Synthesis of Acuminolide and 17-*O*-Acetylacuminolide from (+)-Sclareolide

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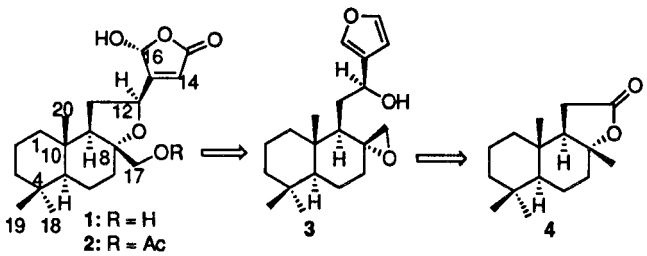
The synthesis of natural acuminolide and 17-*O*-acetylacuminolide is reported. Commerically available (+)-sclareolide was converted to epoxy alcohol **3**, which upon acid-catalyzed cyclization afforded tricycle **14**. Reaction of **14** with $^1O_2$ in the presence of a hindered base gave an inseparable mixture of acuminolide **1a** and 16-epiacuminolide **1b** in a 70:30 ratio. Chromatographic separation of the diacetates of **1a** and **1b** afforded pure **18a** and **18b**. An analogous reaction sequence was used in the synthesis of 17-*O*-acetylacuminolide (**2a**) and 16-*epi*-17-*O*-acetylacuminolide (**2b**).

Introduction

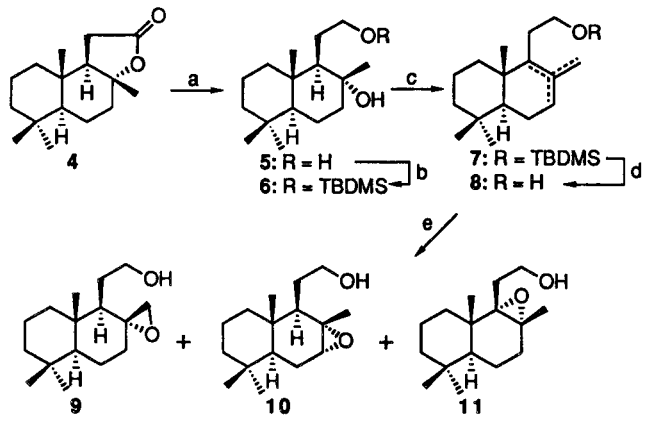
Acuminolide (**1**) and 17-*O*-acetylacuminolide (**2**) are novel cytotoxic labdane diterpenoids recently isolated[1] from the stem bark of *Neouvaria acuminatissima*. Both compounds were shown to possess cytotoxic activity in human cancer cell lines. Compound **1** displayed activity against melanoma (Me12), and **2** was active against prostate (LNCaP) cells. These compounds contain both a β-substituted γ-hydroxybutenolide group and an 8α,-12-epoxy moiety as key components in their structures. The control of the crucial stereogenic centers at C-8 and C-12 in these labdanoids coupled with the timely introduction of the incorporated functional groups, and the potential biological applications of these compounds make them interesting synthetic targets.



Results and Discussion

In considering an optically active approach to acuminolide (**1**), it was anticipated that commercially available (+)-sclareolide (**4**) would be used to construct the chiral centers at C-5, -9, and -10 and that **4** would also serve as an entry to the desired epoxy alcohol **3**, which in turn would be converted to the acuminolide skeleton. The crucial γ-hydroxybutenolide group would then be introduced in the last step of the synthesis via a singlet photooxygenation reaction.

Scheme 1[a]



[a] Key: (a) LAH; THF, Δ; (b) TBDMSCl, Et_3N, 4-DMAP, CH_2CL_2; (c) 12-crown-4, *n*-BuLi, −78 °C; then CF_3SO_2Cl; followed by 4-DMAP, −78 °C to rt (overnight); (d) *n*-Bu_4NF, THF, 0 °C to rt; (e) *m*-CPBA, CH_2Cl_2, 0 °C to rt.

Following this approach, the synthesis of the key synthon **3** is detailed below. Hydride reduction of (+)-sclareolide with LAH (Scheme 1) gave diol **5**[2] in quantitative yield. Selective protection of the less hindered primary alcohol in the presence of the tertiary alcohol was effected with TBDMSCl[3] in the presence of Et_3N and 4-DMAP[4] to afford **6**[5] (98%). Treatment of **6** with *n*-BuLi in the presence of 12-crown-4 followed by reaction of the intermediate alkoxide with trifluoromethanesulfonyl chloride and subsequent reaction of the intermediate sulfonate with 4-DMAP (−78 °C → rt) afforded a 42% yield of an inseparable mixture of exo and endo silyl ethers **7** along with an inseparable mixture of alcohols **8** in 38% yield, after chromatography. Desilylation of **7** with

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(1) Lee, I.-S.; Ma, X.; Chai, H.-B.; Madulid, D. A.; Lamont, R. B.; O'Neill, M. J.; Besterman, J. M.; Farnsworth, N. R.; Soejarto, D. D.; Cordell, G. A.; Pezzuto, J. M.; Kinghorn, A. D. *Tetrahedron* **1995**, *51*, 21.
(2) Hinder, M.; Stoll, M. *Helv. Chem. Acta* **1950**, *33*, 1308.
(3) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(4) Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, 99.
(5) Chackalamannil, S.; Wang, Y.; Xia, Y.; Czarniecki, M. *Tetrahedron Lett.* **1995**, *36*, 5315.

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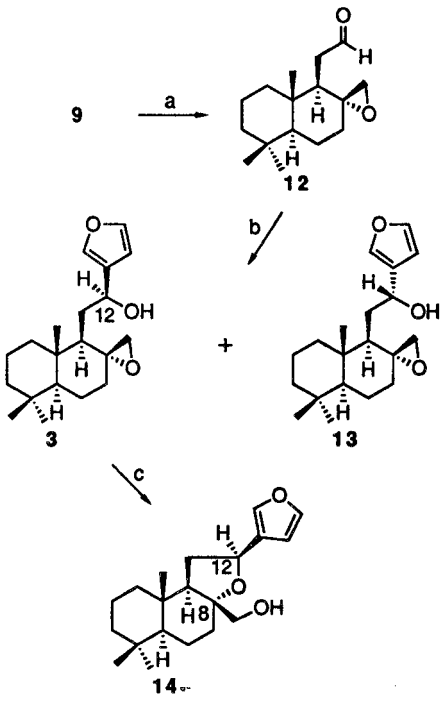
Scheme 2[a]



