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Strategies for the Synthesis of Fusicoccanes via Nazarov Reactions of Dolabelladienones. Total Synthesis of (+)-Fusicoauritone**

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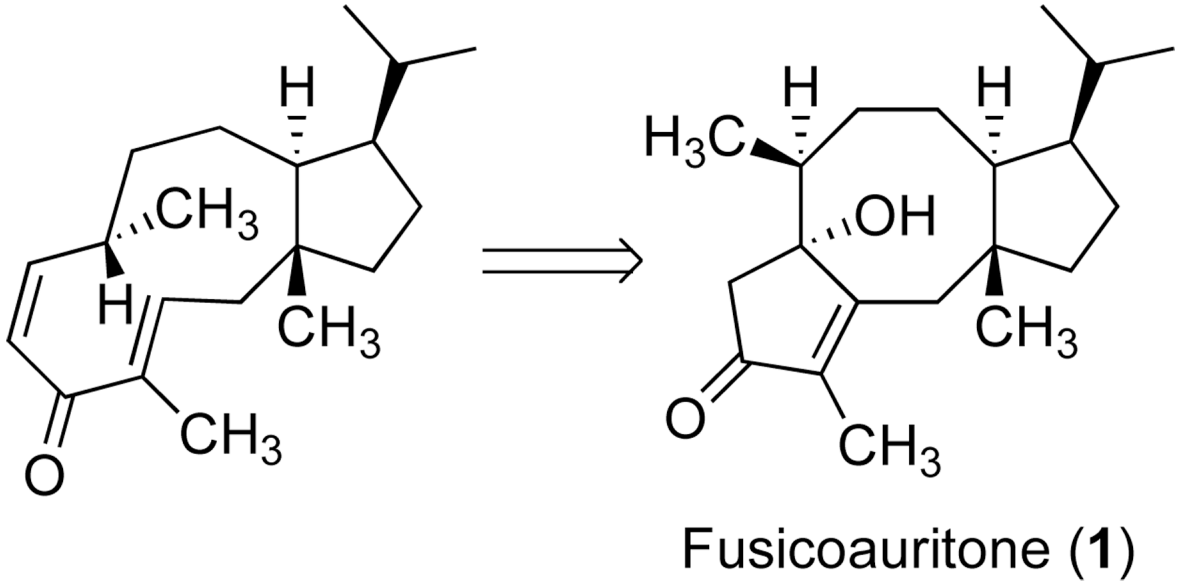
Abstract



Fusicoauritone (**1**)

A synthetic pathway leading to (+)-fusicoauritone (**1**) is highlighted by the use of a Julia condensation for preparation of an eleven-membered dolabelladienone precursor for subsequent Nazarov cyclization to yield the 5-8-5 tricyclic diterpene skeleton.

Keywords

Fusicoccanes; Julia condensation; Medium-ring compounds; Nazarov cyclization; Total synthesis

The fusicoccanes are representative of a family of terpenes which feature a fused 5-8-5 carbocyclic skeleton.[1] Substances exhibiting this structural motif have been isolated from

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a variety of sources including wax secretions of scale insects, fungi, liverworts and more recently, from higher plants. Fusicoccanes,[2] cotylenins[3] and fusicoplagins[4] are diterpenoid examples, whereas the ophiobolins[5] and ceroplastols[6] are sesterterpenes. Fusicoccins and cotylenins exhibit significant phytohormonal activities associated with the activation of plasma membrane H^+-ATPase, and fusicoccin-binding proteins are considered to be key elements in intracellular signal transduction pathways. [7] The putative biogenesis of this tricyclic framework is described by a π-cation cyclization to form an eleven-membered ring, and further transannular events from a [9.3.0]cyclotetradecane precursor lead to fusicoccanes as exemplified by fusicoauritone (**1**) (Figure 1).[8] The initial carbocyclization of geranylgeranyl pyrophosphate yields the dolabellanes, a widely distributed class of marine natural products, via hydration or elimination from cation **2**.[9] In fact, 3,7-dolabelladienes are key biogenic precursors to fusicoccanes, and neodolabellanes as well as the dolastanes (clavularanes), a class of 5-7-6 tricyclic marine terpenes.[10] Interestingly, marine sources produce relatively few examples of secondary metabolites bearing the 5-8-5 skeleton.[11]

