

Published in final edited form as:

Angew Chem Int Ed Engl. 2007 ; 46(6): 915–918. doi:10.1002/anie.200603853.

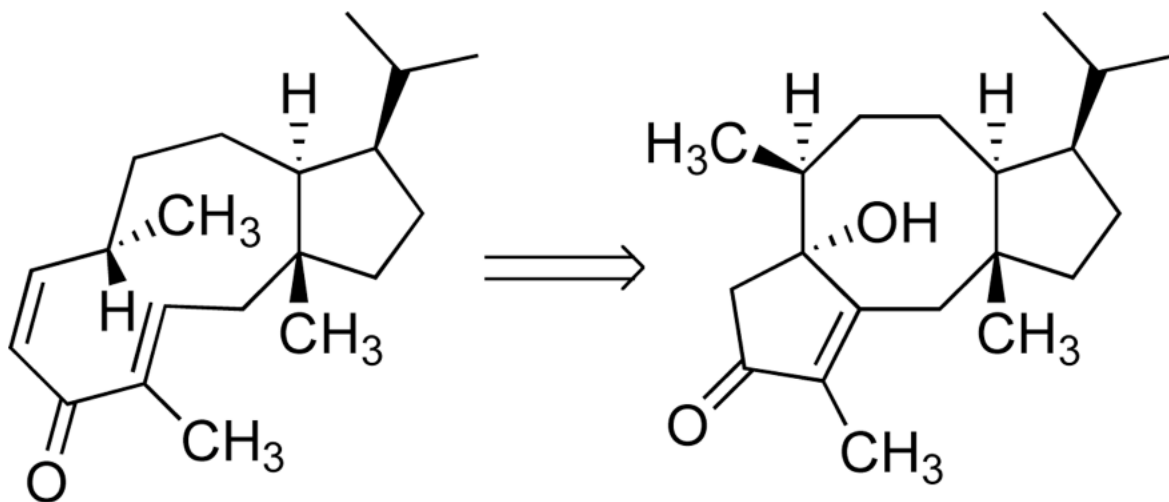
Strategies for the Synthesis of Fusicocanes via Nazarov Reactions of Dolabelladienones. Total Synthesis of (+)- Fusicoauritone**

David R. Williams Leslie A. Robinson C. Richard Nevill Jayachandra P. Reddy

Department of Chemistry, Indiana University, Bloomington, IN 47405-7102 (USA), Fax: (+1) 812-855-8300

David R. Williams: williamd@indiana.edu

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

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

The fusicocanes 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

We thank the National Institutes of Health [National Institute of General Medical Sciences (GM42897)] for support of this research. We also thank Dr. Josef Zapp (Saarland University) for providing us with NMR and MS spectra of authentic **1.

Correspondence to: David R. Williams, williamd@indiana.edu.

Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

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. Fusicoccons 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 fusicocauritone (**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 fusicocauritone (**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 = CH₂OCH₂CH₂OCH₃).

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** [HBF₄; 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 BF₃ 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 fuscocauritone 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]

