Base-Induced and -Directed Rearrangements of 4-Monotosylated Perhydronaphthalene-1,4-diols. Synthesis of (±)-5-*epi*-Nardol

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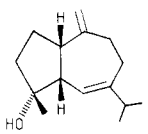
The utility of perhydronaphthalene precursors for the synthesis of sesquiterpenes which possess a cis-fused perhydroazulene skeleton with an exocyclic methylene unit has been examined. For this purpose the tosylates **3**, **4**, **28**, and **29** were prepared, and their behavior under basic conditions was studied. Upon treatment with sodium *tert*-amylate in refluxing benzene, the tosylate **3** gave the desired selective formation of the exo 8-olefin **11** (90%). When the tosylate **4** was treated this way a lesser selectivity (58%) was observed. The tosylates **28** and **29** showed a slow rearrangement with no selectivity and no reaction at all, respectively. The role of the hydroxyl group, the solvent, the base strength, and the metal cation has been investigated. A mechanism for this selective skeletal rearrangement (**3** → **11**) has been proposed. As an application of this intramolecular base-induced rearrangement the unnatural C-5 epimer of nardol (**33**) has been prepared in 11 steps from the monoprotected trans-fused dione **5** in an overall yield of 25%. In the synthesis of **33** again the rearrangement (**34** → **33**) proceeded selectively and in high yield (90%).

The solvolytic rearrangement of appropriately functionalized eudesmanes and eudesmanolides is a generally accepted method for the preparation of guaianes and guaianolides, respectively.[1] The highly developed understanding of the stereochemistry and conformational analysis of substituted perhydronaphthalene systems (e.g. eudesmanes and eudesmanolides) makes this approach a very attractive one. A disadvantage of this strategy, when solvolytic methods are applied, is the formation of mixtures of double bond isomers.[2] Especially for the synthesis of guaiane and guaianolide sesquiterpenes which possess a cis-fused perhydroazulene skeleton with an exocyclic methylene unit such as alismol (**1**)[3] and estafatin (**2**),[4] the disadvantages of the solvolytic rearrangement outweigh the advantages of the above mentioned approach.



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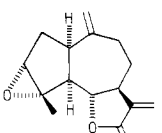

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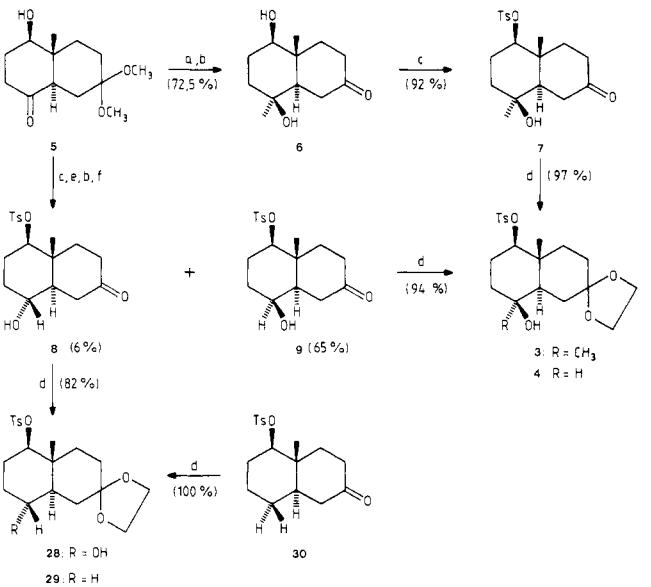
Since a successful method for the preparation of suitable functionalized perhydronaphthalenes for the synthesis of eudesmanes had been developed in our laboratory,[5] it was obvious to investigate the utility of these compounds as intermediates in the synthesis of cis-fused guaianes.[6] To achieve this goal a considerable improvement in the selectivity of the (solvolytic) rearrangement of these perhydronaphthalenes is necessary, and probably strong intramolecular directing effects will be required. In order to explore this condition the tosylates **3** and **4** were prepared, both having an axial hydroxyl group at C-8. The dioxolane at C-2 is a suitable functional group for the introduction of the isopropyl side chain lateron. For the synthesis of **3** and **4** the selectively protected trans-fused dione **5**[5a] was the starting material (Scheme I). Treatment of **5** with an excess of methyllithium in dry THF at −78 °C, directly followed by hydrolysis of the dimethyl acetal function,[8] afforded the crystalline diol **6**. Subsequent treatment of **6** with *p*-toluenesulfonyl chloride (TsCl) in pyridine led to the tosylate **7**, which was converted into its dioxolane **3** by treatment with 2-butanone dioxolane (MED).[9]

For the synthesis of the tosylate **4** the monoacetalized dione **5** was treated with TsCl and sodium borohydride. Subsequent hydrolysis of the dimethyl acetal function[8]

Scheme I[a]



[a] (a) CH_3Li, THF, −78 °C; (b) HCl, acetone, H_2O; (c) TsCl, pyridine; (d) MED, TsOH (cat.), CH_2Cl_2; (e) $NaBH_4$, C_2H_5OH; (f) separation.

(1) For example, see: (a) Heathcock, C. H.; Ratcliffe, R. *J. Am. Chem. Soc.* **1970**, *93*, 1746. (b) Ando, M.; Akahane, A.; Yamaoka, H.; Takase, K. *J. Org. Chem.* **1982**, *47*, 3909. (c) Ando, M.; Kusaka, H.; Ohara, H.; Takase, K.; Yamaoka, H.; Yanagi, Y. *Ibid.* **1989**, *54*, 1952.

(2) Ando, M.; Ono, A.; Takase, K. *Chem. Lett.* **1984**, 493.

(3) Oshima, Y.; Iwakawa, T.; Hikino, H. *Phytochemistry* **1983**, *22*, 183.

(4) Sánchez-Viesca, F.; Romo, J. *Tetrahedron* **1963**, *19*, 1285.

(5) (a) Wijnberg, J. B. P. A.; Vader, J.; de Groot, Ae. *J. Org. Chem.* **1983**, *48*, 4380. (b) Wijnberg, J. B. P. A.; Jongedijk, G.; de Groot, Ae. *Ibid* **1985**, *50*, 2650.

(6) Only a few syntheses of cis-fused guaianes and guaianolides with an exocyclic double bond have been reported so far.[7]

(7) (a) González, A. G.; Galindo, A.; Mansilla, H. *Tetrahedron* **1980**, *36*, 2015. (b) Devreese, A. A.; Demuynck, M.; De Clerq, P. J.; Vandewalle, M. *Ibid.* **1983**, *39*, 3049. (c) Rigby, J. H.; Senanayake, C. *J. Am. Chem. Soc.* **1987**, *109*, 3147.

(8) Purification of the dimethyl acetal by column chromatography led to decomposition.

(9) Baudiun, G.; Pietrasanta, Y. *Tetrahedron* **1973**, *29*, 4225.

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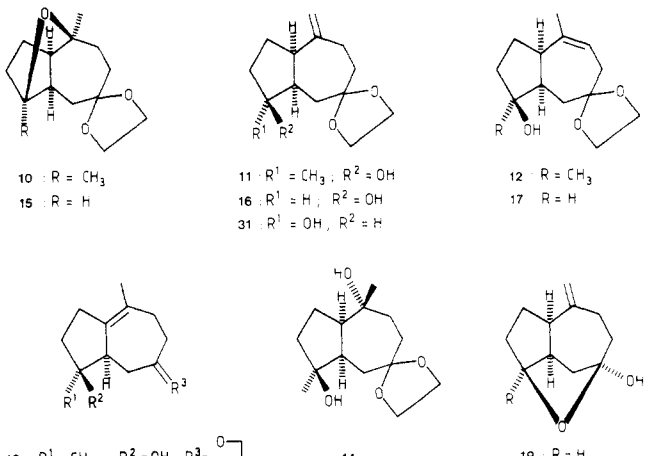
resulted in a 1:11 mixture of **8** and **9**, respectively. After separation by column chromatography, treatment of **9** with MED gave the dioxolane **4**.

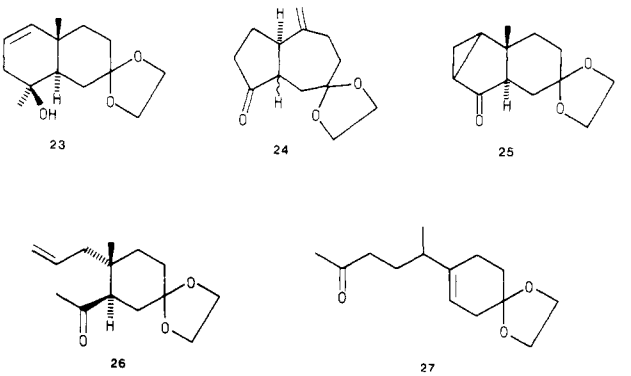
The presence of the axial hydroxyl group in **3** and **4** required basic conditions for the rearrangement process, otherwise elimination of the hydroxyl group can occur.[10] In refluxing aqueous dioxane with lithium carbonate as a buffer, conditions that would be expected to involve little if any alkoxide ion formation, the rearrangement of **3** produced a mixture of the cyclic ether **10** (12%), the exo 8-olefin **11** (9%), the endo 7,8-olefin **12** (9%), the endo 8,8a-olefin **13** (48%), and the diol **14** (16%). The presence of the exo 8-olefin **11** in this mixture[11] encouraged further investigations under stronger basic circumstances. Treatment of the tosylate **3** with potassium *tert*-butoxide in refluxing *tert*-butyl alcohol afforded a mixture of **10** (14%), **11** (53%), **12** (9%), and **13** (14%). Thus, a significant improvement of the selectivity in the direction of **11** was observed. When the tosylate **4** was treated under these circumstances a similar mixture of reaction products was obtained: the cyclic ether **15** (16%), the exo 8-olefin **16** (44%), the endo 7,8-olefin **17** (3%), and the endo 8,8a-olefin **18** (22%). The hydrolysis of the rearranged products **16** and **18** afforded the compounds **19** and **20**, respectively. The IR spectrum of **19** shows no carbonyl absorption this in contrast with **20** (strong carbonyl absorption near 1700 cm^{-1}). The formation of the cyclic hemiacetal **19** can explain these features and supports the cis-fused perhydroazulene structure of **16**. A similar result was found when **11** and **13** were hydrolyzed to give **21** and **22**, respectively. When the tosylate **4** was treated with (dimethylsulfinyl)sodium in dimethyl sulfoxide at 70 °C no improvement of the selectivity was observed. A mixture of the rearranged products **15**, **16**, and **18** in a ratio of 5:6:3, respectively, was formed.