Recognizing the central importance of the dolabellane nucleus in the biosynthesis of several families of diterpenes, we have examined strategies for its preparation,[12] and our efforts have described stereocontrolled transannular reactions to dolastanes and relevant rearrangement products.[13] Recently, synthesis studies toward dolabellane and dolastane diterpenes have been reviewed.[14] A convergent strategy toward the fusicoccanes has been described in a body of work by Kato, Takeshita and co-workers culminating in the total synthesis of (−)-cotylenol.[15] Kishi[16] and Boeckman[17] have independently developed syntheses of ophiobolin C and (±)-ceroplastol I, respectively, and distinctive routes for the synthesis of epoxydictymene have also been reported.[18] Unabated interest in the synthesis of the dicyclopenta[a,d]cyclooctane ring system continues.[19] Herein, we communicate the successful application of our retrosynthetic hypothesis (Figure 1), which features eleven-membered ring formation via an intramolecular alkylation from **3** for utilization of the Nazarov reaction[20] of a dolabelladienone **4** to provide a 5-8-5 tricyclic skeleton as the basis for an effective total synthesis of fusicoauritone (**1**).

Preparation of the appropriately functionalized cyclopentane of **1** required elaboration of three contiguous stereogenic sites (C-10, C-11 and C-14). This task was undertaken (Scheme 1) beginning with optically active cyclopentenyl alcohol **5**[21] via the Johnson ortho-ester Claisen rearrangement. The sigmatropic process occurred with high stereoselectivity,[22] and hydride reduction with subsequent protection gave **7** (MEM = $CH_2OCH_2CH_2OCH_3$).

Hydroboration of the exocyclic olefin **7** led to a primary alcohol that proved to be a single C-10 diastereomer and low temperature Swern oxidation[23] gave an aldehyde that was directly utilized without chromatographic purification to avoid epimerization. Our efforts to elongate the alkyl chain and introduce the remote stereocenter at C-7 were rewarded by further studies of the Claisen rearrangement. Towards this end, (*Z*)-propenyllithium was prepared according to the Whitesides procedure,[24] and nucleophilic addition with crude aldehyde in ether at −50 °C afforded approximately a 6:1 mixture of (*Z*)-allylic alcohols (82% yield). Upon chromatographic separation, the major product **8** was obtained in 65% yield.[25]

Treatment of **8** with triethylorthoacetate in the presence of catalytic propanoic acid at 145 °C produced a facile Claisen rearrangement, and direct hydride reduction of the resulting ethyl ester gave alcohol **9** as a single diastereomer (70% for 2 steps).[26] Subsequent reduction of the (*E*)-alkene in **9** proved to be a challenging problem. A variety of hydrogenation catalysts led to products of double bond migration. Rhodium on alumina efficiently transformed **9**

into the corresponding endocyclic (C10–C14) tetrasubstituted olefin. Other techniques, such as the use of diimide were totally ineffective. Fortunately, a dissolving metal reduction using sodium in a concentrated solution of HMPA and *tert*-butyl alcohol[27] cleanly yielded the saturated alcohol **10** (97%) for straightforward conversion to the desired sulfone **12**.

