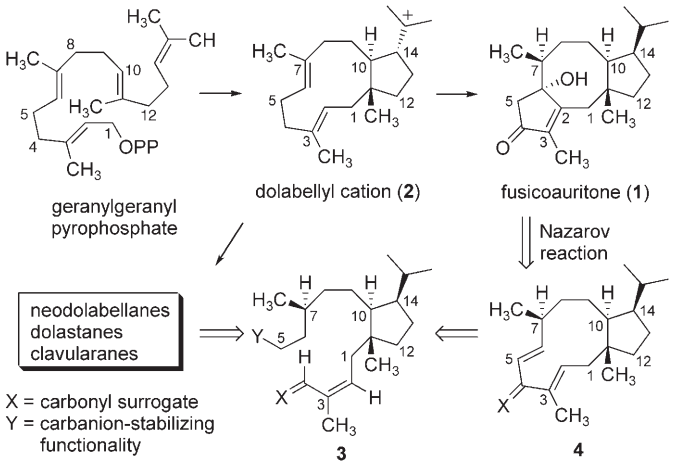
Diterpene Total Synthesis

DOI: 10.1002/ange.200603853

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

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

The fusicoccanes are representative of a family of terpenes that feature a fused 5-8-5 carbocyclic skeleton.[1] Substances exhibiting this structural motif have been isolated from a variety of sources including the 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**) (Scheme 1).[8] The initial carbocyclization of geranylgeranyl pyrophosphate yields the dolabellanes, a widely distributed class of marine natural products, by means of 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]



Scheme 1. Merging concepts of biosynthesis with a retrosynthetic design toward **1**. PP = pyrophosphate.

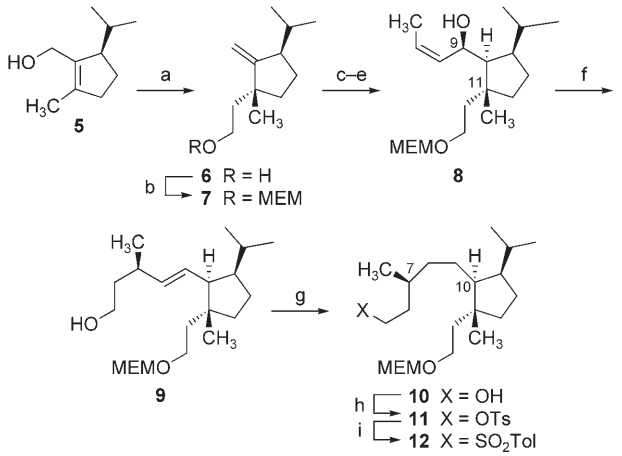
Recognizing the central importance of the dolabellane nucleus in the biosynthesis of several families of diterpenes, we have examined strategies for its preparation,[12] and our efforts have described stereocontrolled transannular reactions to dolastanes and relevant rearrangement products.[13] Recently, 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 et al. [16] and Boeckman et al. [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 (Scheme 1), which features formation of an eleven-membered ring by means of an intramolecular alkylation from **3** for utilization of the Nazarov reaction[20] of 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 (C10, C11, and C14). This task was undertaken (Scheme 2) beginning with optically active cyclopentenyl alcohol **5**[21] by Claisen rearrangement of the Johnson orthoester. 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 diastereomer at C10, and low-temperature Swern oxidation[23] gave an aldehyde that was directly utilized without chromatographic purification to avoid epimerization. Our efforts to extend the alkyl chain and introduce the remote stereocenter at C7 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]

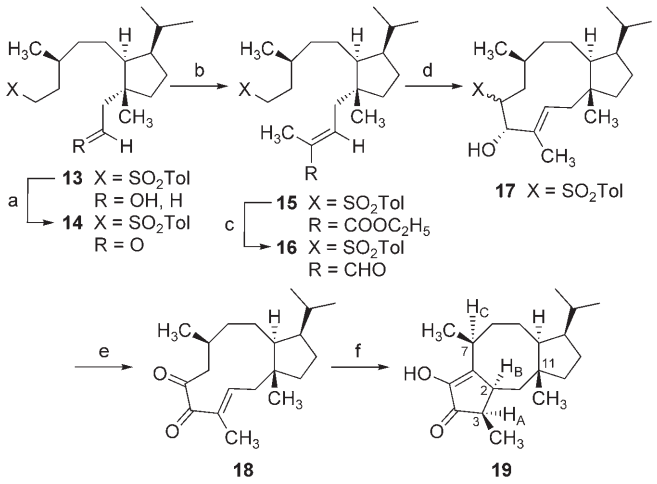
[*] Dr. D. R. Williams, L. A. Robinson, Dr. C. R. Nevill, Dr. J. P. Reddy
Department of Chemistry
Indiana University
Bloomington, IN 47405-7102 (USA)
Fax: (+1) 812-855-8300
E-mail: williamd@indiana.edu

[**] 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**.