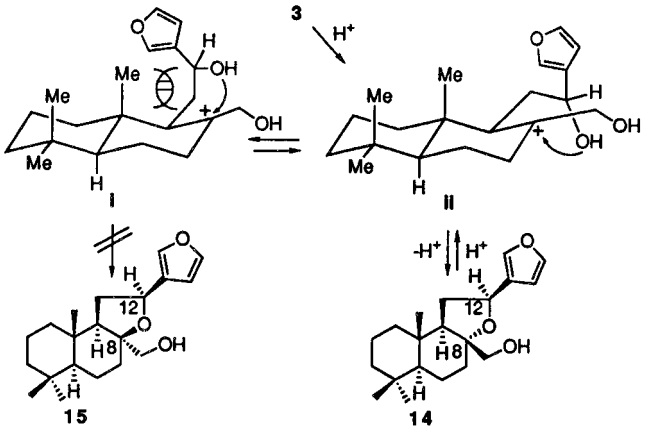
[a] Key: (a) CrO_3·2py, CH_2Cl_2, rt; (b) furyllithium, THF, −78 °C; then aqueous NH_4Cl; (c) *p*-TsOH·H_2O, $MeNO_2$, −20 °C.

n-Bu_4NF[6] gave the bicyclohomofarnesols **8**[7] in 96% yield. Epoxidation of **8** with *m*-CPBA afforded the $\Delta^{8,17}$-epoxide **9**[8a] in 49% yield along with the isomeric epoxides **10** and **11** in 23% and 27% yields, respectively, after chromatography.

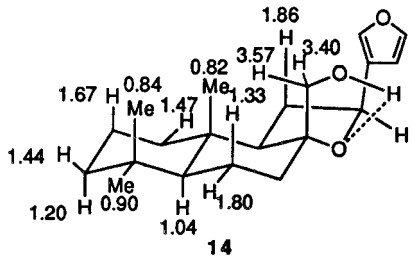
With the desired epoxy alcohol **9** in hand, the introduction of the 12*S* center and the furan group in **3**, which would ultimately serve as an entry to the γ-hydroxybutenolide moiety, was addressed. Reaction of **9** (Scheme 2) with Collins reagent gave crude aldehyde **12**[8b] in essentially quantitative yield. The unstable aldehyde was directly treated with 3-furyllithium at −78 °C, and subsequent acidification with aqueous NH_4Cl followed by chromatography gave the 12*S*-alcohol **3** in 45% yield along with the 12*R*-alcohol **13** in 32% yield. The major alcohol **3** resulted from attack of the lithium reagent on **12** from the slightly less hindered re-face.

At this stage, the stereochemistry of the 12*S* and 12*R* products could not be elucidated. The stereochemistry was actually determined indirectly at the tricyclic stage resulting from acid-catalyzed cyclization of the 12*S*- and 12*R*-alcohols. Reaction of **3** with *p*-TsOH·H_2O in nitromethane at −20 °C gave exclusively tricycle **14** (90%). The assignments of the individual protons in **14** were obtained from a series of COSY, HMQC, and HMBC 2D NMR studies. The stereochemistry depicted in **14** was proven from NOE observations. The assignment of the β-disposition of the C-17 hydroxymethyl substituent in **14** was based on the following NOE result. Irradiation of the 20-Me at δ 0.82 in **14** gave an enhancement of the

Scheme 3



diastereotopic protons at δ 3.57 and 3.40. Additional enhancements were also observed to the axial protons at H-2 and H-6, the pseudoaxial proton at H-11, the H-1 equatorial proton, and the 19-Me. Irradiation of the H-17 diastereotopic proton at δ 3.57 showed an enhancement of the H-6 axial proton (δ 1.33) and a weaker enhancement of the H-11 pseudoaxial proton (δ ~1.86). A reciprocal enhancement to the 20-Me, and an enhancement of the second diastereotopic proton at H-17 (δ 3.40), was also observed. Irradiation of the latter diastereotopic H-17 proton at δ 3.40 showed no enhancement of the H-6 axial proton but showed a strong enhancement to the H-11 pseudoaxial proton along with a weaker enhancement to the 20-Me. These results are consistent with the stereochemical assignments shown in **14**, thus establishing indirectly that the stereogenic center at C-12 in **3**, resulting from 1,2-addition, must be 12*S*.



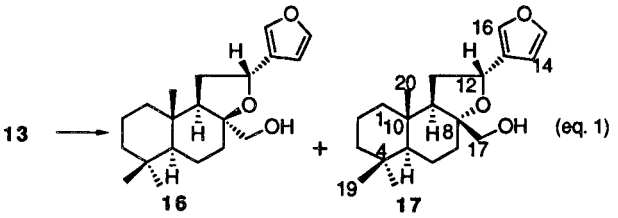
The exclusive formation of the 12*S*,8*R*-isomer **14** from the cyclization of **3**, opposed to the formation of the 12*S*,8*S*-isomer **15**, might be rationalized from the following considerations as detailed in Scheme 3. Reaction of **3** with acid would lead to two transition states **i** and **ii** assuming that the cyclization would occur via a carbocation intermediate or a protonated epoxide having an elongated C-8-O bond in which the C-8 tertiary carbon would have considerable carbocation-like character. Transition state **ii** should be favored over transition state **i** due to the severe steric interaction between the 20-Me and the C-12 center and the additional steric interaction between the 20-Me and the furan ring system. Thus, transition state **ii** would lead to the 12*S*,8*R*-tricycle **14**, a kinetically derived product.

An identical cyclization of the 12*R*-alcohol **13** with *p*-TsOH·H_2O in nitromethane (eq 1) gave a 60:40 ratio of a mixture of (12*R*,8*S*)-**16** and (12*R*,8*R*)-**17** in 94% yield. The two diastereomers were readily separated by chromatography and the relative stereochemistry shown in each compound was corroborated from NOE difference spectra (NOEDS).

(6) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 3782. Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.

(7) Cambie, R. C.; Joblin, K. N.; Preston, A. F. *Aust. J. Chem.* **1971**, *24*, 583 and references within.

(8) (a) Mori, K.; Tamura, H. *Liebigs Ann. Chem.* **1990**, 361. (b) Chauvet, F.; Coste-Maniere, I.; Martres, P.; Perfetti, P.; Waegell, B.; Zahra, J.-P. *Tetrahedron Lett.* **1996**, *37*, 3695.