To effect carbocyclization of the eleven-membered [9.3.0] tetradecane system, we utilized modifications of the Julia condensation.[12] Thus, primary alcohol **13** was prepared via deprotection of **12** [HBF_4; aq. MeOH (85%)], and oxidation followed by Wittig olefination gave the *E*-unsaturated ester **15**. Conversion to the aldehydic sulfone **16** was followed by rapid addition into a vigorously stirred solution of sodium *tert*-amylate (0.15 M in benzene at 35 °C). The gold-colored solution was stirred for an additional one to two minutes and quenched with glacial acetic acid leading to the β-hydroxysulfones **17** (dr 5:1) in yields ranging from 73% to 82% with the recovery of additional amounts of enal **16** (12%). The major cyclization product proved to be the *trans*-β-hydroxysulfone[28] although this stereochemistry was inconsequential for our studies. Transformation of **17** to an appropriate divinylketone substrate required an initial Swern oxidation[23] yielding the corresponding α-sulfonylketones (5:1 ratio). However, the dehydro-elimination of the α-sulfonyl substituent was not feasible. On the other hand, oxidation of the resulting enolate of this system with Davis oxaziridine[29] directly produced α-diketone **18** (85%). Although enolic tautomerization is not evident in the ^1H NMR data of **18**, treatment with BF_3 etherate catalyzed formation of the putative divinylketone intermediate for facile Nazarov cyclization yielding α-hydroxy cyclopentenone **19**.[30] Characterization of **19** with extensive use of NMR data, using nOe difference experiments, confirmed the all *syn* stereochemistry of H_A, H_B and H_C as well as the relationship of the bridgehead (C11) methyl and the newly created α-methylketone.[31]

To effect ring contraction of the dolabelladiene precursor via the Nazarov cyclization with control of enone regiochemistry as presented in **1**, we chose to examine the less substituted divinylketone substrate **23**.[32] As illustrated in Scheme 3, phenylselenation of α-sulfonyl ketone **20** (major product from **17**,Scheme 2) gave **21** for immediate oxidation yielding exclusively the *E*-α,β-unsaturated sulfone **22**.[33] This electron-deficient system exhibited diminished reactivity under Lewis-acid catalyzed Nazarov conditions. A three-step sequence effected replacement of the sulfonyl group with hydrogen. Carbonyl reduction gave solely the β-alcohol,[34] and desulfonylation with sodium naphthalide at −78 °C in THF selectively occurred with retention of double bond geometry. Mild allylic oxidation provided the *Z*-enone of **23** as indicated by vicinal coupling (J_{AB} = 10.7 Hz) in the proton NMR spectrum. Finally, treatment of **23** under protic or Lewis acid conditions resulted in a smooth Nazarov reaction to **24** (and its C-6 epimer).[35] Upon standing for several days, chloroform solutions of **24** yielded colorless crystals which were unambiguously identified by X-ray crystallography as the hydroperoxide **25**,[36] and subsequent reduction with sodium hydrogen sulfite gave **1**. Autoxidation of **24** was postulated to occur via enolization and capture of the conjugated enol by dissolved oxygen. This slow, serendipitous reaction to **25** was not pursued as a viable synthetic conversion. Completion of the total synthesis of fusicoauritone was more efficiently rendered by direct oxidation of a mixture of **24** and its C-6 epimer with *tert*-butylhypochlorite in aqueous acetone providing a 40% yield of synthetic **1** which proved to be identical in all respects with optical rotation data and spectroscopic characterizations of the natural substance.[37]

Supplementary Material

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25. The diastereomeric allylic alcohols were separately subjected to the orthoester Claisen conditions leading to the assignment of stereochemistry as described for **8**. Inversion of the undesired alcohol epimer to provide additional quantities of **8** was not feasible.
26. The stereochemistry of the newly formed chiral center (C7) was confirmed via degradation. The γ,δ-unsaturated ester obtained from Claisen rearrangement of **8** was reduced ($LiBH_4$), followed by ozonolysis with a $NaBH_4$ quench to produce (*R*)-2-methylbutane-1,4-diol, $[\alpha]_D^{24}$ +22.6 (c 0.6, $CHCl_3$).Lautens M, Stammers TA. Synthesis 2002;14:1993.
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28. The *trans*-β-hydroxysulfone is distinguished by a large vicinal coupling constant (*J* = 10 Hz) in the proton NMR spectrum of the major product indicating a diaxial disposition of methine hydrogens. Each sulfone diastereomer independently underwent desulfonylation with 6% Na-Hg in methanol to yield identical samples of allylic alcohol.
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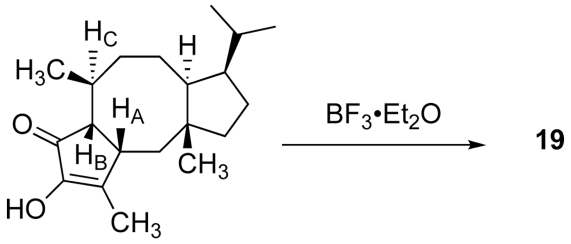
30. Initial Nazarov cyclization attempts also gave varying amounts of isomeric ketone *i*, with tentative stereochemical assignments as shown. This *cis*-fused arrangement is found in naturally occurring ophiobolins. Treatment of *i* with BF_3•Et_2O led to tautomerization to ketone **19**.