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



Scheme 2. Reagents and conditions: a) $(EtO)_3CCH_3$, H_3CCH_2COOH (cat.), 145 °C, 79%, then $LiAlH_4$, Et_2O, 0 °C, 95%; b) MEM-Cl, iPr_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^0, 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%. DMAP = *N*,*N*-dimethylaminopyridine, DMSO = dimethyl sulfoxide, HMPA = hexamethylphosphoramide, Ts = toluene-4-sulfonyl, DMF = *N*,*N*-dimethylformamide.

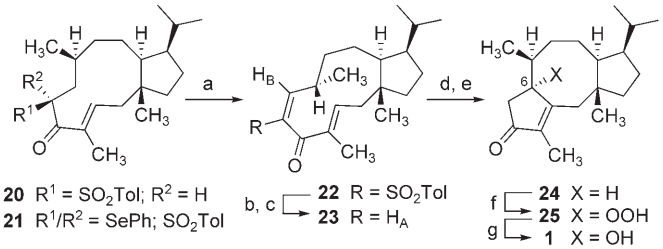


Scheme 3. Reagents and conditions: a) $(COCl)_2$, DMSO, −78 °C, then Et_3N; b) (carbethoxyethylidene)triphenylphosphorane, CH_2Cl_2, 22 °C, 96%; c) DIBAL, CH_2Cl_2, −78 °C, then PCC, CH_2Cl_2, 86%; d) **15** was added to benzene, sodium *t*-amylate, 35 °C, 5 min, reaction was then quenched with HOAc, 73%; e) $(COCl_2)$, DMSO, −78 °C, then Et_3N, followed by KO*t*Bu, THF, 2-[(*p*-chlorophenyl)sulfonyl]-3-(*p*-chlorophenyl)oxaziridine, −78 °C, 85%; f) BF_3·Et_2O, $ClCH_2CH_2Cl$, reflux, 77%. DIBAL = diisobutylaluminum hydride, PCC = pyridinium chlorochromate.

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 two steps).[26] Subsequent reduction of the *E* double bond 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 olefin with an endocyclic (C10–C14) tetrasubstituted double bond. 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 by deprotection of **12** (HBF_4; aq. MeOH (85%)), and oxidation followed by Wittig olefination gave the ester **15** with the *E* double bond (Scheme 3). 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** (d.r. 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 dehydroelimination 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 diketone **18** (85%). Although enolic tautomerization is not evident in the ^1H NMR spectroscopic data of **18**, treatment with BF_3 etherate catalyzed formation of the putative divinylketone intermediate for facile Nazarov cyclization, yielding α-hydroxycyclopentenone **19**.[30] Characterization of **19** with extensive 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 methyl group (at C11) and the newly created α-methylketone.[31]

To effect ring contraction of the dolabelladiene precursor through 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 4, phenylselenation of α-sulfonyl ketone **20** (major product from **17**, Scheme 3) gave **21** for immediate oxidation,



Scheme 4. Reagents and conditions: 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%). HMDS = 1,1,1,3,3,3-hexamethyldisilazane.

yielding exclusively the α,β-unsaturated sulfone **22** with *E* configuration.[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 a hydrogen atom. 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 the vicinal coupling constant ($J_{AB} = 10.7$ Hz) in the ^{1}H NMR spectrum. Finally, treatment of **23** under protic or Lewis acid conditions resulted in a smooth Nazarov reaction to **24** (and its C6 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 by 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 C6 epimer with *tert*-butylhypochlorite in aqueous acetone providing a 40 % yield of synthetic **1**, which proved to be identical to the natural substance in all respects (optical rotation data and spectroscopic characterizations).[37]

Received: September 19, 2006
Revised: October 20, 2006
Published online: December 15, 2006

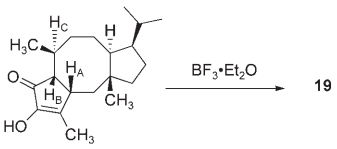
Keywords: fusicoccanes · Julia condensation · medium-ring compounds · Nazarov cyclization · total synthesis