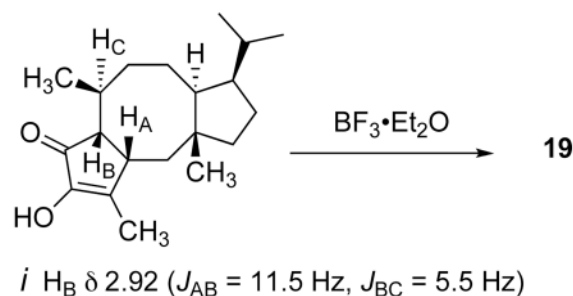
Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Petasis NA, Patane MA. *Tetrahedron* 1992;48:5757.
2. a) Barrow KD, Barton DHR, Chain EB, Ohnsorge UFW, Thomas R. *Chem. Commun* 1968:1198. b) Ballio A, Casinovi CG, D'Alessio V, Grandolini G, Randazzo G, Rossi C. *Experientia* 1974;30:844. c) For recent examples: Kim S, Shin D-S, Lee T, Oh K-B. *J. Nat. Prod* 2004;67:448. [PubMed: 15043428]
3. For a leading reference: Sassa T, Ooi T, Nukina M, Kato N. *Biosci. Biotech. Biochem* 1998;62:1815.
4. Hashimoto T, Tori M, Taira Z, Asakawa Y. *Tetrahedron Lett* 1985;26:6473.
5. Nozoe S, Morisaki M, Tsuda K, Iitaka Y, Takahashi N, Tamura S, Ishibashi K, Shirasaka M. *J. Am. Chem. Soc* 1965;87:4968. [PubMed: 5844472]
6. Iitaka Y, Watanabe I, Harrison IT, Harrison S. *J. Am. Chem. Soc* 1968;90:1092.
7. a) DeBoer B. *Trends Plant Sci* 1997;2:60. b) Asahi K, Honma Y, Hazeki K, Sassa T, Kubohara Y, Sakurai A, Takahashi N. *Biochem. Biophys. Res. Commun* 1997;238:758. [PubMed: 9325163]
8. a) Liu H-J, Wu C-L, Becker H, Zapp J. *Phytochem* 2000;53:845. b) Zapp J, Burkhardt G, Becker H. *Phytochem* 1994;37:787. c) Huneck S, Baxter G, Cameron AF, Connolly JD, Rycroft DS. *Tetrahedron Lett* 1983;24:3787.
9. a) Banjeri A, Jones RB, Mellows G, Phillips L, Sim K-Y. *J. Chem. Soc. Perkin Trans I* 1976:2221. b) For the production of these metabolites in liverwort: Asakawa Y, Lin X, Tori M, Kondo K. *Phytochem* 1990;29:259. c) Williams DR, Heidebrecht RW Jr. *J. Am. Chem. Soc* 2003;125:1843. [PubMed: 12580611] and references therein.
10. Rodriguez AD, González E, Ramirez C. *Tetrahedron* 1998;54:11683.
11. a) Wahlberg I, Eklund A-M, Nishida T, Enzell CR, Berg J-E. *Tetrahedron Lett* 1983;24:843. b) Enoki N, Furusaki A, Suehiro K, Ishida R, Matsumoto T. *Tetrahedron Lett* 1983;24:4341.
12. Williams DR, Coleman PJ, Nevill CR, Robinson LA. *Tetrahedron Lett* 1993;34:7895.
13. a) Williams DR, Coleman PJ, Henry SS. *J. Am. Chem. Soc* 1993;115:11654. b) Williams DR, Coleman PJ. *Tetrahedron Lett* 1995;36:39.
14. Hiersemann M, Helmboldt H. *Top. Curr. Chem* 2005;243:73.
15. For leading references: a) Kato N, Okamoto H, Takeshita H. *Tetrahedron* 1996;52:3921. b) Kato N, Nakanishi K, Takeshita H. *Bull. Chem. Soc. Jpn* 1986;59:1109.
16. Rowley M, Tsukamoto M, Kishi Y. *J. Am. Chem. Soc* 1989;111:2735.
17. a) Boeckman RK Jr, Arvanitis A, Voss ME. *J. Am. Chem. Soc* 1989;111:2737. b) See also: Paquette LA, Wang T-Z, Vo NH. *J. Am. Chem. Soc* 1993;115:1676.
18. a) Jamison TF, Shambayati S, Crowe WE, Schreiber SL. *J. Am. Chem. Soc* 1994;116:5505. b) Paquette LA, Sun L-Q, Friedrich D, Savage PB. *Tetrahedron Lett* 1997;38:195.
19. a) Mehta G, Krishnamurthy N. *Chem. Commun* 1986:1319. b) Dauben WG, Warshawsky AM. *J. Org. Chem* 1990;55:3075. c) Snider BB, Yang K. *J. Org. Chem* 1992;57:3615. d) Rigby JH, McGuire T, Senanayake C, Khemani K. *J. Chem. Soc. Perkin Trans. I* 1994:3449. e) Chase CE, Bender JA, West FG. *Synlett* 1996:1173. f) Wender PA, Nuss JM, Smith DB, Suárez-Sobrinó A, Vågberg J, Decosta D, Bordner J. *J. Org. Chem* 1997;62:4908. g) Sieburth SM, McGee KF Jr, Al-Tel TH. *J. Am. Chem. Soc* 1998;120:587. h) Blake AJ, Highton AJ, Majid TN, Simpkins NS. *Org. Lett* 1999;1:1787. i) Bader SJ, Snapper ML. *J. Am. Chem. Soc* 2005;127:1201. [PubMed: 15669859]
20. Tius MA. *Eur. J. Org. Chem* 2005:2193.
21. Using slight modifications of a known procedure, (*S*)-limonene oxide was converted into **5** in 50% overall yield. White JD, Ruppert JF, Avery MA, Torii S, Nokami J. *J. Am. Chem. Soc* 1981;103:1813.
22. a) Mehta G, Krishnamurthy N. *Tetrahedron Lett* 1987;28:5945. b) For a related [2,3]-sigmatropic rearrangement from **5**: Wright J, Drtina GJ, Roberts RA, Paquette LA. *J. Am. Chem. Soc* 1988;110:5806.
23. Mancuso AJ, Huang S-L, Swern DJ. *J. Org. Chem* 1978;43:2480.