i H_B δ 2.92 (J_{AB} = 11.5 Hz, J_{BC} = 5.5 Hz)

31. NMR studies of **19** demonstrated that irradiation of H_B (δ 3.00) gave a 6% nOe enhancement of H_A (δ 2.61) and no nOe was observed for the bridgehead C_{11} methyl substituent. Irradiation of H_A gave an 8% enhancement of H_B (J_{AB} = 6.0 Hz) and induced a negative 3% nOe of the axial H_C (δ 2.85).
32. A reviewer requested some insight into alternative strategies which were explored toward enone **24**. In fact, we also investigated the use of a Pausen–Khand reaction for cyclization of the eight-membered ring as well as the desired cyclopentenone in a single operation. The required alkyne was readily prepared, but the cyclization was not successful in our hands.
33. The *E*-double bond geometry in **22** was established by irradiation of aromatic hydrogens inducing an nOe with the β-H_B.
34. Assignment of stereochemistry for the hydride reduction of **22** was made following treatment with 6% Na-Hg in EtOH which produced the C-4 diastereomeric allylic alcohol as compared with the desulfonylation product from **17**.
35. Cyclopentenone **24** undergoes facile C-6 epimerization and flash silica gel chromatography leads to an incomplete separation of these diastereomers affording fractions of pure **24** for complete characterization.

36. Crystal data for **25**: colorless block, 0.3×0.3×0.2mm, $C_{20}H_{32}O_3$, *M* = 320.47, monoclinic, 12.571(3) Å, *b* = 8.897(2) Å, *c* = 16.858(4) Å, β = 109.545(10)°, *V* = 1776.8(8) $Å^3$, *T* = 108(2) K, space group $P2_1/n$, *Z* = 4, ρ_{calcd} = 1.198 Mg m^{-3}, μ = 0.0781mm^{-1}, $Mo_{K\alpha}$ (λ = 0.71073). A total of 3045 reflections were measured. The final residuals was *R* = 0.0565 with GOF = 1.341 and largest residual peak 0.21 e $Å^{-3}$.

37. Synthetic and natural **1** were identical in all respects. Optical rotation for natural fusicoauritone was recorded as $[\alpha]_D^{20}$ +14.0 (*c* 0.16, $CHCl_3$). Characterization of synthetic **1** is as follows: R_f 0.28 (30% EtOAc/hexanes); $[\alpha]_D^{24}$ +13.3 (*c* 0.21, $CHCl_3$); IR (neat) 3445, 2970, 2935, 2880, 1702, 1468, 1390, 1050, 1020, 975, 955 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.71 (d, *J* = 12.8 Hz, 1H), 2.46 (d, *J* = 18.4 Hz, 1H), 2.27 (d, *J* = 18.4 Hz, 1H), 2.22 (d, *J* = 13.2 Hz, 1H), 2.19-2.10 (m, 3H), 2.05 (s, 1H), 1.73 (s, 3H), 1.71-1.55 (m, 6H), 1.30-1.25 (m, 3H), 1.11 (d, *J* = 7.2 Hz, 3H), 0.90 (d, *J* = 6.4 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.79 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.8, 173.6, 139.6, 83.1, 48.5, 47.2, 46.9, 44.3, 44.0, 40.3, 33.4, 30.2, 28.0, 24.5, 24.4, 22.9, 20.0, 19.5, 17.6, 9.5; MS (CI, NH_3) *m/z* (rel. intensity) 304 (M^+), 179 (100), 137 (80), 95 (72); HRMS (CI, NH_3) calcd for $C_{20}H_{33}O_2$ [M^++1]: 305.2475, found: 305.2471.