Irradiation of the 20-Me (δ 0.79) in (12*R*,8*R*)-**17** gave an enhancement of the H-17, H-2_{ax}, H-6_{ax}, H-11_{ax}, and H-1_{eq} protons and the 19-Me. While irradiation of the H-12 proton (δ 5.10) showed an enhancement of the H-17, H-11_{ax}, H-14, and H-16 protons, irradiation of the H-17 protons (δ 3.55) showed a reciprocal enhancement to H-12 and the 20-Me and additional enhancements of the H-6_{ax}, H-11_{ax}, and H-7_{eq} protons. A similar NOE study with (12*R*,8*S*)-**16** showed that irradiation of the C-20 Me (δ 1.03) gave a strong enhancement to the 19-Me and the H-12 proton and a weaker enhancement to the H-2_{ax}, H-6_{ax}, H-11_{ax}, H-12_{eq}, and H-1eq protons, but no enhancement of the H-17 protons was observed. Thus, these studies confirm the relative stereochemistry depicted in **16** and **17** and indirectly corroborated the assignment of the 12*R* center in **13**.

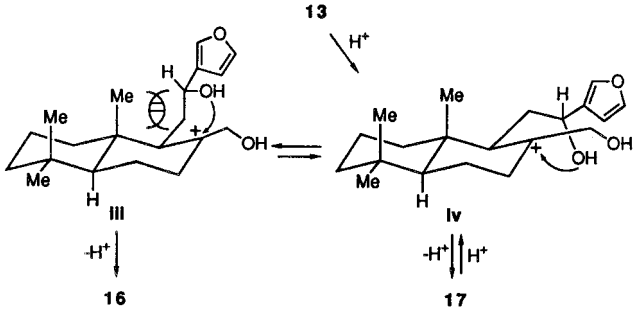
The formation of diastereomers (12*R*,8*S*)-**16** and (12*R*,8*R*)-**17** from the cyclization of **13** might be rationalized from the following considerations. It might be assumed here that the kinetically derived diastereomer **17** (Scheme 4) is obtained via TS **iv** and that this step is reversible, leading to TS **iii**, which upon cyclization would give rise to the more stable thermodynamic product, (12*R*,8*S*)-**16**.

To complete the synthesis of natural acuminolide **1a** and 17-*O*-acetylacuminolide (**2a**), it was assumed that the crucial γ-hydroxybutenolide moiety would be introduced in the last step of the reaction sequence via a photooxygenation reaction with regiospecific removal of the less hindered hydrogen from the intermediate endoperoxide with a hindered base. A molecular model study suggested that the reaction should occur mainly from the less hindered α-face of the molecule. Thus, reaction of **14** with $^1O_2$ in the presence of excess ethyldiisopropylamine[9] and a catalytic amount of rose bengal at −78 °C followed by chromatography gave an inseparable mixture of **1a** and **1b** (90%) in a 70:30 ratio as determined indirectly from the corresponding diacetates. The mixture of **1a** and **1b** appeared as a single spot on TLC analysis. The ^{1}H NMR spectrum (major chemical shifts) was identical with that reported for **1a**; however, the melting point was lower than that of natural **1a**, suggesting that a mixture of C-16 epimers was obtained from the $^1O_2$ reaction. Subsequent diacylation of the mixture of **1a** and **1b** (Scheme 5) in the presence of base gave diacetates **18a** and **18b** in an approximate 70:30 ratio as determined by NMR analysis of the reaction mixture. Fortunately, the diacetates were readily separated by chromatography to afford **18a** (64%, faster moving diastereomer) and **18b** (23%, slower moving diastereomer). The ^{13}C NMR spectrum of **18a** was identical with that reported for the known diacetate[1] derived from acuminolide **1a**.

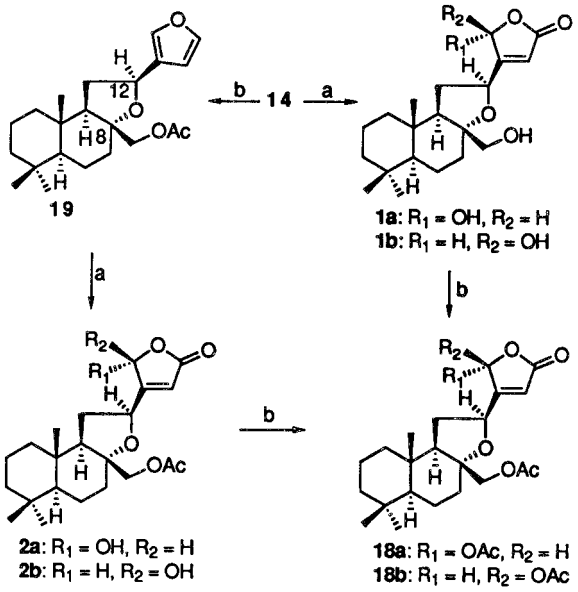
An analogous reaction sequence was used in an approach to 17-*O*-acetylacuminolide **2a**. Acylation of **14** afforded acetate **19** in 96% yield. Reaction of **19** with

(9) Kernan, M. R.; Faulkner, D. J. *J. Org. Chem.* **1988**, *53*, 2773.

Scheme 4



Scheme 5[a]



[a] Key: (a) $^1O_2$, rose bengal, ethyldiisopropylamine, CH_2Cl_2, −78 °C to rt; (b) Ac_2O, py, 4-DMAP, CH_2Cl_2.

singlet oxygen in the presence of ethyldiisopropylamine (−78 °C → rt) followed by chromatography afforded an 87% yield of an inseparable mixture of **2a** and **2b** in an approximate 66:34 ratio. Acylation of **2a** and **2b** followed by chromatography of the diacetate mixture gave **18a** (60%) and **18b** (32%). The ^{13}C NMR spectrum of the faster moving diastereomer **18a** was identical to the ^{13}C NMR spectrum of the known diacetate[1] of **1a**. The ^{13}C NMR spectrum of the slower moving diastereomer **18b** was identical to the spectrum derived from diacylation of **1b**.

Conclusion

An asymmetric route to natural acuminolides has been demonstrated. In addition, the route provides an entry to several epimeric analogues that might provide some insight between structure and antitumor activity.