24. Linstrumelle, G.; Krieger, JK.; Whitesides, GM. *Organic Synthesis*. Masamune, S., editor. Vol. Vol. 55. New York: J. Wiley and Sons; 1976. p. 103-113.
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 (LiBH₄), followed by ozonolysis with a NaBH₄ quench to produce (*R*)-2-methylbutane-1,4-diol, $[\alpha]_D^{24} +22.6$ (c 0.6, CHCl₃). Lautens M, Stammers TA. *Synthesis* 2002;14:1993.
27. Whitesides GM, Ehmann WJ. *J. Org. Chem* 1970;35:3565.
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.
29. For a leading reference: Williams DR, Robinson LA, Amato GS, Osterhout MH. *J. Org. Chem* 1992;57:3740.
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 BF₃•Et₂O led to tautomerization to ketone **19**.



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 C₁₁ 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, C₂₀H₃₂O₃, *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) Å³, *T* = 108(2) K, space group *P*2₁/*n*, *Z* = 4, ρ_{calcd} = 1.198 Mg m⁻³, μ = 0.0781mm⁻¹, MoKα (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 [α]_D²⁰ +14.0 (*c* 0.16, CHCl₃). Characterization of synthetic **1** is as follows: R_f 0.28 (30% EtOAc/hexanes); [α]_D²⁴ +13.3 (*c* 0.21, CHCl₃); IR (neat) 3445, 2970, 2935, 2880, 1702, 1468, 1390, 1050, 1020, 975, 955 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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, NH₃) *m/z* (rel. intensity) 304 (M⁺), 179 (100), 137 (80), 95 (72); HRMS (CI, NH₃) calcd for C₂₀H₃₃O₂ [M⁺+1]: 305.2475, found: 305.2471.