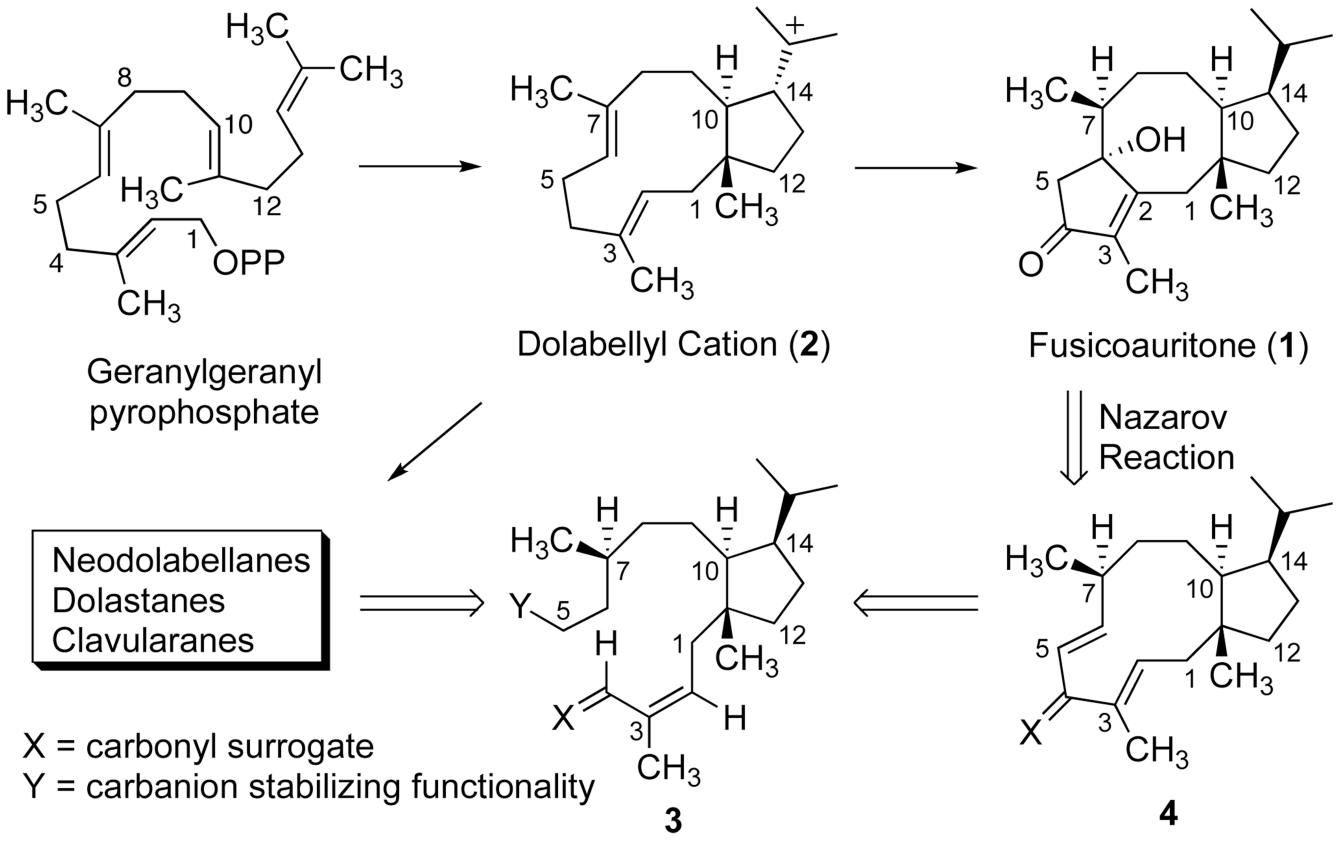
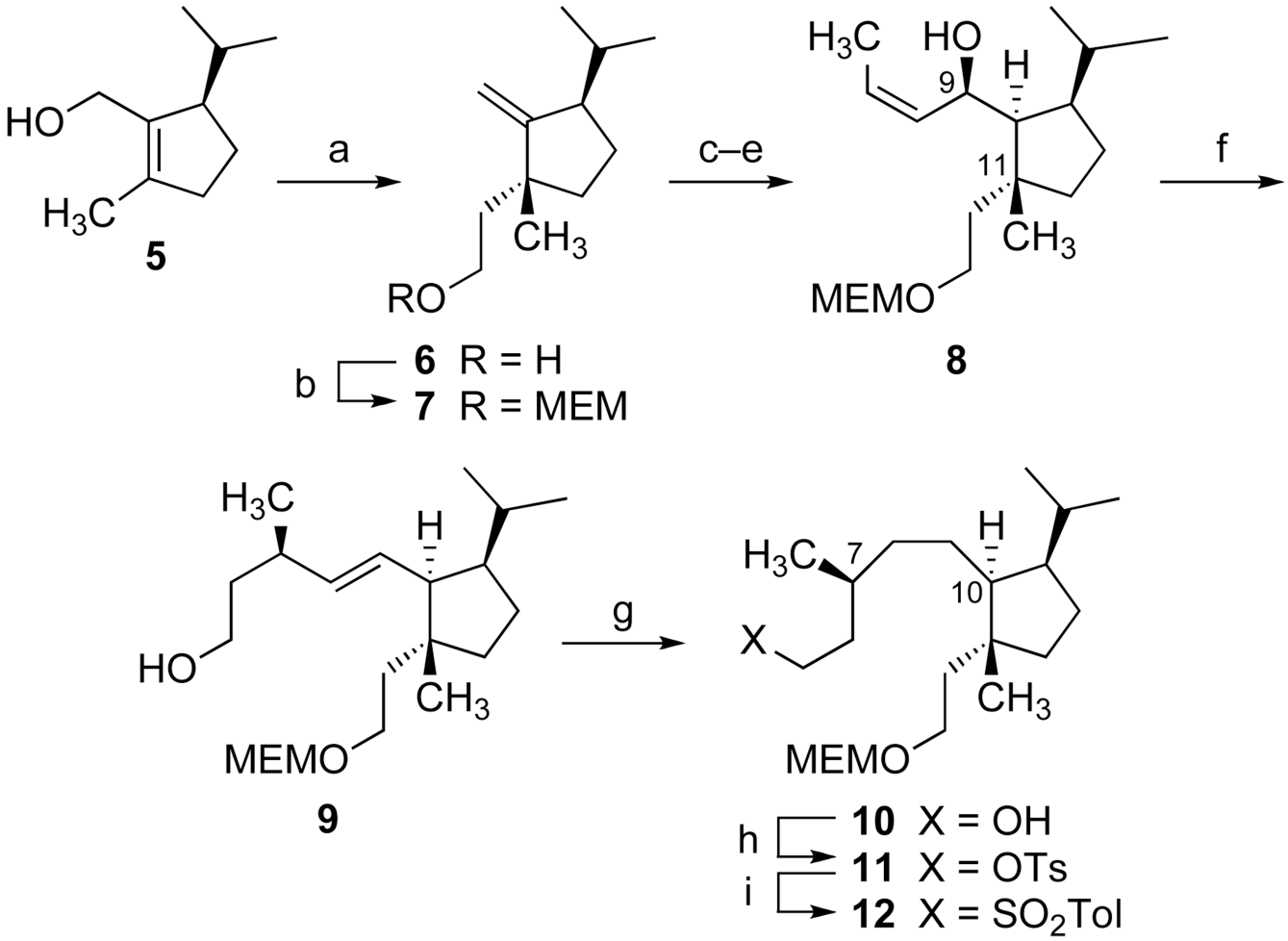