Experimental Section

General Procedures. NMR spectra were obtained at 200, 500, and 600 MHz. C and H microanalyses were obtained from Galbraith Laboratories. HRMS analyses were obtained from the Mass Spectroscopy Facility at Duke. All melting points are uncorrected. Preparative chromatography was performed on Merck silica gel G 60 (70−230 mesh) and Merck silica gel G (230−400 mesh, for pressure chromatography). TLC was performed with Sybron/Brinkmann silica gel G/UV 254 plates,

0.25 mm (analytical). Compounds on chromatography plates were visualized by spraying with 4% phosphomolybdic acid in isopropyl alcohol followed by heating. THF was distilled from sodium benzophenone ketyl. Commercial reagent-grade solvents and chemicals were used as obtained unless otherwise noted.

(1*R*,2*R*,4a*S*,8a*S*)-2-Hydroxy-2,5,5,8a-tetramethyl-1,2,3,4,-4a,5,6,7, 8,8a-decahydro-1-naphthaleneethanol [(−)-(1*R*)-5]. (+)-Sclareolide (**4**) (97%, 10.7 g, 42.8 mmol) in dry THF (70 mL) was added dropwise to a suspension of LAH (2.44 g, 64.2 mmol) in dry THF (180 mL) under N_2 at rt. The reaction mixture was refluxed for 2 h, cooled to 0 °C, quenched with saturated Na_2SO_4 (200 mL), and extracted with CH_2Cl_2. The organic solution was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give 10.9 g (100%) of **5**:[2] mp 132.2−133.0 °C (50% CH_2Cl_2−hexanes); ^{1}H NMR ($CDCl_3$) δ 4.41 (br s, 1H, OH), 3.65−3.82 (m, 2H, *H*CHOH and OH), 3.40 (dt, 1H, HC*H*OH, J = 6.9, 9.6 Hz), 1.87 (dt, 1H, J = 2.9, 11.8 Hz), 1.15 (s, 3H, 2-Me), 0.85 (s, 3H, 8a-Me), 0.76 [s, 6H, 5-(Me)$_2$]; ^{13}C NMR ($CDCl_3$, 77.00) δ 72.73, 63.74, 59.27, 55.94, 43.96, 41.82, 39.27, 38.87, 33.35, 33.19, 27.74, 24.44, 21.42, 20.34, 18.35, 15.27.

(1*R*,2*R*,4a*S*,8a*S*)-1-[2-[(*tert*-Butyldimethylsilyl)-oxy]ethyl]-2-hydroxy-2,5,5,8a-tetramethyl-1,2,3,4,4a,-5,6,7,8,8a-decahydronaphthalene (6). To diol **5** (5.75 g, 22.6 mmol) in dry CH_2Cl_2 (50 mL) were added Et_3N (2.51 g, 24.9 mmol), 4-DMAP (1.10 g, 9.02 mmol), and TBDMSCl (3.75 g, 24.9 mmol). The reaction mixture was stirred at rt for 1 h and concentrated in vacuo to give an oil. Chromatography on silica gel (50 g, 230−400 mesh) eluting with hexanes and ethyl acetate−hexanes gave 8.2 g (98%) of **6**:[5] ^{1}H NMR ($CDCl_3$) δ 3.89 (s, 1H), 3.75−3.86 (m, 1H), 3.47 (6 line ddd, 1H, J = 4.1, 9.8, 9.8 Hz), 1.92 (distorted dt, 1H, J = 3.0, 12.2 Hz), 1.19−1.72 (m, 12H), 1.14 (s, 3H), 0.93 (m), 0.91 (s), and 0.88 (s) [13H], 0.79 (s, 6H), 0.087 (s, 6H); ^{13}C NMR ($CDCl_3$, 77.00) δ 71.64, 64.86, 59.00, 56.14, 43.88, 41.88, 39.47, 38.90, 33.34, 33.19, 27.68, 25.89, 25.89, 25.89, 24.52, 21.45, 20.36, 18.38, 18.22, 15.30, −5.49, −5.54.

Bicyclohomofarnesol Silyl Ethers 7 and Bicyclohomofarnesols 8. *n*-Butyllithium (2.5 M in hexanes, 8.7 mL, 21.8 mmol) was added dropwise to alcohol **6** (6.70 g, 18.2 mmol) and 12-crown-4 (3.84 g, 21.8 mmol) in dry THF (140 mL) under Ar at −78 °C over 15 min. The reaction mixture was stirred at −78 °C for 30 min. CF_3SO_2Cl (3.99 g, 2.52 mL, 23.7 mmol) was added dropwise, and stirring was continued for 2 h. 4-DMAP (5.78 g, 47.4 mmol) was added, and the reaction mixture was stirred at −78 °C for 1 h and then gradually allowed to warm to rt and stirred overnight. Water (100 mL) was added to the reaction mixture followed by neutralization with 10% HCl. The resulting mixture was extracted with CH_2Cl_2. The organic solution was washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated in vacuo to give an oil. Chromatography on silica gel (65 g, 230−400 mesh) eluting with hexanes and ethyl acetate−hexanes gave 2.68 g (42%) of the three isomers of **7** and 1.65 g (38%) of the three isomers of **8**.[7] For two isomers of **7**: δ 5.34−5.42 (m, 3H), 4.78 (s, =C*H*H), 4.49 (s, =CH*H*). The three isomers of **7** on TLC analysis appeared as one spot and could not be separated by chromatography. Alcohols **8** also appeared as one spot on TLC analysis and they could not be separated by chromatography on silica gel. Hence, **7** was desilylated to give alcohols **8**.

Bicyclohomofarnesols 8 From Silyl Ethers 7. *n*-Bu_4NF (1 M in THF, 79.4 mL, 79.4 mmol) was added dropwise to silyl ethers **7** (7.94 g, 22.7 mmol) in THF (180 mL) at 0 °C under N_2. The reaction mixture was allowed to warm to rt, stirred for 2 h, and then diluted with CH_2Cl_2 (200 mL). The organic solution was washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo to give an oil. Chromatography on silica gel (70 g, 230−400 mesh) eluting with 10% ethyl acetate−hexanes gave 5.14 g (96%) of isomers **8**:[7] ^{1}H NMR ($CDCl_3$) δ 5.38−5.47 (m), 4.83 (s, =C*H*H), 4.54 (s, =CH*H*), 3.65 (m), 0.95, 0.88, 0.86, 0.83, 0.81, 0.77, 0.69 (s, angular methyls). Isomers **8** were directly submitted to an epoxidation reaction.