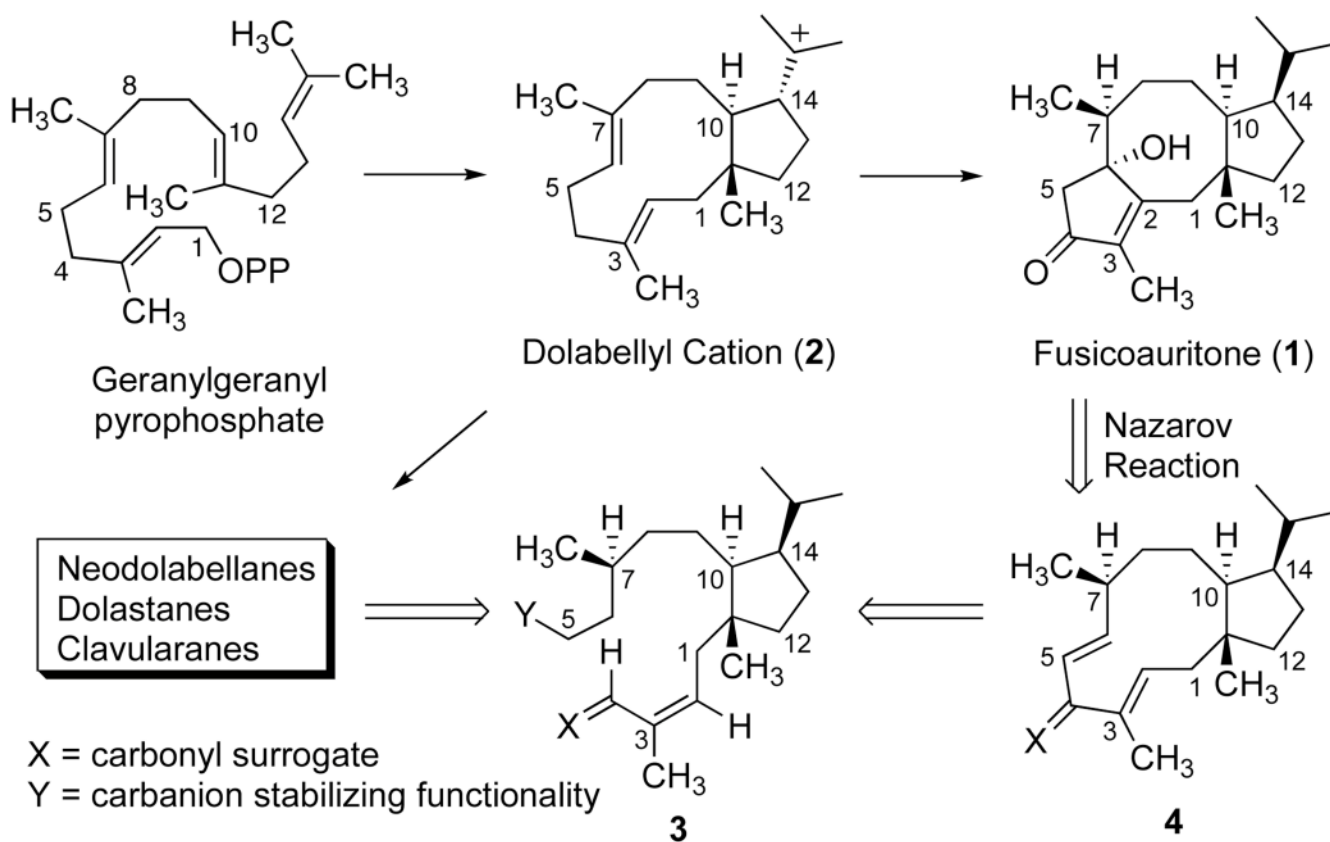
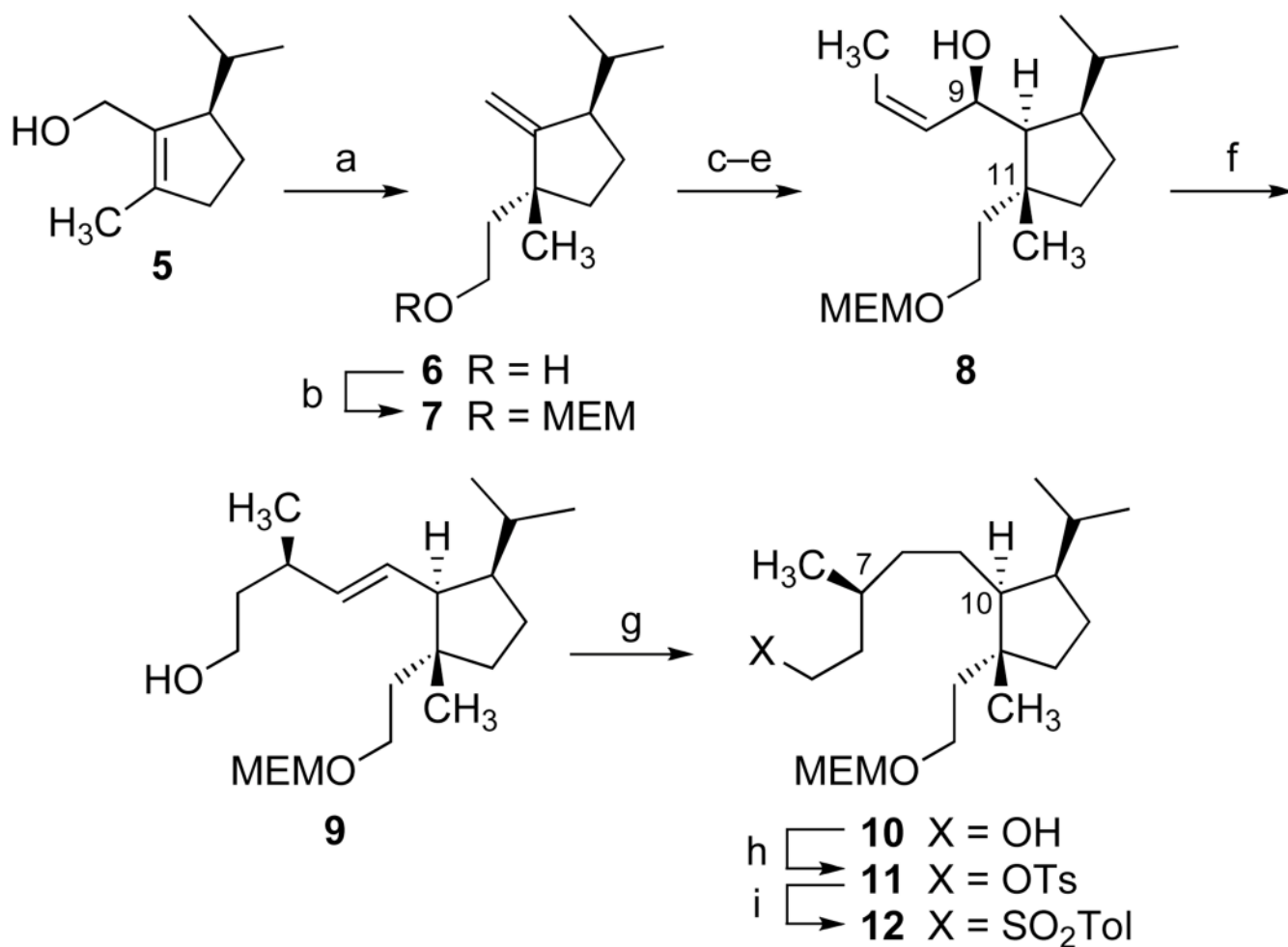
