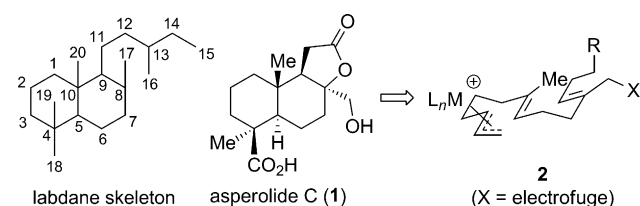


Total Synthesis of (+)-Asperolide C by Iridium-Catalyzed Enantioselective Polyene Cyclization**

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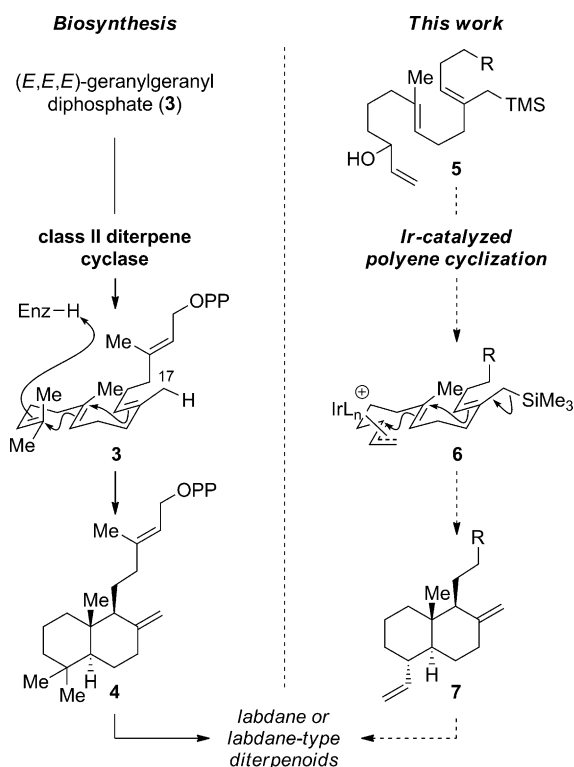
The labdane diterpenes encompass a structurally diverse class of natural products that are widely distributed in terrestrial and marine organisms.^[1] Many of these compounds exhibit notable biological properties, such as antibacterial,^[2] antitumorigenic,^[3] cytotoxic,^[4] anti-inflammatory, and analgesic 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

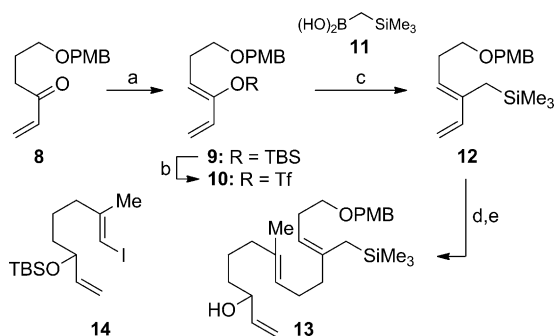
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allylic alcohol **5** (Scheme 2) would be subjected to conditions that generate π -allyl iridium complex **6**. This reactive intermediate would then undergo a series of stereoselective cyclizations before suffering loss of the Me₃Si group to form 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.

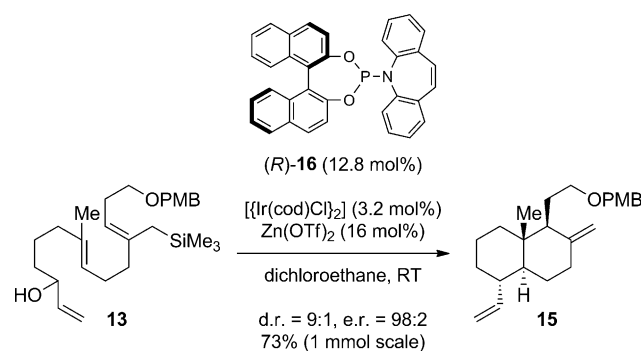


Scheme 3. Reagents and conditions: a) LiHMDS (1.25 equiv), *t*Bu-Me₂SiCl (1.25 equiv), THF/HMPA, -78°C , d.r. > 95:5, 95%; b) PhNTf₂ (1.5 equiv), CsF (2.5 equiv), (MeOCH₂)₂, RT, d.r. > 95:5, 96%; c) **11** (1.5 equiv), [Pd(dppf)Cl₂] $\cdot$ CH₂Cl₂ (10 mol %), Ph₃As (10 mol %), Cs₂CO₃ (2.5 equiv), THF/DMF/H₂O, 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)Cl₂] $\cdot$ CH₂Cl₂ (2.7 mol %), NaOH (3.0 equiv), THF/H₂O, 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-NTf₂-5-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)Cl₂] (10 mol %) as a catalyst in combination with Ph₃As (10 mol %) as a coligand and Cs₂CO₃ 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.

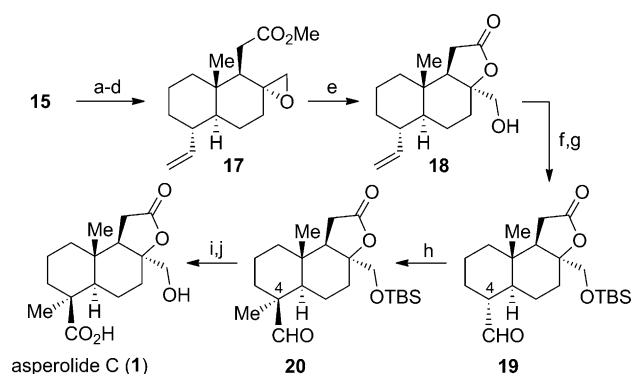
With polyene precursor **13** in hand, the pivotal iridium-catalyzed cyclization cascade was examined (Scheme 4). Gratifyingly, reaction of **13** under standard conditions with [Ir(cod)Cl]₂ (3.2 mol %) and (*R*)-**16** (12.8 mol %) as catalyst precursors, along with Zn(OTf)₂ (16 mol %) as a Lewis acid 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 CH₂Cl₂ 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 ¹³C 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, CH₂Cl₂, RT, 98%; b) DMP (1.5 equiv), CH₂Cl₂, RT, 80%; c) NaClO₂ (4.0 equiv), NaH₂PO₄ (6.0 equiv), 2-methyl-2-butene (70 equiv), *t*BuOH/H₂O, RT; then Me₃SiCHN₂ (1.1 equiv), MeOH, 0°C to RT, 79%; d) DMDO (1.1 equiv), acetone, −78°C to −20°C, 45% (66% brsm); e) CF₃CO₂H (1.2 equiv), CH₂Cl₂, −20°C to 0°C, 70%; f) *t*Bu-Me₂SiCl (3.0 equiv), imidazole (6.0 equiv), DMAP (10 mol%), CH₂Cl₂, RT, 89%; g) OsO₄ (20 mol%), NaIO₄ (5.0 equiv), 2,6-lutidine (2.0 equiv), 1,4-dioxane/H₂O, RT, 81%; h) *t*BuOK (1.25 equiv), MeI (1.25 equiv), THF, −20°C to 0°C, 36%; i) NaClO₂ (6.0 equiv), NaH₂PO₄ (6.0 equiv), 2-methyl-2-butene (30 equiv), *t*BuOH/H₂O, 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 botrysosphaerin, 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 Me₃SiCH₂B(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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