbon skeleton common to labdane-type diterpenoids is assembled biosynthetically from (*E*,*E*,*E*)-geranylgeranyl diphosphate (**3**) through a polyolefin cyclization pathway, which is consistent with the hypotheses of Stork and Eschenmoser.[11,12] The currently accepted mechanism involves protonation-initiated cyclization of **3**, enabled by



Scheme 2. Proposed biosynthesis of labdane-type diterpenoids (labda-13-en-8-yl diphosphate cation omitted for conciseness) and iridium-catalyzed polyene cyclization.

class II diterpene cyclases, to generate a labda-13-en-8-yl diphosphate cation (Scheme 2).[13] This intermediate typically suffers deprotonation of the C(17) methyl group to produce copalyl pyrophosphate **4**. The allylic diphosphate in **4** then engages in other rearrangement and/or cyclization reactions followed by a series of downstream biosynthetic modifications that lead to the introduction of additional functionality. It is estimated that a significant number of polycyclic diterpenoids (ca. 7000) arise from this initial cyclization event.

As part of our program on the study of iridium-catalyzed enantioselective transformations,[14] we became interested in their application to the synthesis of complex molecules. A particularly useful set of reactions that we recently disclosed includes the asymmetric cyclization of polyunsaturated allylic alcohols.[15,16] It was envisioned that this method, which employed arenes to conclude the cationic cascades, might be expanded in new ways to provide a general entry into the alicyclic labdane core. Significantly, this would require the use of an allyl silane as a terminating group. Accordingly, linear

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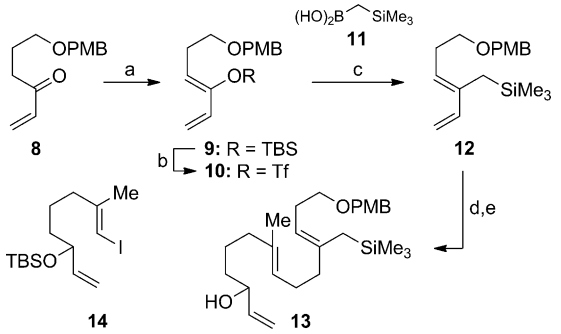
allylic alcohol **5** (Scheme 2) would be subjected to conditions that generate π-allyl iridium complex **6**. This reactive intermediate would then undergo a series of stereoselective cyclizations before suffering loss of the Me_3Si group to form the exomethylene in **7**. The *trans*-decalin system thus obtained would be a valuable intermediate in the synthesis of various labdane or labdane-type diterpenoids.

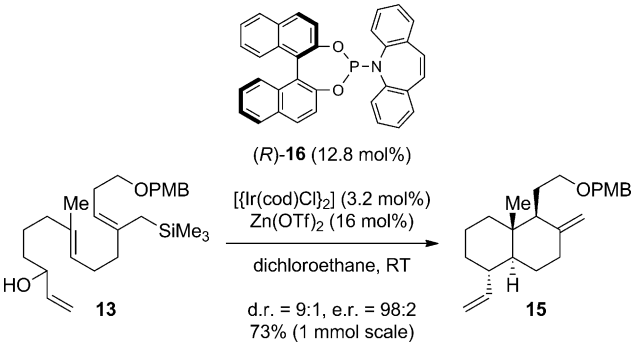
The synthesis of asperolide C (**1**) commenced with the preparation of vinyl ketone **8** (Scheme 3), which was obtained from commercially available γ-butyrolactone in three steps.



Scheme 3. Reagents and conditions: a) LiHMDS (1.25 equiv), *t*Bu-Me_2SiCl (1.25 equiv), THF/HMPA, −78 °C, d.r. > 95:5, 95 %; b) $PhNTf_2$ (1.5 equiv), CsF (2.5 equiv), $(MeOCH_2)_2$, RT, d.r. > 95:5, 96 %; c) **11** (1.5 equiv), $[Pd(dppf)Cl_2]\cdot CH_2Cl_2$ (10 mol %), Ph_3As (10 mol %), Cs_2CO_3 (2.5 equiv), THF/DMF/H_2O, 0 °C to RT, d.r. = 10:1, 62 %; d) 9-BBN (1.1 equiv), THF, 0 °C to RT; then **14** (1.0 equiv), $[Pd(dppf)Cl_2]\cdot CH_2Cl_2$ (2.7 mol %), NaOH (3.0 equiv), THF/H_2O, 0 °C to RT, 61 %; e) PPTS (10 mol %), MeOH, RT, 81 % (2 iterations). PMB = *p*-methoxybenzyl, TBS = *tert*-butylsilyl, dppf = 1,1′-bis(diphenylphosphino)ferrocene, PPTS = pyridinium *p*-toluenesulfonate, HMPA = hexamethylphosphoramide, HMDS = hexamethyldisilazane, Tf = trifluoromethanesulfonyl, 9-BBN = 9-borabicyclo[3.3.1]nonane.