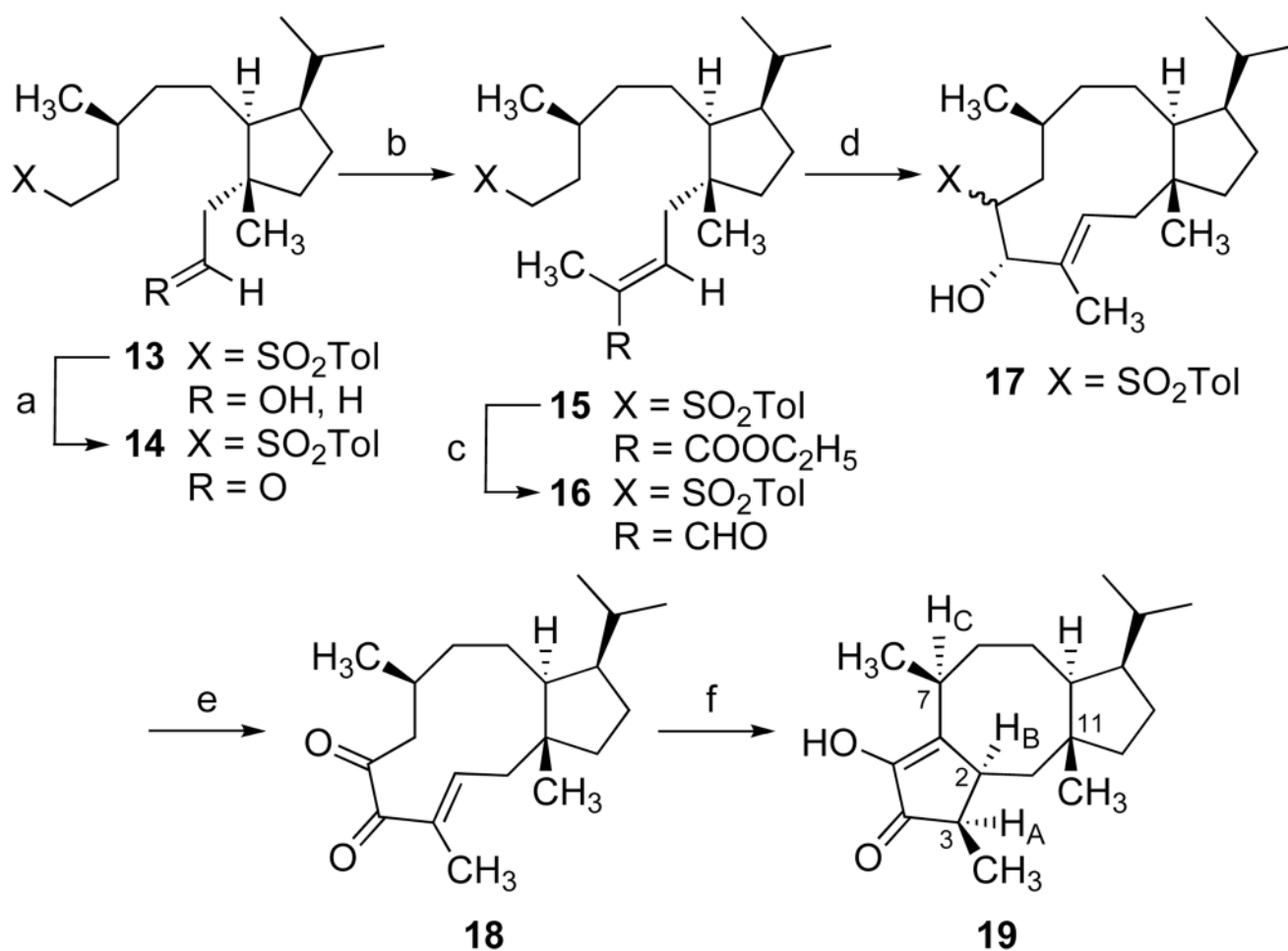