[1] N. A. Petasis, M. A. Patane, *Tetrahedron* **1992**, *48*, 5757.
[2] a) K. D. Barrow, D. H. R. Barton, E. B. Chain, U. F. W. Ohnsorge, R. Thomas, *J. Chem. Soc. Chem. Commun.* **1968**, 1198; b) A. Ballio, C. G. Casinovi, V. D'Alessio, G. Grandolini, G. Randazzo, C. Rossi, *Experimentia* **1974**, *30*, 844; c) For recent examples: S. Kim, D.-S. Shin, T. Lee, K.-B. Oh, *J. Nat. Prod.* **2004**, *67*, 448.
[3] For a leading reference: T. Sassa, T. Ooi, M. Nukina, N. Kato, *Biosci. Biotechnol. Biochem.* **1998**, *62*, 1815.
[4] T. Hashimoto, M. Tori, Z. Taira, Y. Asakawa, *Tetrahedron Lett.* **1985**, *26*, 6473.
[5] S. Nozoe, M. Morisaki, K. Tsuda, Y. Iitaka, N. Takahashi, S. Tamura, K. Ishibashi, M. Shirasaka, *J. Am. Chem. Soc.* **1965**, *87*, 4968.
[6] Y. Iitaka, I. Watanabe, I. T. Harrison, S. Harrison, *J. Am. Chem. Soc.* **1968**, *90*, 1092.
[7] a) B. DeBoer, *Trends Plant Sci.* **1997**, *2*, 60; b) K. Asahi, Y. Honma, K. Hazeki, T. Sassa, Y. Kubohara, A. Sakurai, N. Takahashi, *Biochem. Biophys. Res. Commun.* **1997**, *238*, 758.
[8] a) H.-J. Liu, C.-L. Wu, H. Becker, J. Zapp, *Phytochemistry* **2000**, *53*, 845; b) J. Zapp, G. Burkhardt, H. Becker, *Phytochemistry* **1994**, *37*, 787; c) S. Huneck, G. Baxter, A. F. Cameron, J. D. Connolly, D. S. Rycroft, *Tetrahedron Lett.* **1983**, *24*, 3787.
[9] a) A. Banjeri, R. B. Jones, G. Mellows, L. Phillips, K.-Y. Sim, *J. Chem. Soc. Perkin Trans. 1* **1976**, 2221; b) For the production of these metabolites in liverwort: Y. Asakawa, X. Lin, M. Tori, K. Kondo, *Phytochemistry* **1990**, *29*, 259; c) D. R. Williams, R. W. Heidebrecht, Jr., *J. Am. Chem. Soc.* **2003**, *125*, 1843, and references therein.
[10] A. D. Rodriguez, E. González, C. Ramirez, *Tetrahedron* **1998**, *54*, 11683.
[11] a) I. Wahlberg, A.-M. Eklund, T. Nishida, C. R. Enzell, J.-E. Berg, *Tetrahedron Lett.* **1983**, *24*, 843; b) N. Enoki, A. Furusaki, K. Suehiro, R. Ishida, T. Matsumoto, *Tetrahedron Lett.* **1983**, *24*, 4341.
[12] D. R. Williams, P. J. Coleman, C. R. Nevill, L. A. Robinson, *Tetrahedron Lett.* **1993**, *34*, 7895.
[13] a) D. R. Williams, P. J. Coleman, S. S. Henry, *J. Am. Chem. Soc.* **1993**, *115*, 11654; b) D. R. Williams, P. J. Coleman, *Tetrahedron Lett.* **1995**, *36*, 39.
[14] M. Hiersemann, H. Helmboldt, *Top. Curr. Chem.* **2005**, *243*, 73.
[15] For leading references: a) N. Kato, H. Okamoto, H. Takeshita, *Tetrahedron* **1996**, *52*, 3921; b) N. Kato, K. Nakanishi, H. Takeshita, *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1109.
[16] M. Rowley, M. Tsukamoto, Y. Kishi, *J. Am. Chem. Soc.* **1989**, *111*, 2735.
[17] a) R. K. Boeckman, Jr., A. Arvanitis, M. E. Voss, *J. Am. Chem. Soc.* **1989**, *111*, 2737; b) See also: L. A. Paquette, T.-Z. Wang, N. H. Vo, *J. Am. Chem. Soc.* **1993**, *115*, 1676.
[18] a) T. F. Jamison, S. Shambayati, W. E. Crowe, S. L. Schreiber, *J. Am. Chem. Soc.* **1994**, *116*, 5505; b) L. A. Paquette, L.-Q. Sun, D. Friedrich, P. B. Savage, *Tetrahedron Lett.* **1997**, *38*, 195.
[19] a) G. Mehta, N. Krishnamurthy, *J. Chem. Soc. Chem. Commun.* **1986**, 1319; b) W. G. Dauben, A. M. Warshawsky, *J. Org. Chem.* **1990**, *55*, 3075; c) B. B. Snider, K. Yang, *J. Org. Chem.* **1992**, *57*, 3615; d) J. H. Rigby, T. McGuire, C. Senanayake, K. Khemani, *J. Chem. Soc. Perkin Trans. 1* **1994**, 3449; e) C. E. Chase, J. A. Bender, F. G. West, *Synlett* **1996**, 1173; f) P. A. Wender, J. M. Nuss, D. B. Smith, A. Suárez-Sobrino, J. Vågberg, D. Decosta, J. Bordner, *J. Org. Chem.* **1997**, *62*, 4908; g) S. M. Sieburth, K. F. McGee, Jr., T. H. Al-Tel, *J. Am. Chem. Soc.* **1998**, *120*, 587; h) A. J. Blake, A. J. Highton, T. N. Majid, N. S. Simpkins, *Org. Lett.* **1999**, *1*, 1787; i) S. J. Bader, M. L. Snapper, *J. Am. Chem. Soc.* **2005**, *127*, 1201.
[20] M. A. Tius, *Eur. J. Org. Chem.* **2005**, 2193.
[21] By slight modification of a known procedure, (*S*)-limonene oxide was converted into **5** in 50 % overall yield. J. D. White, J. F. Ruppert, M. A. Avery, S. Torii, J. Nokami, *J. Am. Chem. Soc.* **1981**, *103*, 1813.
[22] a) G. Mehta, N. Krishnamurthy, *Tetrahedron Lett.* **1987**, *28*, 5945; b) For a related [2,3] sigmatropic rearrangement from **5**: J. Wright, G. J. Drtina, R. A. Roberts, L. A. Paquette, *J. Am. Chem. Soc.* **1988**, *110*, 5806.
[23] A. J. Mancuso, S.-L. Huang, D. J. Swern, *J. Org. Chem.* **1978**, *43*, 2480.
[24] G. Linstrumelle, J. K. Krieger, G. M. Whitesides in *Organic Synthesis*, *Vol. 55* (Ed.: S. Masamune), Wiley, New York, **1976**, pp. 103–113.
[25] The diastereomeric allylic alcohols were separately subjected to Johnson 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 by 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, $[\alpha]_D^{24} = +22.6$ ($c = 0.6$, $CHCl_3$). M. Lautens, T. A. Stammers, *Synthesis* **2002**, *14*, 1993.
[27] G. M. Whitesides, W. J. Ehmann, *J. Org. Chem.* **1970**, *35*, 3565.
[28] The *trans*-β-hydroxysulfone is distinguished by a large vicinal coupling constant ($J = 10$ Hz) in the ^{1}H 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: D. R. Williams, L. A. Robinson, G. S. Amato, M. H. Osterhout, *J. Org. Chem.* **1992**, *57*, 3740.