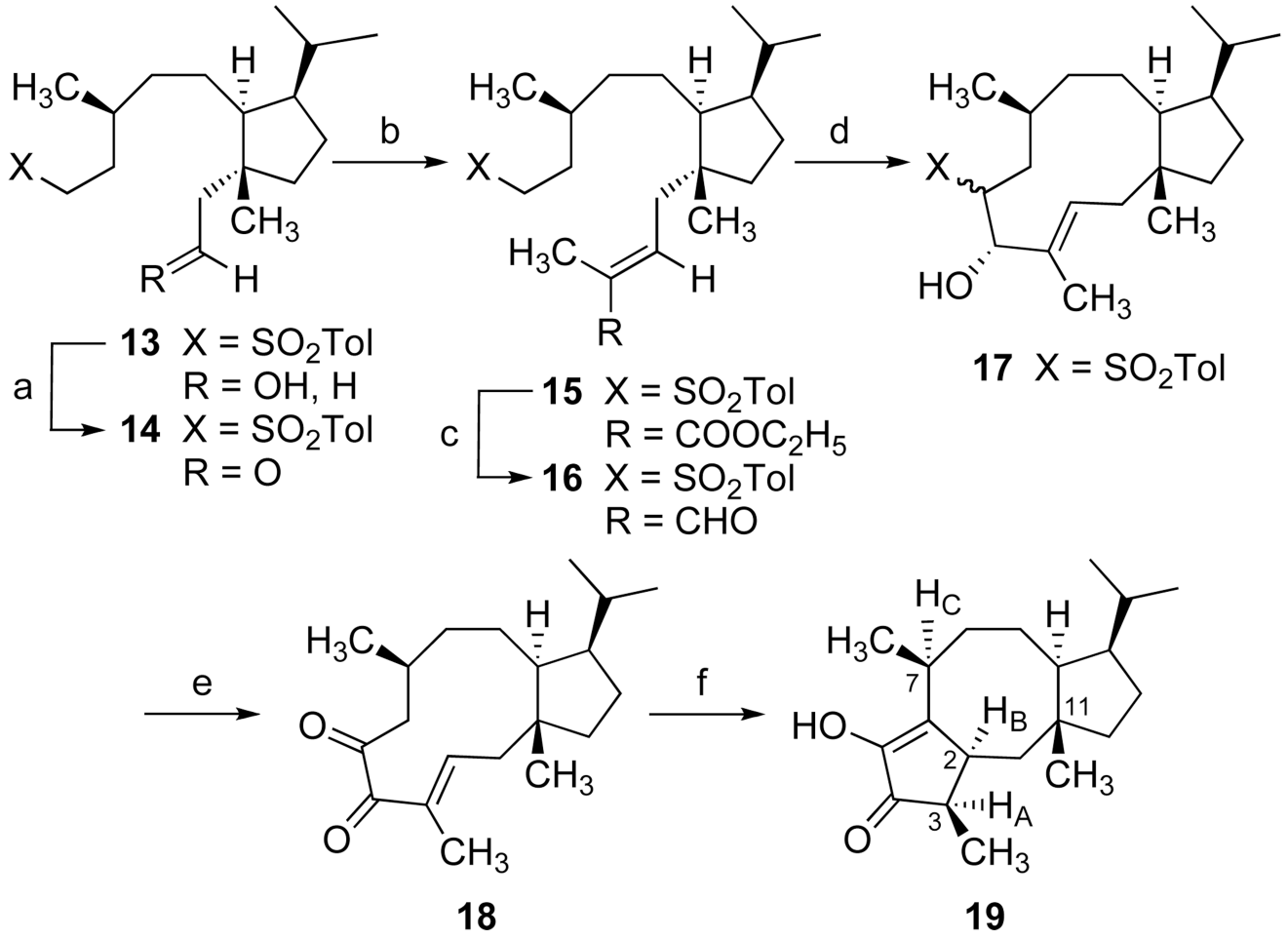