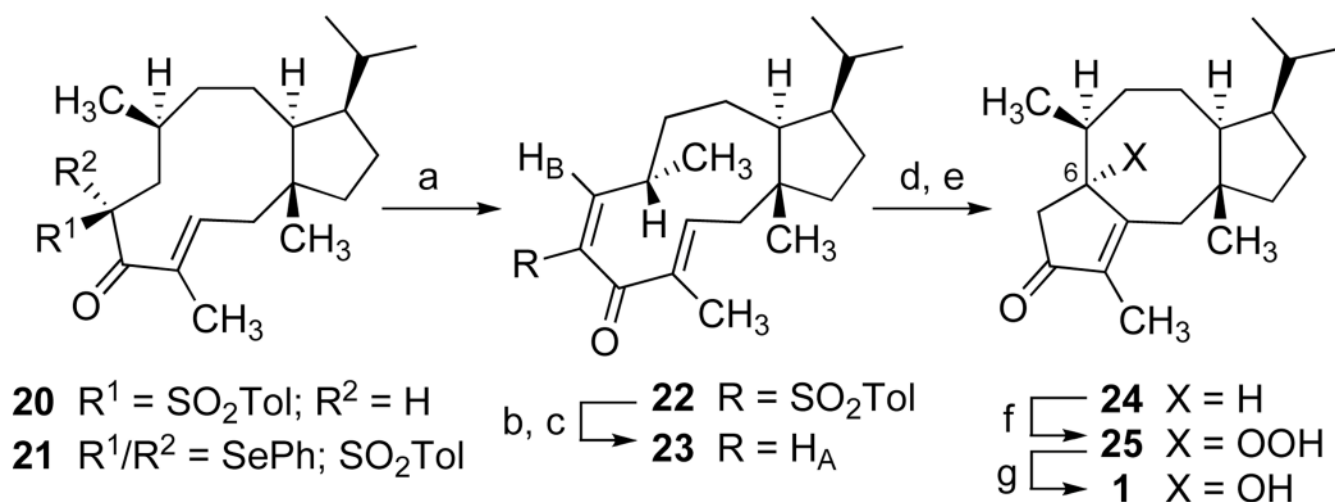
Figure 1. Merging concepts of biosynthesis with a retrosynthetic design toward **1**.