It was finally discovered[12] that treatment of the tosylate **3** with sodium *tert*-amylate in refluxing benzene for 20 h led, according to GC analysis, to a nearly selective formation of the exo 8-olefin **11** (90%). Three minor products were identified as the cyclic ether **10** (3%), the endo 8,8a-olefin **13** (4%), and the unrearranged olefin **23** (3%). When the tosylate **4** was treated this way a more complex mixture of reaction products was obtained with the exo 8-olefin **16** (57%) again as the main product. The mixture consisted further of the cyclic ether **15** (7%), a 2:1 mixture of the epimeric rearranged ketones **24** (7%), the cyclopropyl derivative **25** (4%), and the endo 8,8a-olefin **18** (15%). The formation of the compounds **24** and **25** is difficult to explain. Probably, under the influence of sodium *tert*-amylate, the tosylate **4** and the exo 8-olefin **16** have been oxidized by oxygen present in the reaction flask. Subsequent epimerization and intramolecular substitution[1a] account for the formation of **24** and **25**, respectively. It is obvious that the rearrangement of the secondary β-hydroxyl tosylate **4** is less selective than that of the tertiary β-hydroxyl tosylate **3**. Either the less basic secondary alcoholate or the diminished steric compression (H versus CH_3) may be responsible for this effect.

The solvent and the base strength are also important in this rearrangement process. Although benzene is only slightly less polar than *tert*-butyl alcohol the use of benzene as the solvent caused a considerable improvement of the selectivity. It is known that even with excess of potassium *tert*-butoxide, relative low equilibrium concentrations of alkoxide ions are produced in *tert*-butyl alcohol, particularly when tertiary hydroxyl groups are involved.[13] In addition, the base strength of alkali metal alkoxides is enhanced in aprotic solvents compared with *tert*-butyl alcohol.[14] Thus, to obtain the highest selectivity in this base-induced skeletal rearrangement it is necessary to deprotonate the axial β-hydroxyl group as much as possible. This was supported by treatment of the tosylate **3** with pyridine in refluxing benzene during 135 h. After the workup the recovery of **3** was 100%.

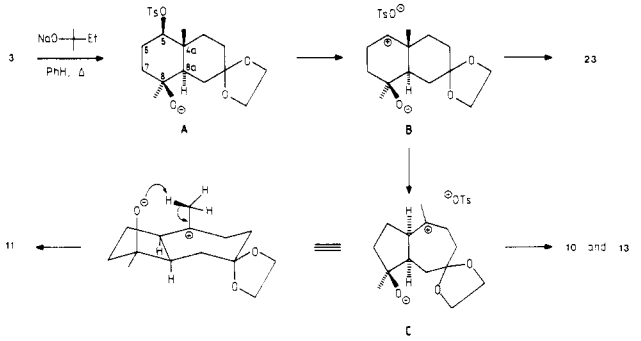
In order to investigate the role of the metal ion in this rearrangement process, we treated the tosylate **3** with potassium and lithium *tert*-amylate in refluxing benzene. When potassium *tert*-amylate was used the selectivity and the reaction time were the same as with sodium *tert*-amylate. On the other hand, the use of lithium *tert*-amylate needed a considerably longer reaction time (92 h) and resulted in a lower yield of **11** (59%), while the percentages of **10** (8%) and **13** (13%) increased. Also Grob-like fragmentations[15] accompanied with a hydride and a methyl shift leading to the compounds **26** (1%) and **27** (3%), respectively, were observed.



These results indicate that potassium or sodium *tert*-amylate in benzene are significantly more reactive and selective toward **3** than is lithium *tert*-amylate and suggest

(10) Garcia-Granados, A.; Molina, A. Cabrera, E. *Tetrahedron* **1986**, *42*, 81.
(11) Brown, E. D.; Sutherland, J. K.; Sam, T. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2332.
(12) Wijnberg, J. B. P. A.; de Groot, Ae. *Tetrahedron Lett.* **1987**, *28*, 3007.
(13) Caine, D. *Org. Prep. Proced. Int.* **1988**, 20, 1.
(14) Pearson, D. E.; Buehler, C. A. *Chem. Rev.* **1974**, *74*, 45.
(15) Grob, C. A. *Angew. Chem.* **1969**, *81*, 343.

Scheme II



that the cations cannot be neglected in this base-induced rearrangement. The fact that the Li^+-O^- bond is stronger than the Na^+-O^- or K^+-O^- bond[16] is probably the reason for the slow rearrangement and diminished selectivity with lithium *tert*-amylate in benzene.

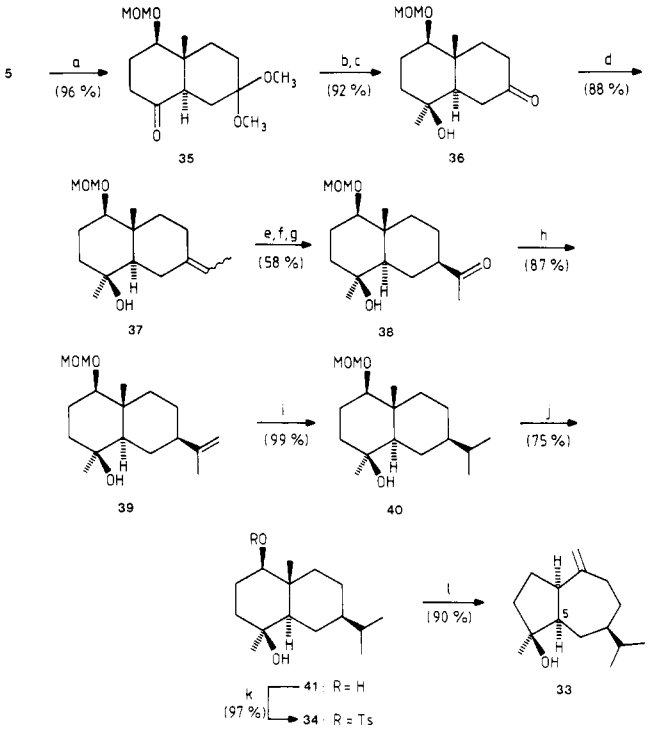
A more detailed examination of the role of the axial β-hydroxyl group in this rearrangement process led us to the preparation of the tosylates **28** and **29** from **8** and the known compound **30**,[17] respectively (Scheme I).

Upon treatment of the secondary α-hydroxyl tosylate **28** with sodium *tert*-amylate in refluxing benzene during 21 h, a recovery of 59% of **28** was found. Only a small amount (13%) of products could be isolated and, according to GC and ^1H NMR analysis, appeared to be a mixture of mainly two compounds, **31** and **32** in a ratio of 1:2.5, respectively. These results indicate that the tosylate **28** reacts much slower and less selective than the tosylates **3** and **4**.

Upon treatment of the tosylate **29** with sodium *tert*-amylate in refluxing benzene no reaction at all was observed after 21 h. This means that neither direct elimination of the tosyloxy group nor an intermolecular base-induced rearrangement occurs. It is clear that the presence of a strategically positioned axial hydroxyl group is essential for a smooth and selective progress of the rearrangement.

These results forced us to revise our primarily proposed mechanism for this rearrangement process.[12] We now believe that the selective skeletal rearrangement of the tosylate **3** to the exo 8-olefin **11** proceeds via A by a slow rate-determining heterolysis (or ion pair formation),[18] *intramolecularly induced by a deprotonated hydroxyl group*, just as in the Grob fragmentation[19] (Scheme II). We assume that the O^- group donates electrons to the C4a–C8 and C6–C7 bond by a "through-bond" inductive mechanism, thus enlarging the electron density of these bonds and their ability to participate in the ionization process.[20] Both bonds are antiperiplanar to the developing carbocationic 2p orbital and therefore the intermediate B is stabilized most effectively by these β-CC bonding electrons.[21] A "through-bond" interaction over *both* the C4a–C8a and C6–C7 bond is concluded from the isolation of the Grob-like fragmentation products **26** and **27**. The observation that the tosylate **28** reacts much slower than the tosylates **3** and **4** may lead to the conclusion that additional acceleration of the ionization process by the axial

Scheme III[a]



[a] (a) MOMCl, *N*,*N*-diisopropylethylamine, CH_2Cl_2; (b) CH_3MgI, ether; (c) PPTS, acetone, H_2O; (d) $Ph_3P{=}CHCH_3$, DMSO; (e) B_2H_6, H_2O_2/NaOH; (f) NDC, pyridine, benzene; (g) $NaOCH_3$, CH_3OH; (h) $Ph_3P{=}CH_2$, DMSO; (i) H_2, Pt/C, C_2H_5OH; (j) HCl, CH_3OH, Δ, 75 min; (k) TsCl, pyridine; (l) Na *tert*-amylate, PhH, Δ.

β-O^- group occurs as a result of a "through-space" interaction.[22,23] The dipolar intermediate B rapidly rearranges to the thermodynamically more stable intermediate C.[17] In C the original angular methyl group and the alkoxide substituent are close together, which leads to the selective formation of **11**. The formation of the minor compounds **10** and **13** can easily be explained by direct trapping of the positive charge by the proximate alkoxide and a thermodynamically favorable deprotonation of intermediate C, respectively. Intramolecularly directed deprotonation of the intermediate B accounts for the formation of the unrearranged olefin **23**.

