Stereospecific Synthesis of 9α-(Acetoxymethyl)-8α,8′-epoxy-3α,4,4-trimethyl-*trans*-decalin-1α-ol Acetate, a Model for the Investigation of Structure-Activity Relationships of the Insect Antifeedant Neoclerodanes

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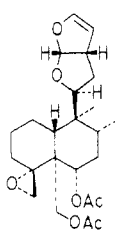
The stereospecific synthesis of 9α-(acetoxymethyl)-8α,8′-epoxy-3α,4,4-trimethyl-*trans*-decalin-1α-ol acetate (**3**) is described. This compound represents the decalin portion of the insect antifeedant diterpenes with the neoclerodane skeleton such as clerodin (**1**) and ajugarin I (**2**) and can therefore serve as a model compound for the investigation of structure–activity relationships. Octalone **8** is a key intermediate in the synthesis of **3**. Reductive alkylation of **8** gives the *trans*-decalone **9** which is transformed into the α,β-unsaturated ketone **10**. An equatorial methyl at C-3 and carbonyl group at C-1 are introduced by means of an alkylative carbonyl transposition followed by catalytic hydrogenation. Reduction of this carbonyl group followed by acetylation affords **14**. Cleavage of the cyclic ether then gives **16**, which in turn can be dehydrohalogenated to **17**. Epoxidation of **17** gives the isomeric epoxides **3** and **19**. Stereospecific epoxidation of **17** to **3** can be accomplished via diol **20**.

A number of the diterpenes possessing the neoclerodane skeleton,[1] as represented by clerodin (**1**)[2] and ajugarin I (**2**),[3] show insect antifeedant activity. It was concluded[4] that the perhydrofuro[2,3-*b*]furan ring in structures as clerodin is the active center of the molecule. Kojima and Kato[5] actually synthesized a number of perhydrofuro-[2,3-*b*]furan derivatives showing insect antifeedant activity against *Spodoptera litura* F. These results, however, cannot explain the antifeedant activity of the ajugarins. In these systems the antifeedant activity is most probably centered in the decalin portion of the molecule. In order to investigate structure–activity relationships of these insect antifeedants we undertook the synthesis of the *trans*-decalin **3**.[6]



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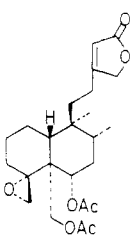

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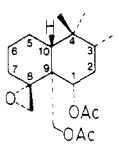

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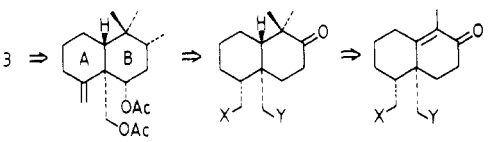
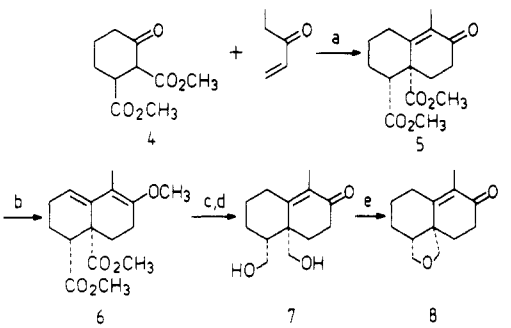
Scheme I



Scheme II[a]



4 5 6 7 8

[a] (a) Triton B, MeOH; (b) $HC(OMe)_3$, BF_3; (c) $LiAlH_4$; (d) H_3O^+; (e) H_3O^+, Δ.

As this molecule represents the decalin unit as present in both clerodin and ajugarin I, a better insight can possibly be obtained into the relation of this moiety with the antifeedant activity.

Our retrosynthetic plan for **3** is outlined briefly in Scheme I. The main features in this strategy are the stereoselective introduction of the methyl substituent at C-3,[7] the oxidation of C-1, and the proper choice of X and Y.