**Scheme 1.**

[a] (EtO)₃CCH₃, H₃CCH₂COOH (cat.), 145 °C, 79%, then LiAlH₄, Et₂O, 0 °C, 95%; [b] MEM-Cl, *i*Pr₂NEt, DMAP, CH₂Cl₂, 92%; [c] BH₃•THF, 0 °C, then aq. H₂O₂, NaOH, 75%; [d] (COCl)₂, DMSO, CH₂Cl₂ at -78 °C, then Et₃N at -50 °C, 99%; [e] (*Z*)-1-propenyllithium, Et₂O, -50 °C, 65%; [f] (EtO)₃CCH₃, H₃CCH₂COOH (cat.), 145 °C; then LiBH₄, MeOH, 70%; [g] Na⁺, HMPA, *t*BuOH, 97%; [h] TsCl, Et₃N, DMAP, CH₂Cl₂, 89%; [i] NaI, H₃CCOC₂H₅, reflux, then NaO₂SC₆H₄CH₃, DMF, 70 °C, 93%.

**Scheme 2.**

[a] (COCl)₂, DMSO, -78 °C, then Et₃N; [b] (carbethoxyethylidene) triphenylphosphorane, CH₂Cl₂, 22 °C, 96%; [c] DIBAL, CH₂Cl₂, -78 °C, then PCC, CH₂Cl₂, 86%; [d] Add **15** to benzene, sodium *t*-amylate, 35 °C, 5 min, then quench HOAc, 73%; [e] (COCl)₂, DMSO, -78 °C, then Et₃N, followed by K⁺O⁻tBu, THF, 2-[(*p*-chlorophenyl)sulfonyl]-3-(*p*-chlorophenyl)oxaziridine, -78 °C, 85%; [f] BF₃•Et₂O, ClCH₂CH₂Cl, reflux, 77%.

**Scheme 3.**

[a] NaHMDS, THF, $-78\text{ }^\circ\text{C}$, PhSeCl, $0\text{ }^\circ\text{C}$, then aq. H_2O_2 , 98%; [b] DIBAL, $-78\text{ }^\circ\text{C}$, 95%;
 [c] sodium naphthalide, THF, $-78\text{ }^\circ\text{C}$, 1 min, then MnO_2 , PhH, 70%; [d] TsOH (cat.),
 $\text{ClCH}_2\text{CH}_2\text{Cl}$, 92%; [e] *t*BuOCl, aq. acetone, 40%; [f] air oxidation; [g] CH_2Cl_2 ; aq.
 NaHSO_3 (95%).