The applicability of this intramolecularly directed rearrangement was tested in the synthesis of the unnatural sesquiterpene (±)-5-*epi*-nardol **33**.[24] The selected approach is a straightforward extension of the aforementioned principles, i.e. synthesis of an appropriately substituted perhydronaphthalenic tosylate **34** with the correct stereochemistry, followed by an intramolecular base-induced rearrangement to (±)-5-*epi*-nardol **33**.

The preparation of **34** started with the monoacetalized dione **5**[5a] (Scheme III). Protection of the hydroxyl group of **5** as its methoxymethyl ether (MOM ether)[25] yielded compound **35** which upon treatment with an excess of methylmagnesium bromide in ether and subsequent careful hydrolysis of the dimethyl acetal function with pyridinium *p*-toluenesulfonate (PPTS) in aqueous acetone gave the monoprotected diol **36**.

(16) Paquette, L. A.; Gilday, J. P. *J. Org. Chem.* **1988**, *53*, 4972.
(17) Heathcock, C. H.; Ratcliffe, R.; Van, J. *ibid.* **1972**, *37*, 1796.
(18) Ion pairs are more likely in nonpolar solvents, see: Bartsch, R. A. *Acc. Chem. Res.* **1975**, *8*, 239.
(19) March, J. *Advanced Organic Chemistry*, 3th ed.; Wiley-Interscience: New York, 1985; p 927.
(20) Lenoir, D.; Apeloig, Y.; Arad, D.; Schleyer, P. v. R. *J. Org. Chem.* **1988**, *53*, 661.
(21) Reference 20 and references cited therein.
(22) Grob, C. A. *Acc. Chem. Res.* **1983**, *16*, 426.
(23) Paddon-Row, M. N. *Acc. Chem. Res.* **1982**, *15*, 245.
(24) (a) Sastry, S. D.; Maheshwari, M. L. *Tetrahedron Lett.* **1966**, 1035. (b) Bauer, R. F. X.; Khan, J. A.; Lotter, H.; Wagner, H. *Helv. Chim. Acta* **1985**, *68*, 2355.
(25) Heathcock, C. H.; Tice, C. M.; Germroth, T. C. *J. Am. Chem. Soc.* **1982**, *104*, 6081.

The isopropyl side chain was introduced via a Wittig reaction of **36** with ethylenetriphenylphosphorane in dimethyl sulfoxide. The resulting product **37**, obtained as a mixture of *Z* and *E* isomers, was hydroborated, oxidized with nicotinium dichromate (NDC) and pyridine in benzene,[26] and finally epimerized with sodium methoxide in dry methanol to afford the acyl derivative **38**. Treatment of **38** with methylenetriphenylphosphorane in dimethyl sulfoxide produced the corresponding isopropenyl derivative **39**. Catalytic reduction of the double bond of **39** gave the saturated compound **40**, which after hydrolysis of the MOM ether function afforded the diol **41**. Finally, the secondary hydroxyl group was tosylated in pyridine to give **34**.

The key step in the synthesis of (±)-5-*epi*-nardol **33**, the base-induced skeletal rearrangement, was performed as usual with sodium *tert*-amylate in refluxing benzene. After the workup and column chromatography (±)-5-*epi*-nardol **33** was isolated in 90% yield. These results showed that the intramolecular alkoxide-induced rearrangement of appropriately substituted perhydronaphthalenes, possessing a strategically positioned axial hydroxyl group, offer simple access to cis-fused perhydroazulenic compounds with an exocyclic double bond. Further investigations of these alkoxide-induced and -directed rearrangements and their applications in the natural product synthesis are currently ongoing in our laboratory.

Experimental Section

Melting points were determined on an Olympus HSA melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a JASCO A-100 infrared spectrophotometer, and peak positions are expressed in cm^{-1}. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded at either 90 MHz on a Varian EM-390 spectrometer or at 300 MHz on a Bruker CXP-300 spectrometer. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 75.460 MHz on a Bruker CXP-300 spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (δ 0.0) as an internal standard. NMR multiplicities are recorded by use of the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet, m, multiplet; br, broad; *J*, coupling constant in hertz. Mass spectral data were determined on either an AEI MS 902 spectrometer or a VG Micromass 7070 F spectrometer at 70 eV. Elemental analyses were determined on a Carlo Erba elemental analyzer 1106. Gas–liquid chromatography (GC) analyses were carried out on a Varian Vista 6000 gaschromatograph with a flame ionization detector and a DB-17 fused silica capillary column, 30 m × 0.25 mm i.d., film thickness 0.25 μm. Peak areas were integrated electronically with a Spectra-Physics integrator SP 4290. Column chromatography was performed using Merck silica gel 60 (70–230 mesh) and ICN alumina B-Super I (activity grade II). Flash chromatography was performed using Merck silica gel 60 (230–400 mesh).

Solvents were dried and distilled fresh by common practice. For all dry reactions, flasks were dried at 150 °C and flushed with dry nitrogen just before use, and reactions were carried out under an atmosphere of dry nitrogen. Product solutions were dried over anhydrous sodium sulfate, unless otherwise noted, prior to evaporation of the solvent under reduced pressure by using a rotary evaporator. 2-Butanone dioxolane (MED) was prepared from 2-butanone as reported.[9]

(4aα,5α,8α,8aβ)-Octahydro-5,8-dihydroxy-4a,8-dimethyl-2(1*H*)-naphthalenone (6). To a solution of 9.92 g (40.99 mmol) of dimethyl acetal **5**[5a] in 350 mL of dry THF, cooled to −78 °C, was added dropwise 90 mL (144.0 mmol) of CH_3Li (1.6 M in ether). When the addition was complete, the reaction mixture was allowed to stir for 1 h at −78 °C. The excess CH_3Li was then quenched by the careful addition of saturated aqueous NH_4Cl solution. The reaction mixture was washed with 300 mL of brine, and the aqueous phase was then continuously back-extracted with CH_2Cl_2. The combined organic layers were dried and evaporated under reduced pressure, and the resulting residue was taken up in a mixure of 50 mL of acetone and 2.5 mL of a 15% aqueous HCl solution. The reaction mixture was allowed to stir at room temperature for 5.5 h and then neutralized with triethylamine. Evaporation of the solvent under reduced pressure and chromatography of the residue on silica gel (ether) gave 6.30 g (72.5%) of pure diol **6**: mp 151–153 °C (from EtOAc); ^1H NMR ($CDCl_3$, 90 MHz) δ 1.15 (s, 3 H), 1.25 (s, 3 H), 1.29–2.77 (m, 13 H), 3.30 (m, 1 H); mass spectrum, *m/e* (relative intensity) 212 (M^+, 13), 194 (100), 141 (58), 137 (53), 136 (71), 111 (55), 109 (47), 101 (58), 95 (69), 83 (40), 72 (91), 43 (98); calcd for $C_{12}H_{20}O_3$ (M^+) *m/e* 212.1412, found *m/e* 212.1412. Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 68.08; H, 9.29.

(4aα,5α,8α,8aβ)-Octahydro-5,8-dihydroxy-4a,8-dimethyl-2(1*H*)-naphthalenone 5-(4-Methylbenzenesulfonate) (7). To a stirred solution of 2.159 g (10.18 mmol) of diol **6** in 20 mL of pyridine was added 2.548 g (13.36 mmol) of TsCl. The reaction mixture was stirred at room temperature for 3 d and then concentrated under reduce pressure. The resulting mixture was taken up in 100 mL of CH_2Cl_2 and washed successively with one 50-mL portion of a 10% aqueous HCl solution, two 25-mL portions of a saturated aqueous $NaHCO_3$ solution, and one 50-mL portion of brine. The organic layer was dried, and the solvent was removed under reduced pressure. The crude product was flash chromatographed on silica gel (2:1 petroleum ether (bp 40–60 °C)/EtOAc) to give 3.432 g (92%) of pure monotosylated ketone **7**: mp 157 °C dec (from petroleum ether (bp 60–80 °C)/EtOAc); ^1H NMR ($CDCl_3$, 90 MHz) δ 1.10 (s, 3 H), 1.23 (s, 3 H), 1.25–2.73 (m, 12 H), 2.43 (s, 3 H), 4.25 (m, 1 H), 7.33 (d, *J* = 8 Hz, 2 H), 7.80 (d, *J* = 8 Hz, 2 H); mass spectrum, *m/e* (relative intensity) 366 (M^+), 194 (100). Anal. Calcd for $C_{19}H_{26}O_5S$: C, 62.27; H, 7.15. Found: C, 62.09; H, 6.86.

(4'aα,5'α,8'α,8'aβ)-Octahydro-4'a,8'-dimethylspiro[1,3-dioxolane-2,2'(1'*H*)-naphthalene]-5',8'-diol 5'-(4-Methylbenzenesulfonate) (3). To a solution of 2.828 g (7.73 mmol) of monotosylated ketone **7** in a mixture of 15 mL of CH_2Cl_2 and 15 mL of MED was added catalytic amounts of ethylene glycol and *p*-toluenesulfonic acid monohydrate. The reaction mixture was stirred at room temperature for 24 h, after which time 0.5 mL of triethylamine was added. The reaction mixture was then diluted with 100 mL of CH_2Cl_2 and washed with 50 mL of brine. The organic layer was dried and evaporated under reduced pressure to give the crude monotosylated dioxolane **3**. Recrystallization from methanol and flash chromatography of the mother liquor on silica gel (1:1 petroleum ether (bp 40–60 °C)/EtOAc) afforded 3.066 g (97%) of pure **3**: mp 150 °C dec; ^1H NMR ($CDCl_3$, 90 MHz) δ 1.12 (s, 3 H), 1.14 (s, 3 H), 1.17–2.34 (m, 12 H), 2.45 (s, 3 H), 3.94 (br s, 4 H), 4.27 (m, 1 H), 7.30 (d, *J* = 8 Hz, 2 H), 7.77 (d, *J* = 8 Hz, 2 H); mass spectrum, *m/e* (relative intensity) 392 (M^+ − 18, 15), 220 (41), 176 (24), 172 (48), 99 (100), 91 (52). Anal. Calcd for $C_{21}H_{30}O_6S$: C, 61.44; H, 7.37. Found: C, 61.36; H, 7.28.