(1*R*,2*R*,4a*S*,8a*S*)-2-(Epoxymethylene)-5,5,8a-trimethyl-1,2,3,4,4a,5,6,7,8,8a-decahydro-1-naphthaleneethanol (9), (1*R*,2*S*,3*R*,4a*S*,8a*S*)-2,3-Epoxy-2,5,5,8a-tetramethyl-1,2,3,4,-4a,5,6,7,8,8a-decahydro-1-naphthaleneethanol (10), and (1*S*,2*R*,4a*S*,8a*S*)-1,2-Epoxy-2,5,5,8a-tetramethyl-1,2,3,4,-4a,5,6,7,8,8a-decahydro-1-naphthaleneethanol (11). *m*-CPBA (80−90%, 15.2 g, 74.9 mmol) was added in several portions to isomeric alcohols **8** (6.8 g, 28.8 mmol) in dry CH_2Cl_2 (280 mL) at 0 °C. The reaction mixture was allowed to warm to rt, stirred for 2 h, and then neutralized with 1% NaOH. The resulting mixture was washed with H_2O and brine, dried (Na_2SO_4), and concentrated in vacuo to afford an oil. Chromatography on silica gel (100 g, 230−400 mesh) eluting with 10% ethyl acetate−hexanes gave 2.0 g (27%) of **11**, 3.6 g (49%) of **9**,[8a] and 1.6 g (23%) of **10**. For **11**: ^{1}H NMR ($CDCl_3$) δ 3.74−3.89 (m, 1H), 3.54−3.73 (m, 1H), 2.79 (br s, 1H), 1.67−2.08 (m, 5H), 1.07−1.62 (m) and 1.30 (s) [11H], 0.99 (s, 3H), 0.84 (s, 3H), 0.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 77.00) δ 72.21, 62.82, 61.56, 42.06, 41.31, 38.28, 34.63, 33.43, 32.79, 28.88, 27.65, 21.72, 21.37, 18.24, 17.05, 16.96. For **10**: ^{1}H NMR ($CDCl_3$) δ 3.81 (ddd, 1H, J = 4.9, 8.8, 10.3 Hz), 3.62 (dt, 1H, J = 7.6, 10.3 Hz), 3.00 (br dd, 1H, J = 1.3, 2.5 Hz), 2.31 (br s, 1H), 2.12 (dd, 1H, J = 4.5, 15.0 Hz), 1.25−1.86 (m) and 1.33 (s) [12H], 1.08−1.20 (m) and 1.05 (dd, J = 4.7, 12.6 Hz) [2H], 0.87 (s) and 0.85 (s) [6H], 0.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 77.00) δ 63.76, 61.02, 58.72, 51.11, 45.73, 41.91, 38.68, 35.55, 32.95, 32.58, 29.02, 22.99, 22.81, 21.85, 18.54, 14.15. Epoxides **10** and **11** were not characterized further. For **9**:[8a] ^{1}H NMR ($CDCl_3$) δ 3.54−3.71 (m, 1H), 3.35−3.52 (m, 1H), 2.97 (br s, 1H), 2.87 (dd, 1H, J = 1.9, 4.0 Hz), 2.58 (d, 1H, J = 3.8 Hz), 1.32−2.02 (m, 10H), 1.20 (dd, 1H, J = 4.8, 13.1 Hz), 0.87−1.14 (m) and 0.90 (s) [6H], 0.83 (s, 3H), 0.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 77.00) δ 63.61, 59.58, 54.78, 52.45, 50.92, 41.76, 40.12, 38.70, 36.19, 33.42, 33.36, 25.20, 21.68, 21.52, 18.58, 14.58.

(1*R*,2*R*,4a*S*,8a*S*)-2-(Epoxymethylene)-5,5,8a-trimethyl-1,2,3,4,4a,5,6,7,8,8a-decahydro-1-naphthaleneacetaldehyde (12). CrO_3 (7.9 g, 78.7 mmol) was added to pyridine (12.4 g, 157 mmol) in dry CH_2Cl_2 (600 mL). The reaction mixture was stirred at rt for 30 min and then cooled to 0 °C under N_2. Alcohol **9** (2.5 g, 9.84 mmol) in dry CH_2Cl_2 (50 mL) was added over 15 min. The reaction mixture was allowed to warm to rt, stirred for 3 h, and then passed through a short column of silica gel (10 g, 230−400 mesh) eluting with CH_2Cl_2 (700 mL) to give 2.5 g (100%) of crude **12**:[8b] ^{1}H NMR ($CDCl_3$) δ 9.57 (dd, 1H, J = 1.4, 3.0 Hz), 2.65 (dd, 1H, J = 1.8, 4.0 Hz), 2.52 (d, 1H, J = 4.1 Hz), 2.32 (dd, 1H, J = 5.3, 8.1 Hz) 2.15 (ddd, 1H, J = 1.3, 5.3, 16.6 Hz), 1.78−2.02 (m) and 1.99 (dd, J = 3.1, 8.2 Hz) [3H], 1.37−1.62 (m, 6H), 1.01−1.29 (m, 3H), 0.92 (s, 3H), 0.85 (s, 6H); ^{13}C NMR ($CDCl_3$, 77.00) δ 200.77, 58.29, 54.21, 49.48, 48.24, 41.31, 38.89, 38.72, 36.62, 35.10, 33.08, 32.88, 21.26, 21.12, 18.16, 14.19. Crude **12** (> 95% pure via ^{13}C NMR) was subjected directly to 1,2-addition, since it was relatively unstable.

3-[1*S*-Hydroxy-2-[(4a*S*,5*R*,6*R*,8a*S*)-1,2,3,4,4a,5,6,7,8,8a-decahydro-1,1,4a-trimethyl-5-naphthyl]ethyl]furan (3) and 3-[1(*R*)-Hydroxy-2-[(4a*S*,5*R*,6*R*, 8a*S*)-1,2,3,4,4a,5,6,7,8,-8a-decahydro-1,1,4a-trimethyl-5-naphthyl]ethyl]furan (13). *n*-BuLi (2.5 M in hexane, 9.8 mL, 24.5 mmol) was added dropwise to 3-bromofuran (3.62 g, 24.6 mmol) in dry THF (180 mL) at −78 °C under Ar over 15 min, and the reaction mixture was stirred for 30 min. Aldehyde **12** (2.46 g, 9.84 mmol) in dry THF (20 mL) was added dropwise over 20 s. The reaction mixture was stirred at −78 °C for 1 h and then quenched with a saturated NH_4Cl solution. Water (50 mL) was added, and the mixture was extracted with CH_2Cl_2. The organic solution was washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated in vacuo to give an oil. Chromatography on silica gel (120 g, 230−400 mesh) eluting with 15% ethyl acetate−hexanes gave 1.4 g (45%) of **3** and 1.0 g (32%) of **13**. For **3**: mp 73.5−74.2 °C; ^{1}H NMR ($CDCl_3$) δ 7.37 (s) and 7.36 (s) [2H], 6.35 (m, 1H), 4.47 (dt, 1H, J = 3.7, 9.2 Hz), 3.77 (br d, 1H, J = 4.1 Hz), 2.93 (dd, 1H, J = 1.8, 3.6 Hz), 2.64 (d, 1H, J = 3.6 Hz), 1.35−2.01 (m, 10H), 1.21 (dd, 1H, J = 4.9, 13.0 Hz), 0.94−1.14 (m, 3H), 0.91 (s, 3H), 0.83 (s, 3H), 0.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 77.00) δ 143.02, 138.82, 130.06, 108.38,