[30] Initial attempts at the Nazarov cyclization also gave varying amounts of the isomeric ketone shown below, with tentative stereochemical assignments labeled as shown. This *cis*-fused arrangement is found in naturally occurring ophiobolins. Treatment of the isomeric ketone with $BF_3{\cdot}Et_2O$ led to tautomerization to ketone **19**.



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

[31] NMR studies of **19** demonstrated that irradiation of H_B ($\delta =$ 3.00 ppm) gave a 6% nOe enhancement of H_A ($\delta = 2.61$ ppm) and no nOe was observed for the methyl substituent at the bridgehead (C11). Irradiation of H_A gave an 8% enhancement of the signal for H_B ($J_{AB} = 6.0$ Hz) and induced a negative 3% nOe of the axial H_C ($\delta = 2.85$ ppm).

[32] A reviewer requested some insight into alternative strategies 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 the aromatic protons of the tolyl group which induced an nOe with the adjacent 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 allylic alcohols diastereomeric at C4, and these were compared with the desulfonylation product from **17**.

[35] Cyclopentenone **24** undergoes facile C6 epimerization. Flash silica gel chromatography led to an incomplete separation of these diastereomers, which afforded fractions of pure **24** for complete characterization.

[36] Crystal data for **25**: colorless block, $0.3 \times 0.3 \times 0.2$ mm, $C_{20}H_{32}O_3$, $M_w = 320.47$, monoclinic, $a = 12.571(3)$, $b = 8.897(2)$, $c =$ 16.858(4) Å, $\beta = 109.545(10)°$, $V = 1776.8(8)$ Å^3, $T = 108(2)$ K, space group $P2_1/n$, $Z = 4$, $\rho_{calcd} = 1.198$ Mg m^{-3}, $\mu = 0.0781$ mm^{-1}, $Mo_{K\alpha}$ ($\lambda = 0.71073$). 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}. CCDC-624501 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[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**: $R_f = 0.28$ (30% EtOAc/hexanes); $[\alpha]_D^{24} = +13.3$ ($c = 0.21$, $CHCl_3$); IR (neat): $\tilde{\nu} = 3445$, 2970, 2935, 2880, 1702, 1468, 1390, 1050, 1020, 975, 955 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.71$ (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 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 207.8$, 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 ppm; 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.