(4aα,5α,8β,8aβ)-Octahydro-5,8-dihydroxy-4a-methyl-2-(1*H*)-naphthalenone 5-(4-Methylbenzenesulfonate) (8) and (4aα,5α,8α,8aβ)-Octahydro-5,8-dihydroxy-4a-methyl-2-(1*H*)-naphthalenone 5-(4-Methylbenzenesulfonate) (9). A sample of 1.900 g (7.85 mmol) of dimethyl acetal **5**[5a] was treated with TsCl, using conditions similar to those employed for the preparation of the monotosylated diol **7**. After workup the resulting product was taken up in 40 mL of ethanol and cooled to 0 °C, and then 1.00 g (26.46 mmol) of $NaBH_4$ in a mixture of 10 mL of ethanol and 1 mL of a 15% aqueous NaOH solution was added dropwise. When the addition was complete, the reaction mixture was allowed to stir for 2 h at 0 °C, and then the ice bath was removed and stirring was continued for 1 h. The reaction mixture was diluted with 150 mL of water and extracted with four 50-mL portions of CH_2Cl_2. The combined organic layers were washed with 50 mL of brine and dried. The solvent was evaporated under reduced pressure, and the remaining residue was taken up in a mixture of 25 mL of acetone and 5 mL of a 5% aqueous HCl solution. The reaction mixture was allowed to stir at room temperature for 2 h and then diluted with 75 mL of CH_2Cl_2. The organic layer was washed with 50 mL of a saturated aqueous

(26) Cossio, F. P.; Lopez, M. C.; Palomo, C. *Tetrahedron* **1987**, *43*, 3963.

$NaHCO_3$ solution followed by brine, dried, and then evaporated under reduced pressure. The resulting product was chromatographed on silica gel (1:1 petroleum ether (bp 40–60 °C)/EtOAc) to give 1.79 g (65%) of pure β-alcohol **9** along with 0.17 g (6%) of pure α-alcohol **8**.

8: ^1H NMR ($CDCl_3$, 90 MHz) δ 1.10 (s, 3 H), 1.11–2.83 (m, 12 H), 2.48 (s, 3 H), 3.43 (dt, J = 4.5, 10.5 Hz, 1 H), 4.23 (dd, J = 6.5, 9.5 Hz, 1 H), 7.33 (d, J = 8 Hz, 2 H), 7.74 (d, J = 8 Hz, 2 H); mass spectrum, m/e (relative intensity) 171 (86), 91 (100).

9: mp 120–122 °C (from diisopropyl ether); ^1H NMR ($CDCl_3$, 90 MHz) δ 1.31 (s, 3 H), 1.33–2.93 (m, 12 H), 2.48 (s, 3 H), 3.67 (m, 1 H), 4.24 (dd, J = 4, 12 Hz, 1 H), 7.32 (d, J = 8 Hz, 2 H), 7.79 (d, J = 8 Hz, 2 H); mass spectrum, m/e (relative intensity) 352 (M^+), 180 (100), 172 (36), 91 (59). Anal. Calcd for $C_{18}H_{24}O_5S$: C, 61.34; H, 6.86. Found: C, 61.08; H, 6.65.

(4′aα,5′α,8′α,8′aβ)-Octahydro-4′a-methylspiro[1,3-dioxolane-2,2′(1′*H*)-naphthalene]-5′,8′-diol 5′-(4-Methylbenzenesulfonate) (4). The β-hydroxyl tosylate **4** was prepared from **9** as described for the synthesis of the tosylate **3**. The workup and chromatography on silica gel (1:1 petroleum ether (bp 40–60 °C)/EtOAc) afforded in a 94% yield pure **4**: mp 124–126 °C (from diisopropyl ether); ^1H NMR ($CDCl_3$, 90 MHz) δ 1.00–2.27 (m, 12 H), 1.11 (s, 3 H), 2.44 (s, 3 H), 3.67 (m, 1 H), 3.92 (s, 4 H), 4.29 (dd, J = 5, 11 Hz, 1 H), 7.31 (d, J = 8 Hz, 2 H), 7.78 (d, J = 8 Hz, 2 H); mass spectrum, m/e (relative intensity) 378 (M^+ – 18), 171 (100), 91 (95). Anal. Calcd for $C_{20}H_{28}O_6S$: C, 60.58; H, 7.12. Found: C, 60.43; H, 7.07.

Rearrangement of Tosylate 3. a. With Lithium Carbonate in Aqueous Dioxane. To a solution of 0.410 g (1.00 mmol) of tosylate **3** in 15 mL of dioxane was added 7.5 mL of water and 0.802 g (10.85 mmol) of lithium carbonate. The reaction mixture was heated at reflux for 30 h, allowed to come to room temperature, and then filtered. The filtrate was diluted with 50 mL of brine and extracted with three 50-mL portions of CH_2Cl_2. The combined organic layers were dried and evaporated under reduced pressure. The remaining residue, according to GC analysis a mixture of five products in a ratio of 1.3:1:5.3:1:1.8, was chromatographed on basic alumina (activity II) (15:1 to 0:1 petroleum ether (bp 40–60 °C)/EtOAc) to give, in order of elution, the cyclic ether **10** (0.028 g, 12%), an inseparable 1:1 mixture of the exo 8-olefin **11** and the endo 7,8-olefin **12** (0.043 g, 18%), the endo 8,8a-olefin **13** (0.115 g, 48%), and the diol **14** (0.042 g, 16%). Physical and spectroscopic data of the products **10**, **12**, **13**, and **14** follow.

(1′α,3′aβ,4′α,8′aβ)-Octahydro-1′,4′-dimethylspiro[1,3-dioxolane-2,7′(1′*H*)-[1,4]epoxyazulene] (10): ^1H NMR ($CDCl_3$, 90 MHz) δ 1.23 (s, 3 H), 1.25 (s, 3 H), 1.40–2.14 (m, 11 H), 2.45 (br s, 1 H), 3.92 (s, 4 H); mass spectrum, m/e (relative intensity) 238 (M^+, 8), 176 (15), 143 (34), 139 (14), 99 (100), 87 (16), 86 (87), 43 (27); calcd for $C_{14}H_{22}O_3$ (M^+) m/e 238.1569, found m/e 238.1569.

(3α,3aβ,8aβ)-2,3,3a,4,6,8a-Hexahydro-3,8-dimethylspiro-[azulene-5(1*H*),2′-[1,3]dioxolan]-3-ol (12): ^1H NMR (main peaks, $CDCl_3$, 90 MHz) δ 1.29 (s, 3 H), 1.75 (br s, 3 H), 3.93 (m, 4 H), 5.46 (br t, J = 7.5 Hz, 1 H); mass spectrum, m/e (relative intensity) 238 (M^+, 16), 165 (10), 139 (10), 119 (12), 99 (100), 93 (11), 86 (12), 81 (21), 79 (11), 43 (13).

***trans*-2,3,3a,4,6,7-Hexahydro-3,8-dimethylspiro[azulene-5(1*H*),2′-[1,3]dioxolan]-3-ol (13)**: mp 128–130 °C (from petroleum ether (bp 40–60 °C)); ^1H NMR ($CDCl_3$, 90 MHz) δ 1.28 (s, 3 H), 1.30–2.66 (m, 12 H), 1.65 (br s, 3 H), 3.94 (m, 4 H); mass spectrum, m/e (relative intensity) 238 (M^+, 28), 220 (36), 130 (30), 119 (42), 118 (40), 105 (28), 99 (100), 91 (41), 86 (64), 43 (48); calcd for $C_{14}H_{22}O_3$ (M^+) m/e 238.1569, found m/e 238.1568. Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 70.63; H, 9.48.

(3α,3aβ,8β,8aβ)-Octahydro-3,8-dimethylspiro[azulene-5-(1*H*),2′-[1,3]dioxolane]-3,8-diol (14): ^1H NMR ($CDCl_3$, 90 MHz) δ 1.23 (s, 3 H), 1.26 (s, 3 H), 1.42–2.58 (m, 14 H), 3.93 (s, 4 H); mass spectrum, m/e (relative intensity) 256 (M^+, 2), 238 (37), 223 (13), 209 (16), 194 (30), 143 (28), 139 (31), 115 (70), 100 (62), 99 (100), 43 (69); calcd for $C_{14}H_{24}O_4$ (M^+) m/e 256.1674, found m/e 256.1677.

b. With Potassium *tert*-Butoxide in *tert*-Butyl Alcohol. To a solution of 0.970 g (8.66 mmol) of potassium *tert*-butoxide in 15 mL of dry *tert*-butyl alcohol was added 0.344 g (0.84 mmol) of tosylate **3**. The mixture was heated at reflux for 43 h, allowed to come to room temperature, and then poured into 50 mL of water. The aqueous solution was extracted with three 25-mL portions of $CHCl_3$. The combined organic layers were washed with 25 mL of brine, dried over anhydrous K_2CO_3, and then evaporated under reduced pressure. The remaining residue was chromatographed on basic alumina (activity II) (10:1 to 3:1 petroleum ether (bp 40–60 °C)/EtOAc) to give, in order of elution, **10** (0.028 g, 14%) and, according to GC and ^1H NMR analysis, a mixture (0.152 g, 76%) of **11**, **12**, and **13** in a ratio of 5.8:1:1.5, respectively.