Figure 1.
Merging concepts of biosynthesis with a retrosynthetic design toward **1**.



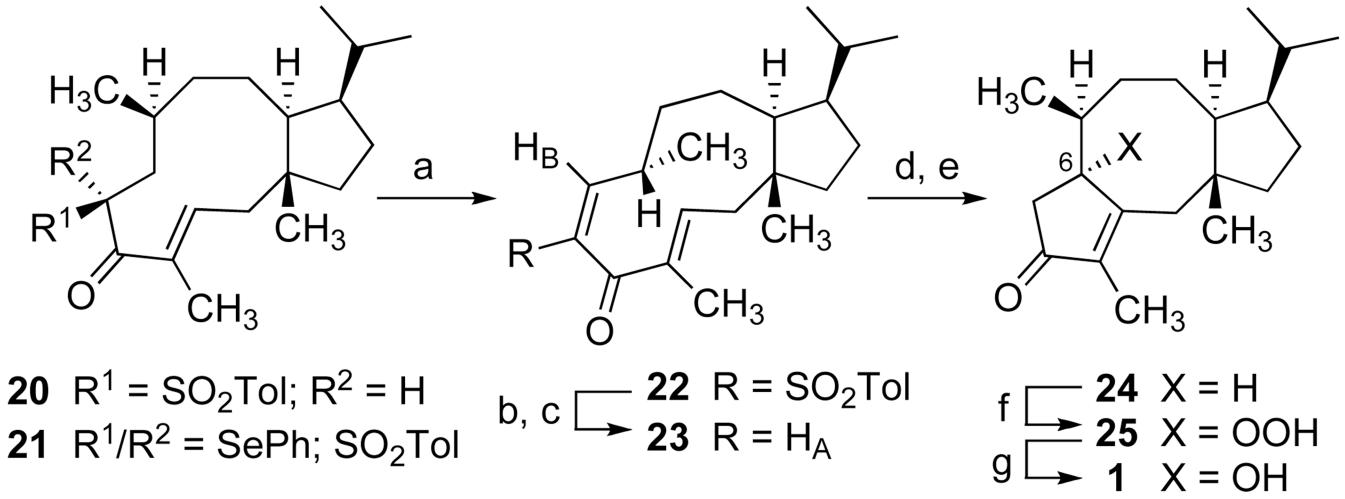
Scheme 1.