68.11, 59.95, 54.80, 52.37, 51.05, 41.75, 40.34, 38.58, 36.08, 33.42, 31.60, 21.67, 21.53, 18.60, 14.60. Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.55; H, 9.72. For **13**: ^{1}H NMR ($CDCl_3$) δ 7.40 (m) and 7.37 (m) [2H], 6.31 (s, 1H), 4.79 (m, 1H), 3.32 (br d, 1H, J = 4.1 Hz), 2.89 (dd, 1H, J = 1.9, 3.7 Hz), 1.31−1.92 (m, 11H), 1.04−1.28 (m, 2H), 0.97 (dd, 1H, J = 2.6, 12.2 Hz), 0.87 (s, 3H), 0.81 (s) and 0.79 (s) [6H]; ^{13}C NMR ($CDCl_3$, 77.00) δ 142.90, 139.33, 129.22, 108.76, 66.24, 59.70, 54.63, 50.81, 48.14, 41.68, 39.86, 38.68, 36.24, 33.37, 29.82, 21.71, 21.55, 18.56, 14.75; IR (neat) 3423, 1501, 1460, 1445, 1390, 1366, 1158, 1061, 1024, 875, 732 cm^{-1}. Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.48; H, 9.63.

(1*S*,3*R*,3a*R*,5a*S*,9a*S*)-1-(3-Furyl)-3a-(hydroxymethyl)-6,6,9a-trimethyl-1,2,3, 3a,4,5,5a,6,7,8,9,9a-dodecahydronaphtho[2,1-*b*]furan (14). *p*-TsOH·H_2O (128 mg, 0.673 mmol) was added to epoxide alcohol **3** (756 mg, 2.38 mmol) in CH_3NO_2 (45 mL) at −20 °C under N_2. The reaction mixture was stirred at −20 °C for 1 h and then poured into a 0.1 N NaOH solution (30 mL). The mixture was extracted with CH_2Cl_2, and the organic solution was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give an oil. Chromatography on silica gel (35 g, 200−425 mesh, pH = 7) eluting with 12% ethyl acetate−hexanes gave 682 mg (90%) of **14**: mp 103.2−103.6 °C (hexanes); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.40 (s, 2H, H_{15}, H_{16}), 6.43 (s, 1H, H_{14}), 5.02 (m, 1H, H_{12}), 3.57 (d, 1H, H_{17}, J = 10.7 Hz), 3.40 (dd, 1H, H_{17}, J = 1.8, 10.7 Hz), 2.35 (dt, 1H, H_{7eq}, J = 3.0, 11.7 Hz), 2.13 (m, 1H, H_{11eq}), ∼1.86 (m, H_{9ax}, H_{11ax}) and 1.80 (dq, H_{6eq}, J = 3.2, 14.1 Hz), 1.67 (qt, 1H, H_{2ax}, J = 3.4, 13.8 Hz), ∼1.47 (H_{1eq}, H_{2eq}) and ∼ 1.44 (H_{3eq}) [3H, overlapping multiplets], 1.33 (8 line dddd, 1H, H_{6ax}, J = 3.2, 3.2, 12.9, 12.9 Hz), ∼1.24 (H_{7ax}) and 1.20 (partially resolved dt, J = 3.9, 13.5 Hz) [2H], 1.11 (dt, 1H, H_{1ax}, J = 2.8, 12.8 Hz), 1.04 (dd, H_{5ax}, 1H, J = 2.6, 12.5 Hz), 0.90 (s, 3H, 18-Me), 0.84 (s, 3H, 19-Me), 0.82 (s, 3H, 20-Me); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 143.97 (C-15), 139.26 (C-16), 128.00 (C-13), 108.98 (C-14), 83.35 (C-8), 73.09 (C-12), 63.01 (C-17), 61.27 (C-9), 57.25 (C-5), 42.40 (C-3), 39.86 (C-1), 36.53 (C-10), 34.86 (C-7), 33.52 (C-18), 33.14 (C-4), 30.25 (C-11), 21.06 (C-19), 20.42 (C-6), 18.47 (C-2), 15.46 (C-20). Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.55; H, 9.50.