c. With Sodium *tert*-Amylate in Benzene. To a mixture of 0.5 mL of dry *tert*-amyl alcohol and 20 mL of dry benzene was added 0.066 g (2.20 mmol, as a 80% dispersion in mineral oil) of sodium hydride. The mixture was heated at reflux for 0.5 h, allowed to come to room temperature, and then 0.410 g (1.00 mmol) of tosylate **3** was added. The solution was heated at reflux for 20 h and, after cooling to room temperature, poured into 50 mL of brine. The two-phase mixture was separated, and the aqueous layer was extracted with three 25-mL portions of ether. The combined organic layers were dried over anhydrous K_2CO_3 and evaporated under reduced pressure. The resulting residue, according to GC analysis a mixture of **10** (3%), **11** (90%), **13** (4%), and the unrearranged olefin **23** (3%), was crystallized from petroleum ether (bp 40–60 °C) to give pure **(3α,3aβ,8aβ)-octahydro-3-methyl-8-methylenespiro[azulene-5(1*H*),2′-[1,3]dioxolan]-3-ol (11)** (0.187 g, 78.5%): mp 84.5–85 °C; ^1H NMR ($CDCl_3$, 90 MHz) δ 1.27 (s, 3 H), 1.43–2.00 (m, 13 H), 3.92 (s, 4 H), 4.85–4.97 (m, 2 H); mass spectrum, m/e (relative intensity) 238 (M^+, 18), 220 (18), 181 (15), 165 (15), 133 (17), 119 (20), 105 (17), 99 (100), 93 (18), 91 (22), 86 (55), 79 (18), 43 (38); calcd for $C_{14}H_{22}O_3$ (M^+) m/e 238.1569, found m/e 238.1568. Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 70.51; H, 9.43.

d. With Potassium *tert*-Amylate in Benzene. The tosylate **3** (0.410 g, 1.00 mmol) was treated as described above, using potassium hydride (0.088 g, 2.20 mmol) in place of sodium hydride. The workup and chromatography on basic alumina (activity II) (15:1 to 4:1 petroleum ether (bp 40–60 °C)/EtOAc) gave, in order of elution, **10** (0.015 g, 6%), **23** (0.002 g, 1%), **11** (0.207 g, 87%), and **13** (0.004 g, 2%).

e. With Lithium *tert*-Amylate in Benzene. The tosylate **3** (0.410 g, 1.00 mmol) was treated for 92 h as described above, using 1.5 mL (2.25 mmol) of a 15% solution of *n*-butyllithium in hexane in place of sodium hydride. After workup, the resulting residue, according to GC analysis a mixture of seven products, was chromatographed on basic alumina (activity II) (12.5:1 to 3:1 petroleum ether (bp 40–60 °C)/EtOAc) to give, in order of elution, **10** (0.019 g, 8%), the cyclohexane derivative **26** (0.003 g, 1%), the cyclohexene derivative **27** (0.007 g, 3%), **23** (0.005 g, 2%), **11** (0.141 g, 59%), and **13** (0.031 g, 13%). Physical and spectroscopic data of the products **23**, **26**, and **27** follow.

(4′aα,8′α,8′aβ)-3′,4′,4′a,7′,8′,8′a-Hexahydro-4′a,8′-dimethylspiro[1,3-dioxolane-2,2′(1′*H*)-naphthalen]-8′-ol (23): ^1H NMR ($CDCl_3$, 300 MHz) δ 1.17 (s, 3 H), 1.21 (s, 3 H), 1.23–1.86 (m, 8 H), 2.11 (dd, J = 4.4, 18.5 Hz, 1 H), 2.27 (dt, J = 2.7, 18.5 Hz, 1 H), 3.96 (m, 4 H), 5.45 (ddd, J = 2.7, 4.4, 10.0 Hz, 1 H), 5.59 (br d, J = 10.0 Hz, 1 H); mass spectrum, m/e (relative intensity) 238 (M^+, 0.2), 220 (5), 142 (26), 99 (100), 86 (19), 43 (14); calcd for $C_{14}H_{22}O_3$ (M^+) m/e 238.1569, found m/e 238.1570.

(7α,8β)-1-[8-Methyl-8-(2-propenyl)-1,4-dioxaspiro[4.5]-dec-7-yl]ethanone (26): ^1H NMR ($CDCl_3$, 300 MHz) δ 1.04 (s, 3 H), 1.21–2.49 (m, 8 H), 2.15 (s, 3 H), 2.76 (dd, J = 3.0, 13.0 Hz, 1 H), 3.94 (s, 4 H), 4.99–5.11 (m, 2 H), 5.84 (m, 1 H); mass spectrum, m/e (relative intensity) 238 (M^+, 2), 195 (18), 167 (58), 139 (12), 111 (12), 99 (100), 93 (10), 87 (31), 86 (36), 81 (18), 43 (52); calcd for $C_{14}H_{22}O_3$ (M^+) m/e 238.1569, found m/e 238.1563.

8-(1-Methyl-4-oxopentyl)-1,4-dioxaspiro[4.5]dec-7-ene (27): ^1H NMR ($CDCl_3$, 300 MHz) δ 1.10 (d, J = 7.3 Hz, 3 H), 1.48–2.60 (m, 11 H), 2.14 (s, 3 H), 3.91 (br s, 4 H), 5.22 (dd, J = 4.9, 8.8 Hz, 1 H); mass spectrum, m/e (relative intensity) 238 (M^+, 4), 181 (3), 119 (3), 118 (7), 105 (5), 100 (13), 99 (100), 91 (6), 86 (6), 79 (6), 55 (6), 43 (14); calcd for $C_{14}H_{22}O_3$ (M^+) m/e 238.1569, found m/e 238.1565.

Rearrangement of Tosylate 4. a. With Potassium *tert*-Butoxide in *tert*-Butyl Alcohol. The tosylate **4** (0.597 g, 1.51 mmol) was treated with potassium *tert*-butoxide as described for the rearrangement of the tosylate **3**. The workup and chroma-

tography on silica gel (3:1 to 2:1 petroleum ether (bp 40–60 °C)/EtOAc) gave, in order of elution, the cyclic ether **15** (0.055 g, 16%) and according to GC and ^{1}H NMR analysis, a mixture (0.233 g, 69%) of the exo 8-olefin **16**, the endo 7,8-olefin **17**, and the endo 8,8a-olefin **18** in a ratio of 16:1:8, respectively. Physical and spectroscopic data of the products **15** and **17** follow.

(1′α,3′aβ,4′α,8′aβ)-Octahydro-4′-methylspiro[1,3-dioxolane-2,7′(1′*H*)-[1,4]epoxyazulene] (15): ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.29 (s, 3 H), 1.31–2.18 (m, 11 H), 2.42 (br s, 1 H), 3.94 (s, 4 H), 3.95 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 75.460 MHz) δ 25.46 (t), 27.62 (q), 29.58 (t), 32.72 (t), 36.22 (t), 37.25 (t), 45.76 (d), 46.88 (d), 63.90 (t), 64.43 (t), 81.27 (s), 84.04 (d), 110.49 (s); mass spectrum, *m/e* (relative intensity) 224 (M^+, 6), 195 (10), 181 (6), 167 (13), 143 (33), 125 (55), 101 (24), 100 (23), 99 (100), 86 (76), 43 (83); calcd for $C_{13}H_{20}O_3$ (M^+) *m/e* 224.1412, found *m/e* 224.1412.

(3α,3aβ,8aβ)-2,3,3a,4,6,8a-Hexahydro-8-methylspiro[azulene-5(1*H*),2′-[1,3]dioxolan]-3-ol (17): ^{1}H NMR (main peaks, $CDCl_3$, 90 MHz) δ 5.39 (br t, *J* = 7.5 Hz, 1 H); mass spectrum, *m/e* (relative intensity) 224 (M^+, 30), 206 (33), 165 (44), 141 (48), 125 (18), 123 (21), 118 (20), 99 (100), 91 (15), 87 (39), 86 (95), 81 (33), 79 (27), 73 (23), 43 (22).

b. With (Dimethylsulfinyl)sodium in Dimethyl Sulfoxide. To a stirred solution of 7.5 mL of 0.35 M (dimethylsulfinyl)sodium in dimethyl sulfoxide was added dropwise a solution of 0.479 g (1.21 mmol) of tosylate **4** in 7.5 mL of dimethyl sulfoxide. The mixture was heated at 70 °C for 5 h, allowed to stir at room temperature for 16 h, and then poured into 100 mL of water. The aqueous solution was extracted with five 30-mL portions of ether. The combined organic layers were washed with 75 mL of brine, dried, and then evaporated under reduced pressure. The resulting residue was chromatographed on silica gel (5:1 to 2:1 petroleum ether (bp 40–60 °C)/EtOAc) to give, in order of elution, **15** (0.066 g, 24%) and, according to GC and ^{1}H NMR analysis, a mixture (0.119 g, 44%) of **16** and **18** in a ratio of 7:3, respectively.

c. With Sodium *tert*-Amylate in Benzene. The tosylate **4** (0.396 g, 1.00 mmol) was treated with sodium *tert*-amylate (5 equiv) for 16 h as described for the rearrangement of the tosylate **3**. The workup and chromatography on basic alumina (activity II) (15:1 to 2:1 petroleum ether (bp 40–60 °C)/EtOAc) gave, in order of elution, a 2:1 mixture of the epimeric rearranged ketones **24** (0.016 g, 7%), **15** (0.016 g, 7%), the cyclopropyl derivative **25** (0.009 g, 4%), pure **16** (0.060 g, 27%), and 0.100 g (45%) of a 2:1 mixture of **16** and **18**, respectively. Physical and spectroscopic data of the products **16**, **18**, **24**, and **25** follow.

(3α,3aβ,8aβ)-Octahydro-8-methylenespiro[azulene-5-(1*H*),2′-[1,3]dioxolan]-3-ol (16): ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.10–2.90 (m, 13 H), 3.90 (s, 4 H), 4.18 (m, 1 H), 4.81 (br s, 1 H), 4.88 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 75.460 MHz) δ 26.41 (t), 32.23 (t), 33.49 (2 t), 39.03 (t), 41.58 (d), 46.01 (d), 64.10 (t), 64.26 (t), 75.78 (d), 110.04 (t), 111.30 (s), 151.36 (s); mass spectrum, *m/e* (relative intensity) 224 (M^+, 17), 206 (18), 165 (24), 141 (20), 123 (20), 99 (53), 91 (15), 87 (39), 86 (100), 79 (18), 43 (19); calcd for $C_{13}H_{20}O_3$ (M^+) *m/e* 224.1412, found *m/e* 224.1417.