[a] $(EtO)_3CCH_3$, H_3CCH_2COOH (cat.), 145 °C, 79%, then $LiAlH_4$, Et_2O, 0 °C, 95%; [b] MEM–Cl, *i*Pr_2NEt, DMAP, CH_2Cl_2, 92%; [c] BH_3•THF, 0 °C, then aq. H_2O_2, NaOH, 75%; [d] $(COCl)_2$, DMSO, CH_2Cl_2 at −78 °C, then Et_3N at −50 °C, 99%; [e] (*Z*)-1-propenyllithium, Et_2O, −50 °C, 65%; [f] $(EtO)_3CCH_3$, H_3CCH_2COOH (cat.), 145 °C; then $LiBH_4$, MeOH, 70%; [g] Na°, HMPA, *t*BuOH, 97%; [h] TsCl, Et_3N, DMAP, CH_2Cl_2, 89%; [i] NaI, $H_3CCOC_2H_5$, reflux, then $NaO_2SC_6H_4CH_3$, DMF, 70 °C, 93%.



Scheme 2.

[a] $(COCl)_2$ DMSO, −78 °C, then Et_3N; [b] (carbethoxyethylidene) triphenylphosphorane, CH_2Cl_2, 22 °C, 96%; [c] DIBAL, CH_2Cl_2, −78 °C, then PCC, CH_2Cl_2, 86%; [d] Add **15** to benzene, sodium *t*-amylate, 35 °C, 5 min, then quench HOAc, 73%; [e] $(COCl_2)$, DMSO, −78 °C, then Et_3N, followed by $K^{+-}OtBu$, THF, 2-[(*p*-chlorophenyl)sulfonyl]-3-(*p*-chlorophenyl)oxaziridine, −78 °C, 85%; [f] BF_3•Et_2O, $ClCH_2CH_2Cl$, reflux, 77%.



Scheme 3.

[a] NaHMDS, THF, −78 °C, PhSeCl, 0 °C, then aq. H_2O_2, 98%; [b] DIBAL, −78 °C, 95%; [c] sodium naphthalide, THF, −78 °C, 1 min, then MnO_2, PhH, 70%; [d] TsOH (cat.), $ClCH_2CH_2Cl$, 92%; [e] *t*BuOCl, aq. acetone, 40%; [f] air oxidation; [g] CH_2Cl_2; aq. $NaHSO_3$ (95%).