(1*R*,3*R*,3a*S*,5a*S*,9a*S*)-1-(3-Furyl)-3a-(hydroxymethyl)-6,6,9a-trimethyl-1,2,3,3a,4,5,5a,6,7,8,9,9a-dodecahydronaphtho[2,1-*b*]furan (16) and (1*R*,3*R*,3a*R*,5a*S*,9a*S*)-1-(3-Furyl)-3a-(hydroxymethyl)-6,6,9a-trimethyl-1,2,3,3a,4,5,-5a,6,7,8,9,9a-dodecahydronaphtho[2,1-*b*]furan (17). *p*-TsOH·H_2O (61.7 mg, 0.324 mmol) was added to epoxide alcohol **13** (430 mg, 1.35 mmol) in $MeNO_2$ (26 mL) at −20 °C under N_2. The reaction mixture was stirred at −20 °C for 1 h and then poured into a 0.1 N NaOH solution (20 mL). The mixture was extracted with CH_2Cl_2, and the organic solution was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to afford a 60:40 ratio of crude **16** (faster moving diasteromer) and **17** (slower moving diastereomer). Chromatography on silica gel (30 g, 230−400 mesh) eluting with 10% ethyl acetate−hexanes (700 mL) gave 248 mg (58%) of **16** and 150 mg (35%) of **17**. For **16**: mp 84.5−85.6 °C (direct from column); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38 (m, 2H, H_{15}, H_{16}), 6.39 (dd, 1H, H_{14}, J = 0.92, 1.4 Hz), 4.90 (dd, 1H, H_{12}, J = 6.6, 9.8 Hz), 3.38 (d, 1H, H_{17}, J = 11.0 Hz), 3.34 (d, 1H, H_{17}, J = 11.0 Hz), 2.20 (4 line ddd, 1H, H_{11eq}, J = 6.5, 13.5 Hz), 2.01 (m, 2H, H_{11ax}, H_{7eq}), ∼1.75 (H_9), ∼1.70 (H_{7ax}), ∼1.66 (H_{1eq}), and OH [overlapping m, 4H], ∼1.54 (H_{6eq}), ∼1.52 (H_{2ax}), and ∼1.49 (H_{6ax}) [overlapping m, 3H], ∼1.43 (H_{3eq}), and ∼1.41 (H_{2eq}) [overlapping m, 2H], 1.15 (dt, 1H, H_{3ax}, J = 3.5, 13.3 Hz), 1.03 (s, 3H, 20-Me), 0.95 (H_{1ax}), 0.91 (s, 19-Me), 0.89 (H_{5ax}) and 0.87 (s, 18-Me) [8H]; ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 143.55 (C-15), 138.96 (C-16), 127.91 (C-13), 108.79 (C-14), 85.22 (C-8), 72.38 (C-12), 70.26 (C-17), 55.07 (C-9), 49.85 (C-5), 42.39 (C-1), 42.14 (C-3), 36.11 (C-10), 34.94 (C-11), 33.26 (C-4), 33.13 (C-18), 28.93 (C-7), 21.78 (C-19), 18.43 (C-2), 17.82 (C-6), 16.15 (C-20). Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.11; H, 9.41. For **17**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.39 (s, 1H, H_{15}), 7.37 (s, 1H, H_{16}), 6.34 (s, 1H, H_{14}), 5.10 (dd, 1H, H_{12}, J = 2.2, 9.3 Hz), 3.55 (s, 2H, H_{17}), 2.39 (dt, 1H, H_{7eq}, J = 3.0, 11.6 Hz), 2.17 (ddd, 1H, H_{11ax}, J = 9.3, 11.5, 13.5 Hz), 2.01 (br s, 1H), ∼1.81 (overlapping m, 2H, H_{9ax}, H_{6eq}), 1.71 (ddd, 1H, H_{11eq}, J = 2.5, 7.1, 11.5 Hz), 1.63 (m, 1H, H_{2ax}), ∼1.42 (m, 3H, H_{1eq}, H_{2eq}, H_{3eq}), ∼1.33 (H_{6ax}) and ∼1.28 (H_{7ax}) [overlapping m, 2H], 1.18 (dt, 1H, H_{3ax}, J = 3.7, 13.4 Hz), 1.04 (dd, 1H, H_{5ax}, J = 2.5, 12.1 Hz) and ∼1.03 (H_{1ax}) [overlapping m, 2H], 0.89 (s, 3H, 18-Me), 0.84 (s, 3H, 19-Me), 0.79 (s, 3H, 20-Me); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 143.61 (C-15), 139.06 (C-16), 128.83 (C-13), 108.49 (C-14), 83.89 (C-8), 71.16 (C-12), 61.20 (C-17), 59.37 (C-9), 57.37 (C-5), 42.36 (C-3), 39.68 (C-1), 36.36 (C-10), 34.44 (C-7), 33.54 (C-18), 33.12 (C-4), 31.02 (C-11), 21.10 (C-19), 20.25 (C-6), 18.41 (C-2), 15.08 (C-20); HRMS calcd for $C_{20}H_{30}O_3$ (M^+) 318.2195, found 318.2192.

Acuminolide (1a) and 16-*epi*-Acuminolide (1b). Furan **14** (80 mg, 0.252 mmol), ethyldiisopropylamine (325 mg, 2.52 mmol), and rose bengal (2 mg) in dry CH_2Cl_2 was cooled to −78 °C while passing a stream of anhydrous O_2 through the solution. The reaction mixture was then irradiated with a 200 W tungsten lamp placed 10 cm from the reaction vessel for 6 h at −78 °C. Chromatography on silica gel (8 g, 200−425 mesh, pH = 7) eluting with ethyl acetate−hexanes gave 79 mg (90%) of an approximate 70:30 inseparable mixture of **1a** and **1b**: mp 194.4−195.6 °C (ethyl acetate−hexanes); ^{1}H NMR ($CDCl_3$) δ 6.22 (s, 1H), 6.03 (d, 1H, J = 1.1 Hz), 4.94 (m, 1H), 3.68 (d, 1H, J = 11 Hz), 3.34 (d, 1H, J = 11 Hz), 2.39 (m, 1H), 2.23 (m, 1H), 0.89 (s, 3H), 0.83 (s, 3H), 0.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.4 (C-15), 168.8 (C-13), 117.5 (C-14), 98.5 (C-16), 84.6 (C-8), 74.2 (C-12), 62.5 (C-17), 60.9 (C-9), 57.1 (C-5), 42.2 (C-3), 39.7 (C-1), 36.4 (C-10), 34.3 (C-7), 33.4 (C-18), 33.1 (C-4), 29.1 (C-11), 21.0 (C-19), 20.3 (C-6), 18.4 (C-2), 15.5 (C-20). The ratio of **1a** and **1b** was determined indirectly from the corresponding diacetates **18a** and **18b**.