***trans*-2,3,3a,4,6,7-Hexahydro-8-methylspiro[azulene-5-(1*H*),2′-[1,3]dioxolan]-3-ol (18)**: ^{13}C NMR ($CDCl_3$, 75.460 MHz) δ 21.96 (q), 28.55 (t), 30.00 (t), 35.98 (t), 37.11 (t), 43.38 (t), 45.90 (d), 64.09 (t), 64.14 (t), 76.80 (d), 111.81 (s), 129.17 (s), 137.79 (s); mass spectrum, *m/e* (relative intensity) 224 (M^+, 14), 206 (40), 123 (25), 118 (27), 99 (38), 91 (16), 87 (43), 86 (100), 79 (15), 43 (18).

Epimeric ketones 24: IR ($CHCl_3$) 1750, 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.13–3.23 (m), 3.94 (br s), 4.80 (m), 4.90 (m); mass spectrum (major compound), *m/e* (relative intensity) 222 (M^+, 27), 207 (6), 153 (18), 112 (15), 99 (34), 87 (18), 86 (100), 79 (19), 55 (23); mass spectrum (minor compound), *m/e* (relative intensity) 222 (M^+, 24), 207 (7), 153 (20), 112 (15), 99 (45), 87 (22), 86 (100), 79 (19), 55 (26).

(1aα,1bβ,5aα,6aα)-Octahydro-1b-methylspiro[cyclopropa]indene-4(1*H*),2′-[1,3]dioxolan]-6-one (25): IR ($CHCl_3$) 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.03 (m, 2 H), 1.22 (s, 3 H), 1.25–2.10 (m, 8 H), 2.25 (br d, *J* = 13.5 Hz, 1 H), 3.93 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.460 MHz) δ 13.76 (t, *J* = 165 Hz), 22.78 (q), 26.37 (d, *J* = 176 Hz), 27.02 (t), 30.81 (t), 32.75 (d, *J* = 171 Hz), 35.27 (t), 36.21 (t), 46.47 (d), 63.74 (t), 64.23 (t), 107.97 (s), 212.05 (s); mass spectrum, *m/e* (relative intensity) 222 (M^+, 5), 126 (9), 100 (7), 99 (100), 86 (16), 79 (5), 55 (19); calcd for $C_{13}H_{18}O_3$ (M^+) *m/e* 222.1256, found *m/e* 222.1257.

(1α,3aβ,7α,8aβ)-Octahydro-4-methylene-1,7-epoxyazulen-7(1*H*)-ol (19) and *trans*-2,3,3a,4,6,7-Hexahydro-3-hydroxy-8-methyl-5(1*H*)-azulenone (20). To a solution of 0.100 g (0.45 mmol) of the foregoing 2:1 mixture of **16** and **18** in 15 mL of acetone was added 0.5 mL of a 15% aqueous HCl solution. The reaction mixture was allowed to stir at room temperature for 4.5 h and then neutralized with 5 mL of a saturated aqueous $NaHCO_3$ solution. The reaction mixture was concentrated under reduced pressure and diluted with 50 mL of water. After extraction with three 25-mL portions of CH_2Cl_2, the combined organic layers were washed with 50 mL of brine and dried. Evaporation of the solvent under reduced pressure and flash chromatography of the residue on silica gel (5:1 petroleum ether (bp 40–60 °C)/EtOAc) gave, in order of elution, 0.049 g (61%) of **19** and 0.025 g (31%) of **20**.

19: mp 117–118 °C (from petroleum ether (bp 40–60 °C)); IR ($CHCl_3$) 3580, 3360 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.50–3.13 (m, 12 H), 3.43 (br s, 1 H), 4.77 (br s, 2 H), 4.82 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75.460 MHz) δ 28.09 (t), 30.97 (t), 32.30 (t), 41.00 (t), 41.71 (t), 48.31 (d), 49.31 (d), 87.98 (d), 108.47 (s), 114.18 (t), 151.29 (s); mass spectrum, *m/e* (relative intensity) 180 (M^+, 15), 165 (11), 162 (13), 151 (26), 135 (100), 120 (30), 108 (47), 107 (47), 105 (49), 97 (30), 93 (57), 92 (35), 91 (59), 82 (61), 81 (43), 79 (88), 67 (71), 55 (41), 41 (60); calcd for $C_{11}H_{16}O_2$ (M^+) *m/e* 180.1150, found *m/e* 180.1153. Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.45; H, 8.75.

20: IR ($CHCl_3$) 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.60–3.07 (m, 12 H), 1.71 (br s, 3 H), 4.22 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75.460 MHz) δ 21.91 (q), 29.12 (t), 31.13 (t), 33.14 (t), 42.07 (t), 43.49 (t), 44.10 (d), 76.49 (d), 128.91 (s), 136.70 (s), 213.57 (s); mass spectrum, *m/e* (relative intensity) 180 (M^+, 61), 162 (71), 137 (22), 124 (45), 123 (71), 121 (28), 120 (36), 119 (35), 118 (25), 109 (38), 107 (40), 105 (48), 95 (29), 93 (52), 91 (57), 81 (27), 79 (100), 77 (41), 67 (31), 55 (32), 53 (28), 43 (33), 41 (49); calcd for $C_{11}H_{16}O_2$ (M^+) *m/e* 180.1150, found *m/e* 180.1144.

(1α,3aβ,7α,8aβ)-Octahydro-1-methyl-4-methylene-1,7-epoxyazulen-7(1*H*)-ol (21). The exo 8-olefin **11** (0.282 g, 1.18 mmol) was hydrolyzed as described above for the mixture of **16** and **18**. The workup and chromatography on silica gel (4:1 petroleum ether (bp 40–60 °C)/EtOAc) afforded 0.197 g (86%) of pure **21**: mp 104–106 °C (from petroleum ether (bp 60–80 °C)); IR ($CHCl_3$) 3590, 3375 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.41 (s, 3 H), 1.50–2.62 (m, 11 H), 3.01 (m, 1 H), 3.42 (br s, 1 H), 4.77 (br s, 2 H); mass spectrum, *m/e* (relative intensity) 194 (M^+, 13), 179 (16), 176 (25), 165 (25), 136 (41), 133 (32), 122 (36), 121 (31), 119 (47), 105 (36), 93 (54), 91 (44), 82 (36), 81 (74), 79 (54), 55 (32), 43 (100). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.23; H, 9.43.

***trans*-2,3,3a,4,6,7-Hexahydro-3-hydroxy-3,8-dimethyl-5-(1*H*)-azulenone (22).** The endo 8,8a-olefin **13** (0.122 g, 0.51 mmol) was hydrolyzed as described above for **11**. The workup and chromatography on silica gel (4:1 petroleum ether (bp 40–60 °C)/EtOAc) afforded 0.069 g (69%) of pure **22**: IR ($CHCl_3$) 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.33 (s, 3 H), 1.35–3.09 (m, 12 H), 1.71 (br s, 3 H); mass spectrum, *m/e* (relative intensity) 194 (M^+, 28), 179 (12), 176 (75), 136 (70), 133 (39), 123 (40), 119 (36), 118 (44), 105 (39), 93 (59), 91 (58), 79 (60), 43 (100); calcd for $C_{12}H_{18}O_2$ (M^+) *m/e* 194.1307, found *m/e* 194.1304.

(4′aα,5′α,8′β,8′aβ)-Octahydro-4′a-methylspiro[1,3-dioxolane-2,2′(1′*H*)-naphthalene]-5′,8′-diol 5′-(4-Methylbenzenesulfonate) (28). The α-hydroxyl tosylate **28** was prepared from **8** as described for the synthesis of the tosylate **3**. The workup and chromatography on silica gel (1:1 petroleum ether (bp 40–60 °C)/EtOAc) afforded in a 82% yield pure **28**: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.89 (s, 3 H), 1.10–2.17 (m, 12 H), 2.44 (s, 3 H), 3.35 (m, 1 H), 3.97 (s, 4 H), 4.26 (dd, *J* = 6.5, 9.5 Hz, 1 H), 7.33 (d, *J* = 8 Hz, 2 H), 7.78 (d, *J* = 8 Hz, 2 H); mass spectrum, *m/e* (relative intensity) 224 (M^+ – 172, 5), 206 (26), 172 (80), 154 (37), 128 (20), 99 (59), 91 (100); calcd for $C_{20}H_{28}O_6S$ (M^+) *m/e* 396.1606, found *m/e* 396.1611.

(4′aα,5′α,8′aβ)-Octahydro-4′a-methylspiro[1,3-dioxolane-2,2′(1′*H*)-naphthalen]-5′-ol 5′-(4-Methylbenzenesulfonate) (29). The tosylate **29** was prepared from **30**[17] as described for the synthesis of the tosylate **3**. The workup and chromatography on silica gel (3:1 petroleum ether (bp 40–60 °C)/EtOAc) afforded

in quantitative yield pure **29**: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.88 (s, 3 H), 1.03–1.91 (m, 13 H), 2.43 (s, 3 H), 3.91 (s, 4 H), 4.26 (m, 1 H), 7.32 (d, J = 8 Hz, 2 H), 7.79 (d, J = 8 Hz, 2 H); mass spectrum, m/e (relative intensity) 380 (M^+), 208 (6), 112 (26), 99 (100); calcd for $C_{20}H_{28}O_5S$ (M^+) m/e 380.1658, found m/e 380.1659.

Treatment of Tosylate 28 with Sodium *tert*-Amylate. The tosylate **28** (0.382 g, 0.96 mmol) was treated with sodium *tert*-amylate (2.2 eq) for 21 h as described for the rearrangement of the tosylate **3**. The workup and chromatography on silica gel (2:1 petroleum ether (bp 40–60 °C)/EtOAc) gave, in order of elution, 0.027 g (13%) of a mixture of mainly **31** and **32** in a ratio, according to GC analysis, of 1:2.5, respectively, and 0.225 g (59%) of the starting material **28**.