Initial attempts to directly transform enone **8** to enol triflate **10** (LiHMDS, 2-NTf_2-5-chloropyridine, THF, −78 °C) proved unsuccessful. Therefore, a two-step protocol was examined, which involved conversion of **8** into enol silane **9** followed by exchange of the silyl group with the required triflate. Formation of **9** under standard conditions was hampered by polymerization of **8**. However, the desired intermediate could be obtained in good yield (95 %) and excellent *Z* selectivity (d.r. > 95:5) when **8** was added to a premixed solution of LiHMDS and *tert*-butyldimethylsilyl chloride in THF at −78 °C, using HMPA as a cosolvent. Enol triflate **10** was obtained with complete retention of the olefin geometry by treatment with triflic fluoride, generated in situ following the procedure of Corey and co-workers (96 %).[17] Cross-coupling of enol triflate **10** and boronic acid **11** was achieved under the conditions of Johnson and Braun, by using $[Pd(dppf)Cl_2]$ (10 mol %) as a catalyst in combination with Ph_3As (10 mol %) as a coligand and Cs_2CO_3 as a base to produce the desired product **12** in 62 % yield ($Z/E = 10:1$).[18–20] The terminal olefin in diene **12** was hydroborated with 9-BBN and the resulting trialkylborane was directly subjected to *B*-alkyl Suzuki coupling with known vinyl iodide **14** to afford the desired polyene (61 %).[15,21] Removal of the TBS protective group required carefully chosen conditions. Whereas attempts with TBAF or *para*-toluenesulfonic acid led to decomposition of the material, PPTS (10 mol %) was found to catalyze the desired transformation. However, as a result of the poor stability of the product in acidic media, the reaction was usually halted at 60 % conversion.[22] Re-subjection of the recovered starting material led to allylic alcohol **13** in 81 % combined yield.

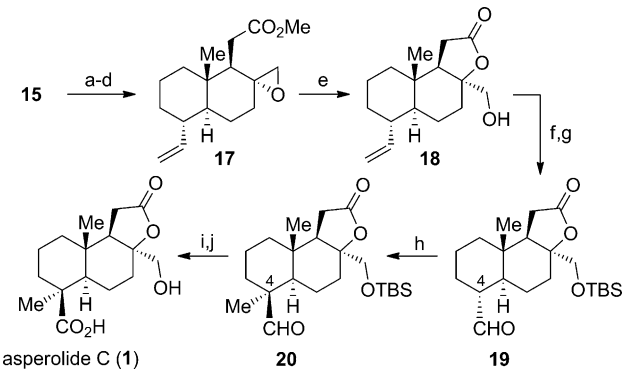
With polyene precursor **13** in hand, the pivotal iridium-catalyzed cyclization cascade was examined (Scheme 4). Gratifyingly, reaction of **13** under standard conditions with $[\{Ir(cod)Cl\}_2]$ (3.2 mol %) and (*R*)-**16** (12.8 mol %) as catalyst precursors, along with $Zn(OTf)_2$ (16 mol %) as a Lewis acid delivered decalin **15** with excellent stereoselectivity (d.r. = 9:1, e.r. = 98:2) and in 73 % yield.[15,23]



Scheme 4. Iridium-catalyzed enantioselective polyene cyclization cascade.

The synthesis of asperolide C (**1**) continued with deprotection of **15** followed by stepwise oxidation of the liberated primary hydroxy group. The carboxylic acid thus obtained was treated with trimethylsilyldiazomethane to afford the corresponding methyl ester (62 % over 4 steps, Scheme 5). Epoxidation of the exomethylene group with freshly prepared DMDO at −20 °C proceeded from the sterically more accessible α face to deliver oxirane **17** in moderate yield (45 %, 66 % brsm). Exposure of **17** to trifluoroacetic acid in anhydrous CH_2Cl_2 at 0 °C led to selective epoxide opening and efficient cyclization to furnish lactone **18** (70 %).[24]