16-*O*-17-*O*-Diacetylacuminolide (18a) and 16-*O*-17-*O*-Diacetyl-16-epiacuminolide (18b). Acetic anhydride (20.5 mg, 0.201 mmol) in pyridine (0.5 mL) was added to a solution of diols **1a** and **1b** (23.5 mg, 0.0671 mmol) and 4-DMAP (16.4 mg, 0.134 mmol) in pyridine (0.5 mL), and the reaction mixture was stirred overnight at rt. The solvent was removed in vacuo, and chromatography of the residue on silica gel (6 g, 200−425 mesh, pH = 7) with 7% ethyl acetate−hexanes gave 18.6 mg (64%) of **18a** and 6.8 mg (23%) of **18b**. Integration of the resonance signals at δ 6.98 and 6.88 in the crude reaction mixture gave an approximate 70:30 ratio of **18a** and **18b**. For **18a**: ^{1}H NMR ($CDCl_3$) δ 6.88 (s, 1H), 6.21 (br s, 1H), 4.82 (m, 1H), 4.53 (d, 1H, J = 11.8 Hz), 3.62 (d, 1H, J = 11.8 Hz), 2.17 (s, 3H), 2.11 (s, 3H), 0.88 (s, 3H), 0.87 (s, 3H), 0.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 Hz) δ 171.1 (C-15), 169.3 (OAc), 169.0 (OAc), 168.6 (C-13), 116.9 (C-14), 92.2 (C-16), 82.4 (C-8), 74.0 (C-12), 65.3 (C-17), 61.8 (C-9), 57.2 (C-5), 42.2 (C-3), 39.9 (C-1), 36.3 (C-10), 35.0 (C-7), 33.4 (C-18), 33.1 (C-3), 29.1 (C-11), 21.0 (*C*H_3-CO), 20.9 (C-19), 20.7 (*C*H_3CO), 20.4 (C-6), 18.3 (C-2), 15.8 (C-20). The ^{13}C NMR spectrum of **18a** was identical to the spectrum of the known diacetate[1] derived from diacylation of natural **1a** or acylation of **2a**. For **18b**: ^{1}H NMR ($CDCl_3$) δ 6.99 (s, 1H), 6.10 (br dd, 1H, J = 0.9, 2.0 Hz), 4.83 (m, 1H), 4.45 (d, 1H, J = 11.9 Hz), 3.70 (d, 1H, J = 11.9 Hz), 2.17 (s, 3H), 2.11 (s, 3H), 2.08−2.24 (m, 1H), 0.89 (s, 3H), 0.87 (s, 3H), 0.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 171.0, 169.4, 168.9, 117.3, 93.1, 82.2, 73.8, 65.2, 61.6, 57.2, 42.2, 39.9, 36.3, 35.0, 33.4, 33.1, 29.1, 21.0, 21.0, 20.8, 20.4, 18.3, 15.74; HRMS calcd for $C_{24}H_{34}O_7$ $(M - H)^+$ 433.2226, found 433.2225.

(1*S*,3*R*,3a*R*,5a*S*,9a*S*)-1-(3-Furyl)-3a-(acetoxymethyl)-6,6,9a-trimethyl-1,2,3,3a,4,5,5a,6,7,8,9,9a-dodecahydronaphtho[2,1-*b*]furan (19). Acetic anhydride (48.1 mg, 0.472 mmol) in dry pyridine (0.2 mL) was added to **14** (100 mg, 0.314 mmol) and 4-DMAP (38.3 mg, 0.314 mmol) in dry pyridine (0.8 mL) at rt. The reaction mixture was stirred for 24 h, and the pyridine was removed in vacuo. The resulting mixture was chromatographed on silica gel (6 g, 200−425 mesh, pH = 7); eluting with 3% ethyl acetate−hexanes gave 109 mg (96%) of a colorless thick oil, which after standing at rt for several days solidified to give **19**: mp 66.0−67.0 °C (from column); ^{1}H NMR ($CDCl_3$) δ 7.36 (m, 2H), 6.32 (s, 1H), 5.06 (dd, 1H, J = 8.0, 10.7 Hz), 4.37 (d, 1H, J = 11.6 Hz), 3.82 (d, 1H, J = 11.6 Hz),

2.21 (m, 2H), 2.04 (s, 3H), 1.01−1.93 (m, 12H), 0.89 (s), 0.87 (s), and 0.83 (s) [9H]; ^{13}C NMR ($CDCl_3$, 50 MHz, 77.00) δ 171.45, 143.15, 138.43, 128.85, 108.64, 81.14, 73.68, 65.67, 61.97, 57.23, 42.28, 39.90, 36.20, 35.23, 33.42, 33.10, 30.88, 20.98, 20.37, 18.44, 15.87. Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.09; H, 9.11.

17-*O*−Acetylacuminolide (2a) and 17-*O*−Acetyl-16-*epi*-acuminolide (2b). A mixture of furan **19** (78.0 mg, 0.217 mmol), ethyldiisopropylamine (280 mg, 2.17 mmol), and rose bengal (2 mg) in dry CH_2Cl_2 (8 mL) was cooled to −78 °C while a stream of dry O_2 was passed through the solution. The reaction mixture was irradiated with a 200 W tungsten lamp placed 10 cm from the reaction vessel for 5 h at −78 °C, allowed to warm to rt after removal of the reaction tube from the −78 °C bath, and then allowed to stand at rt for an additional 30 min. The solvent was removed in vacuo, and chromatography on silica gel (8 g, 200−425 mesh, pH = 7) eluting with 50% ethyl acetate−hexanes gave 73.7 mg (87%) of an approximate 66:34 inseparable mixture of **2a** and **2b**: mp 212.1−213.2 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 6.11 (s, 1H), 6.06 (br s, 1H), 4.93 (m, 1H), 4.46 (d, 1H, J = 11.8 Hz), 3.73 (d, 1H, J = 11.8 Hz), 2.17−2.29 (m, 2H), 2.11 (s, 3H), 0.89 (s, 3H), 0.87 (s, 3H), 0.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 171.3, 170.3, 169.3, 116.9, 98.0, 82.4, 74.4, 65.1, 61.6, 57.1, 42.2, 39.8, 36.3, 34.9, 33.4, 33.1, 28.7, 21.0, 20.9, 20.3, 18.3, 15.8. The ratio of **2a** and **2b** was determined indirectly from the corresponding diacetates **18a** and **18b**.

16-*O*-17-*O*-Diacetylacuminolide (18a) and 16-*O*-17-*O*-Diacetyl-16-*epi*-acuminolide (18b). From 2a and 2b. Acetic anhydride (10.0 mg, 0.098 mmol) in pyridine (0.5 mL) was added to a solution of hydroxy acetates **2a** and **2b** (25.6 mg, 0.0653 mmol) and 4-DMAP (8.0 mg, 0.065 mmol) in pyridine (0.5 mL), and the reaction mixture was stirred overnight at rt. The solvent was removed in vacuo, and chromatography of the residue on silica gel (6 g, 200−425 mesh, pH = 7) eluting with 7% ethyl acetate−hexanes gave 16.9 mg (60%) of **18a** and 9.1 mg (32%) of **18b**. The ^{13}C NMR spectrum of the faster moving diastereomer **18a** was identical to the ^{13}C NMR spectrum of the known diacetate[1] of **1a**. The ^{13}C NMR spectrum of the slower moving diastereomer **18b** was identical to the ^{13}C NMR spectrum derived from diacylation of **1b**. Integration of the resonance signals at δ 6.99 and 6.88 in the crude reaction mixture gave an approximate 66:34 ratio of **18a** and **18b**.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **10**, **11**, **17**, and **18b** (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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