31: ^{1}H NMR (main peaks, $CDCl_3$, 90 MHz) δ 3.95 (s, 4 H), 4.77 (br s, 1 H), 4.88 (br s, 1 H); mass spectrum, m/e (relative intensity) 224 (M^+, 22), 165 (20), 153 (11), 141 (15), 123 (12), 99 (62), 87 (33), 86 (100), 79 (14), 43 (15).

32: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.05–2.70 (m, 12 H), 1.65 (br s, 3 H), 3.72 (m, 1 H), 3.96 (s, 4 H); mass spectrum, m/e (relative intensity) 224 (M^+, 8), 206 (52), 191 (12), 144 (13), 123 (24), 99 (45), 87 (39), 86 (100), 79 (14), 43 (17).

Treatment of Tosylate 29 with Sodium *tert*-Amylate. The tosylate **29** (0.485 g, 1.28 mmol) was treated with sodium *tert*-amylate (2.2 eq) for 21 h as described for the rearrangement of the tosylate **3**. Workup and chromatography on silica gel (3:1 petroleum ether (bp 40–60 °C)/EtOAc) gave 0.470 g (97%) of the starting material **29**.

(4α,4aα,8aβ)-Octahydro-7,7-dimethoxy-4-(methoxymethoxy)-4a-methyl-1(2*H*)-naphthalenone (35). To a solution of 5.169 g (21.36 mmol) of keto alcohol **5**[5a] in 100 mL of CH_2Cl_2 were added 25 mL of diisopropylethylamine and 7.0 mL (85.6 mmol) of chloromethyl methyl ether. The reaction mixture was stirred at room temperature for 18 h, and then another 5.6 mL of diisopropylethylamine and 1.6 mL (21.9 mmol) of chloromethyl methyl ether were added. Stirring was continued at room temperature for an additional 4 h, after which time 50 mL of concentrated ammonia and 100 mL of water were added. The two-phase mixture was separated, and the aqueous layer was extracted with three 50-mL portions of CH_2Cl_2. The combined organic layers were washed with 75 mL of brine, dried, and evaporated under reduced pressure. The resulting residue was chromatographed on basic alumina (activity II) (3:1 petroleum ether (bp 40–60 °C)/EtOAc) to give 5.846 g (96%) of pure MOM ether **35**: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.82 (s, 3 H), 1.13–2.60 (m, 11 H), 3.10 (s, 3 H), 3.20 (s, 3 H), 3.38 (s, 3 H), 3.72 (dd, J = 4, 10 Hz, 1 H), 4.70 (AB q, J = 7 Hz, 2 H); mass spectrum, m/e (relative intensity) 286 (M^+, 23), 225 (24), 241 (20), 193 (23), 101 (100), 88 (29), 45 (27); calcd for $C_{15}H_{26}O_5$ (M^+) m/e 286.1780, found m/e 286.1783.

(4aα,5α,8α,8aβ)-Octahydro-8-hydroxy-5-(methoxymethoxy)-4a,8-dimethyl-2(1*H*)-naphthalenone (36). To 100 mL of 0.65 M methylmagnesium iodide in ether was added dropwise a solution of 4.493 g (15.71 mmol) of MOM ether **35** in 100 mL of dry ether. The reaction mixture was allowed to stir at room temperature for 15 h and then heated at reflux for 1.5 h. The excess methylmagnesium iodide was then quenched by the careful addition of saturated aqueous NH_4Cl solution. After addition of 100 mL of water, the two-phase mixture was separated, and the aqueous layer was extracted with four 50-mL portions of CH_2Cl_2. The combined organic layers were washed with 200 mL of brine, dried, and evaporated under reduced pressure. The remaining residue was taken up in 120 mL of acetone, and 12 mL of water and 0.200 g PPTS were added. After stirring at room temperature for 65 h the reaction mixture was poured into 200 mL of a saturated aqueous $NaHCO_3$ solution and extracted with six 75-mL portions of ether. The combined organic layers were washed with 100 mL of brine, dried, and evaporated under reduced pressure. The resulting product was chromatographed on basic alumina (activity II) (20:1 to 3:1 petroleum ether (bp 40–60 °C)/EtOAc) to give 3.689 g (92%) of pure **36**: mp 88–90 °C (from diisopropyl ether); ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.12 (s, 3 H), 1.15–2.80 (m, 12 H), 1.26 (s, 3 H), 3.21 (dd, J = 5, 10 Hz, 1 H), 3.38 (s, 3 H), 4.70 (AB q, J = 7 Hz, 2 H); mass spectrum, m/e (relative intensity) 256 (M^+, 1.8), 224 (28), 194 (52), 185 (97), 179 (45), 166 (79), 155 (63), 137 (53), 124 (52), 116 (100); calcd for $C_{14}H_{24}O_4$ (M^+) m/e 256.1674, found m/e 256.1677. Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.59; H, 9.44. Found: C, 65.83; H, 9.68.

(1α,4aα,4aα,8aβ)-Decahydro-7-ethylidene-4-(methoxymethoxy)-1,4a-dimethyl-1-naphthalenol (37). To a stirred solution of 40 mL of 0.9 M (dimethylsulfinyl)sodium in dry dimethyl sulfoxide at room temperature was added 13.357 g (36.0 mmol) of ethyltriphenylphosphonium bromide. After stirring at room temperature for 30 min, a solution of 3.689 g (14.41 mmol) of keto alcohol **36** in 25 mL of dry dimethyl sulfoxide was added dropwise. The reaction mixture was heated at 55 °C for 1 h and then stirred at room temperature for 20 h. The reaction mixture was poured into 200 mL of water and extracted with eight 40-mL portions of EtOAc. The combined organic layers were washed with 100 mL of brine, dried, and evaporated under reduced pressure. The remaining residue was chromatographed on basic alumina (activity II) (10:1 to 3:1 petroleum ether (bp 40–60 °C)/EtOAc) to give 3.414 g (88%) of oily **37**: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.14 (s, 3 H), 1.19 (s, 3 H), 1.20–2.80 (m, 13 H), 1.60 (br d, J = 6.5 Hz, 3 H), 3.14 (dd, J = 5, 10.5 Hz, 1 H), 3.37 (s, 3 H), 4.67 (AB q, J = 7 Hz, 2 H), 5.21 (br q, J = 6.5 Hz, 1 H); mass spectrum, m/e (relative intensity) 268 (M^+, 4.5), 218 (63), 205 (77), 188 (100), 178 (28), 165 (21), 148 (36), 133 (21), 121 (30), 107 (31), 93 (25), 85 (28), 45 (63); calcd for $C_{16}H_{28}O_3$ (M^+) m/e 268.2038, found m/e 268.2030.

(2α,4aα,5α,8α,8aβ)-1-(Decahydro-8-hydroxy-5-(methoxymethoxy)-4a,8-dimethyl-2-naphthalenyl)ethanone (38). To a stirred suspension of 0.853 g (22.55 mmol) of $NaBH_4$ in 10 mL of dry THF was added dropwise 3.36 mL (27.32 mmol) of boron trifluoride etherate. This solution was added dropwise to a stirred solution of 3.320 g (12.34 mmol) of alcohol **37** in 20 mL of dry THF at 0 °C. The reaction mixture was stirred at 0 °C for 4 h, after which time a mixture of 14 mL of THF and 1.4 mL of water was added dropwise, immediately followed by addition of 8.4 mL of 3 N NaOH in water and 8.4 mL of 30% hydrogen peroxide. The reaction mixture was stirred at room temperature for 65 h and then poured into 150 mL of brine. The two-phase mixture was separated, and the aqueous layer was extracted with four 75-mL portions of ether. The combined organic layers were dried and evaporated under reduced pressure. The resulting oil was dissolved in 45 mL of benzene, and this solution was added dropwise to a mixture of 11.51 g (24.8 mmol) of NDC and 3.97 mL (49.6 mmol) of pyridine in 20 mL of benzene. The reaction mixture was stirred at room temperature for 16 h and then heated at reflux for 2 h. The mixture was allowed to come to room temperature and filtered through Celite, and the filter cake was washed with two 200-mL portions of EtOAc. The solvents were evaporated under reduced pressure, and the resulting residue was dissolved in 50 mL of absolute methanol. After addition of 10 mL of 0.43 M sodium methoxide in absolute methanol, the solution was stirred at room temperature for 20 h and then poured into 150 mL of brine. The aqueous solution was extracted with seven 50-mL portions of ether, and the combined organic layers were dried and then evaporated under reduced pressure. The remaining residue was chromatographed on basic alumina (activity II) (5:1 to 3:1 petroleum ether (bp 40–60 °C)/EtOAc) to give 2.038 g (58%) of pure **38**: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.07 (s, 3 H), 1.14 (s, 3 H), 1.15–2.60 (m, 13 H), 2.16 (s, 3 H), 3.17 (dd, J = 5, 10 Hz, 1 H), 3.37 (s, 3 H), 3.67 (AB q, J = 7 Hz, 2 H); mass spectrum m/e (relative intensity) 284 (M^+, 1.7), 222 (25), 213 (33), 207 (28), 194 (25), 181 (52), 161 (60), 139 (31), 121 (50), 95 (29), 93 (28), 71 (25), 45 (100), 43 (91); calcd for $C_{16}H_{28}O_4$ (M^+) m/e 284.1987, found m/e 284.1986.