With the tricyclic scaffold of the target constructed, the final stages of the total synthesis were addressed. After masking the primary hydroxy group in **18** as a TBS ether (TBSCl, imidazole, DMAP, 89 %), Lemieux–Johnson oxidation afforded aldehyde **19** in 81 % yield. Introduction of the quaternary center at C(4) by enolate alkylation was complicated by the presence of a γ-lactone ($pK_a \approx 20$). We reasoned that the direct alkylation of an aldehyde ($pK_a \approx 17$) could offer the necessary chemoselectivity in the deprotonation event. In the experiment, treatment of a solution of **19** in THF at −20 °C with *t*BuOK (1.25 equiv),[25] followed by addition of iodomethane (1.25 equiv) and warming to 0 °C delivered **20** as a single isolable product. Pinnick oxidation of aldehyde **20** to the corresponding carboxylic acid (76 %) and cleavage of the TBS group (74 %) completed the first total synthesis of asperolide C (**1**). The ^1H and ^{13}C NMR spectra of the synthetic material were in agreement with those reported



Scheme 5. Reagents and conditions: a) DDQ (1.1 equiv), pH 7 buffer, CH_2Cl_2, RT, 98%; b) DMP (1.5 equiv), CH_2Cl_2, RT, 80%; c) $NaClO_2$ (4.0 equiv), NaH_2PO_4 (6.0 equiv), 2-methyl-2-butene (70 equiv), *t*BuOH/H_2O, RT; then Me_3SiCHN_2 (1.1 equiv), MeOH, 0°C to RT, 79%; d) DMDO (1.1 equiv), acetone, −78°C to −20°C, 45% (66% brsm); e) CF_3CO_2H (1.2 equiv), CH_2Cl_2, −20°C to 0°C, 70%; f) *t*Bu-Me_2SiCl (3.0 equiv), imidazole (6.0 equiv), DMAP (10 mol%), CH_2Cl_2, RT, 89%; g) OsO_4 (20 mol%), $NaIO_4$ (5.0 equiv), 2,6-lutidine (2.0 equiv), 1,4-dioxane/H_2O, RT, 81%; h) *t*BuOK (1.25 equiv), MeI (1.25 equiv), THF, −20°C to 0°C, 36%; i) $NaClO_2$ (6.0 equiv), NaH_2PO_4 (6.0 equiv), 2-methyl-2-butene (30 equiv), *t*BuOH/H_2O, RT, 76%; j) TBAF (1.5 equiv), THF, 0°C, 74%. DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone, DMP = Dess–Martin periodinane, DMDO = dimethyldioxirane, DMAP = 4-dimethylaminopyridine, TBAF = tetra-*n*-butylammonium fluoride, brsm = based on recovered starting material.

for the natural product. It should be noted that asperolide C (**1**) was originally isolated as an inseparable 3:4 mixture with the known terpene botryosphaerin, which precluded thorough characterization. With a pure sample of **1** in hand, we could measure its optical rotation for the first time ($[\alpha]_D^{26} = +2.5$ ($c = 0.25$, MeOH)).

In conclusion, the first total synthesis of the tetranorlabdane diterpenoid asperolide C (**1**) has been achieved. This study represents a rare example of the use of an enantioselective polyene cyclization reaction in a natural product synthesis and the first that strategically relies on modern iridium catalysis to construct the carbobicyclic core scaffold. Additionally, the described route features a series of cross-coupling reactions to efficiently assemble the linear polyene precursor. Specifically, the Pd-mediated coupling of a dienol triflate with $Me_3SiCH_2B(OH)_2$ provides a novel access route to allylic silanes. Moreover, a chemo- and diastereoselective alkylation of an aldehyde enolate was employed to complete the target structure. The synthetic strategy provides a general entry into the labdane-type diterpenoids and has significant potential for enabling the total synthesis of other terpene natural products.

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Communications

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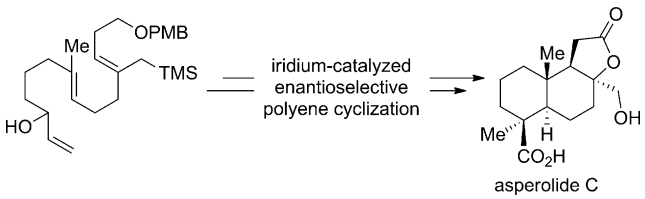

asperolide C

Domino rings: A general synthetic entry into labdane-type diterpenoids has been developed based on an iridium-catalyzed enantioselective polyene cyclization cascade. The potential of this process is demonstrated in the first total synthesis of the tetranorlabdane diterpene asperolide C (PMB = *p*-methoxybenzyl, TMS = trimethylsilyl).