(1α,4aα,4aα,7α,8aβ)-Decahydro-4-(methoxymethoxy)-1,4a-dimethyl-7-(1-methylethenyl)-1-naphthalenol (39). To a stirred solution of 25 mL of 1.0 M (dimethylsulfinyl)sodium in dry dimethyl sulfoxide was added 7.14 g (2.00 mmol) of methyltriphenylphosphonium bromide. The mixture was stirred at room temperature for 30 min, and then a solution of 1.988 g (7.00 mmol) of alcohol **38** in 15 mL of dry dimethyl sulfoxide was added dropwise. The reaction mixture was stirred at 50 °C for 2 h and allowed to come to room temperature, and stirring was continued for 17 h. The reaction mixture was diluted with 150 mL of water and extracted with eight 30-mL portions of EtOAc. The combined organic layers were washed with 75 mL of brine and dried. The solvent was evaporated under reduced pressure, and the remaining residue was chromatographed on basic alumina (activity II) (15:1 petroleum ether (bp 40–60 °C)/EtOAc) to give 1.721 g (87%) of

pure **39**: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.03–2.20 (m, 13 H), 1.07 (s, 3 H), 1.14 (s, 3 H), 1.76 (br s, 3 H), 3.17 (dd, J = 4.5, 10 Hz, 1 H), 3.38 (s, 3 H), 4.68 (AB q, J = 7 Hz, 2 H), 4.73 (br s, 2 H); mass spectrum m/e (relative intensity) 282 (M^+, 1.9), 267 (23), 205 (24), 192 (45), 179 (78), 162 (38), 149 (28), 135 (31), 121 (42), 107 (45), 101 (35), 95 (43), 81 (29), 71 (26), 45 (100), 43 (61); calcd for $C_{17}H_{30}O_3$ (M^+) m/e 282.2195, found m/e 282.2193.

(1α,4α,4aα,7α,8aβ)-Decahydro-4-(methoxymethoxy)-1,4a-dimethyl-7-(1-methylethyl)-1-naphthalenol (40). A mixture of 1.691 g (6.00 mmol) of isopropenyl alcohol **39** and 0.195 g of 10% platinum on charcoal in 130 mL of ethanol was hydrogenated in a Parr hydrogenator under 50 psi of hydrogen for 70 min. The reaction mixture was filtered through Celite, and the filter cake was washed with 75 mL of EtOAc. The solvents were evaporated under reduced pressure to give 1.688 g (99%) of pure **40**: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.89 (d, J = 7 Hz, 6 H), 1.00–2.10 (m, 14 H), 1.03 (s, 3 H), 1.13 (s, 3 H), 3.15 (dd, J = 5.5, 9.5 Hz, 1 H), 3.37 (s, 3 H), 4.67 (AB q, J = 7 Hz, 2 H); mass spectrum, m/e (relative intensity) 284 (M^+, 1.1), 222 (21), 213 (34), 207 (33), 194 (30), 181 (100), 164 (41), 161 (29), 121 (30), 109 (43), 101 (35), 95 (36), 83 (44), 71 (24), 45 (95), 43 (46); calcd for $C_{17}H_{32}O_3$ (M^+) m/e 284.2351, found m/e 284.2361.

(1α,4α,4aα,7α,8aβ)-Decahydro-1,4a-dimethyl-7-(1-methylethyl)-1,4-naphthalenediol (41). A solution of 1.663 g (5.85 mmol) of isopropyl alcohol **40** and two drops of concentrated HCl in 20 mL of methanol was heated at reflux for 75 min, allowed to come to room temperature, and then neutralized with 0.3 N KOH in methanol. The reaction mixture was concentrated under reduced pressure, and the resulting residue was taken up in 100 mL of CH_2Cl_2. The organic layer was washed with 50 mL of brine, dried, and evaporated under reduced pressure. Chromatography of the residue on silica gel (5:1 to 2:1 petroleum ether (bp 40–60 °C)/EtOAc) gave 1.072 g (75%) of pure diol **41**: mp 121 °C (from diisopropyl ether); ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.90 (d, J = 7 Hz, 6 H), 0.95 (s, 3 H), 1.03–2.10 (m, 15 H), 1.14 (s, 3 H), 3.24 (dd, J = 4, 10 Hz, 1 H); mass spectrum, m/e (relative intensity) 240 (M^+, 0.5), 222 (32), 207 (22), 183 (40), 181 (87), 164 (64), 161 (50), 137 (21), 121 (69), 109 (52), 101 (58), 95 (61), 83 (39), 72 (100), 43 (63); calcd for $C_{15}H_{28}O_2$ (M^+) m/e 240.2089, found m/e 240.2093.

(1α,4α,4aα,7α,8aβ)-Decahydro-1,4a-dimethyl-7-(1-methylethyl)-1,4-naphthalenediol 4-(4-Methylbenzenesulfonate) (34). The tosylate **34** was prepared from **41** (0.918 g, 3.82 mmol) as described for the synthesis of the tosylate **3**. Workup and chromatography on silica gel (2:1 petroleum ether (bp 40–60 °C)/EtOAc) afforded 1.445 g (97%) of pure **34**: mp 104 °C (from petroleum ether (bp 80–100 °C)); ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.86 (d, J = 7 Hz, 6 H), 0.90–1.90 (m, 14 H), 1.01 (s, 3 H), 1.10 (s, 3 H), 2.43 (s, 3 H), 4.26 (m, 1 H), 7.32 (d, J = 8 Hz, 2 H), 7.81 (d, J = 8 Hz, 2 H). Anal. Calcd for $C_{22}H_{34}O_4S$: C, 66.97; H, 8.69. Found: C, 67.09; H, 8.77.

(±)-5-*epi*-Nardol (33). The tosylate **34** (0.394 g, 1.00 mmol) was treated with sodium *tert*-amylate (5 equiv) for 17 h as described for the rearrangement of the tosylate **3**. The workup and chromatography on silica gel (30:1 to 25:1 petroleum ether (bp 40–60 °C)/EtOAc) afforded 0.200 g (90%) of (±)-5-*epi*-nardol **33**:[27] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.84 (d, J = 6.9 Hz, 6 H), 0.96–2.00 (m, 13 H), 1.27 (s, 3 H), 2.53 (m, 1 H), 2.78 (m, 1 H), 4.80 (br s, 1 H), 4.84 (s, 1 H); mass spectrum, m/e (relative intensity) 222 (M^+, 16), 204 (69), 191 (49), 161 (95), 135 (31), 121 (100), 109 (54), 95 (62), 81 (58), 71 (46), 43 (64); calcd for $C_{15}H_{26}O$ (M^+) m/e 222.1984, found m/e 222.1985.

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Registry No. (±)-**3**, 124095-81-4; (±)-**4**, 124149-98-0; (±)-**5**, 87262-05-3; (±)-**6**, 124095-82-5; (±)-**7**, 123994-89-8; (±)-**8**, 123994-90-1; (±)-**9**, 124095-83-6; (±)-**10**, 124095-84-7; (±)-**11**, 123994-91-2; (±)-**12**, 124095-85-8; (±)-**13**, 123994-92-3; (±)-**14**, 123994-93-4; (±)-**15**, 123994-94-5; (±)-**16**, 123994-95-6; (±)-**17**, 123994-96-7; (±)-**18**, 123994-97-8; (±)-**19**, 123994-98-9; (±)-**20**, 123994-99-0; (±)-**21**, 124095-86-9; (±)-**22**, 123995-00-6; (±)-**23**, 124095-87-0; (±)-*cis*-**24**, 123995-01-7; (±)-*trans*-**24**, 123995-15-3; (±)-**25**, 123995-02-8; (±)-**26**, 123995-03-9; (±)-**27**, 123995-04-0; (±)-**28**, 124095-88-1; (±)-**29**, 123995-05-1; (±)-**30**, 123995-06-2; (±)-**31**, 124095-89-2; (±)-**32**, 123995-07-3; (±)-**33**, 124095-90-5; (±)-**34**, 123995-08-4; (±)-**35**, 123995-09-5; (±)-**36**, 123995-10-8; (±)-(*E*)-**37**, 123995-11-9; (±)-(*Z*)-**37**, 123995-16-4; (±)-**38**, 123995-12-0; (±)-**39**, 123995-13-1; (±)-**40**, 123995-14-2; (±)-**41**, 124095-91-6; MED, 126-39-6; $Ph_3P{=}CHCH_3$, 1754-88-7; $Ph_3P{=}CH_2$, 3487-44-3.

(27) According to GC analysis, the purity of **33** was 97%.

Stereoselective Synthesis and Absolute Stereochemistry of Sinefungin

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Sinefungin has been synthesized from D-ribose, L-ornithine, and adenine. L-Ornithine was converted to its δ-nitro analogue **10**, which was coupled to the ribose derived aldehyde **11** by a potassium fluoride catalyzed nitro-aldol reaction. The resulting nitro alcohol **12** was further transformed by dehydration and reduction of the nitrovinyl intermediate to the oxime, which was oxidatively cleaved to ketone **16**. The proper (*S*) stereochemistry at C-6 resulted from a stereoselective hydride reduction of this ketone to the epimeric alcohols in a 92/8 ratio and an S_N2 displacement of the corresponding *O*-tosylate by azide anion. The stereochemistry at C-6 was proved by correlation with the pyrrolidine obtained by cyclization of the tosylate to the α-[(4-methylphenyl)sulfonyl]amino group. The absolute stereochemistry of the pyrrolidine was determined by X-ray crystallographic analysis. Conversion of the azide **23** to sinefungin was accomplished by conversion of the ribose moiety to the corresponding β-acetate, adenosylation, reduction of the azide group to amino, and cleavage of the *tert*-butyl ester and *N*-tosyl protecting groups. The resulting synthetic sinefungin is identical with the natural material, thus providing a stereoselective synthesis and unequivocally establishing the absolute stereochemistry at C-6 as *S*.

The isolation of the antibiotic A-9145, sinefungin, was reported[1] from the fermentation broth of *Streptomyces griseolus*. Sinefungin, later[2] assigned structure **1**, is also produced by *Streptomyces incarnatus*.[3] It is a structural analogue of *S*-adenosylmethionine (**2**, SAM) and of *S*-adenosylhomocysteine (**3**, SAH) and exhibits a variety of biological effects including antiviral,[4] antifungal,[3,5] anti-

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