An octalone with suitably functionalized carbon atoms was constructed by Robinson annulation of keto diester **4**[8] with ethyl vinyl ketone to give **5**.[9] At this stage the two esters functionalities had to be transformed into groups

(1) Rogers, D.; Unal, G. G.; Williams, D. J.; Ley, S. V.; Sim, G. A.; Joshi, B. S.; Ravindranath, K. R. *J. Chem. Soc.*, Chem. Commun. **1979**, 97.

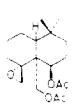
(2) Barton, D. H. R.; Cheung, H. T.; Cross, A. D.; Jackman, L. M.; Martin-Smith, M. *J. Chem. Soc.* **1961**, 5061.

(3) (a) Kubo, I; Lee, Y.-W.; Balogh-Nair, V.; Nakanishi, K.; Chapya, A. *J. Chem. Soc., Chem. Commum.* **1976**, 949. (b) Kubo, I; Kido, M.; Fukuyama, Y. *Ibid.* **1980**, 897.

(4) (a) Kato, N.; Takahashi, M; Shibayama, M.; Munakata, K. *Agric. Biol. Chem.* **1972**, *36*, 2579. (b) Hosozawa, S.; Kato, N.; Munakata, K. *Ibid.* **1974**, *38*, 823. (c) Hosozawa, A.; Kato, N.; Munakata, K.; Chen., Y.-L. *Ibid.* **1974**, *38*, 1045.

(5) (a) Kojima, Y.; Kato, N. *Tetrahedron Lett.* **1979**, 4667. (b) Kojima, Y.; Kato, N. *Agric. Biol. Chem.* **1980**, *44*, 855. (c) Kojima, Y.; Kato, N. *Tetrahedron Lett.* **1980**, 5033.

(6) The synthesis of a *cis*-decalin (i) containing epoxidiacetate functions has been reported recently (Jackson, W. P.; Ley, S. V. *J. Chem. Soc., Chem. Commun.* **1979**, 732). Although this molecule is a poor model for structure–activity investigations since its spatial structure is quite different from the *trans*-decalin moiety in clerodin and ajugarin I, it did show insect antifeedant activity.



(7) In order to avoid confusion the numbering corresponding with that of the target compound **3** is used throughout the discussion.

(8) This compound was prepared according to the procedure described for the corresponding diethyl ester (Sen, K.; Bagchi, P. *J. Org. Chem.* **1958**, *23*, 1125). The dimethyl ester **4** has been prepareed via a different route (Exner, O.; Protiva, M. *Chem. Listy* **1954**, *48*, 1550; *Chem. Abstr.* **1955**, *49*, 11569c).

(9) The cis orientation of the two methoxycarbonyl groups was demonstrated in a similar annulation reaction (Dutt, S.; Banerjee, A.; Bhattacharyya, P. K. *Indian J. Chem.* **1974**, *12*, 360).

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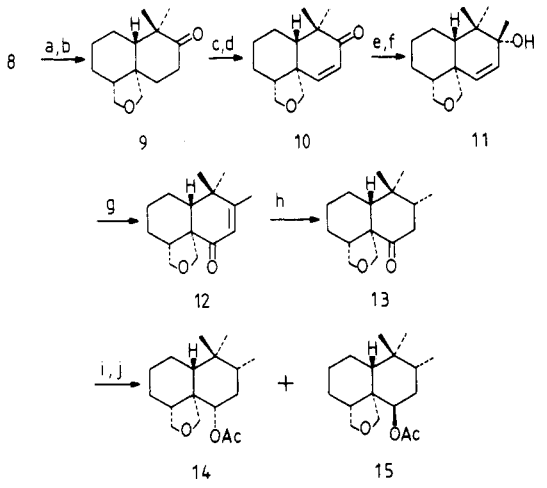
Scheme III[a]



[a] (a) Li, NH_3, H_2O (1 equiv); (b) MeJ; (c) Br_2, HOAc; (d) LiBr, Li_2CO_3, DMF, Δ; (e) MeLi; (f) H_2O; (g) pyridinium chlorochromate; (h) Pd, H_2; (i) $NaBH_4$; (j) Ac_2O, py, 4-(dimethylamino)pyridine.

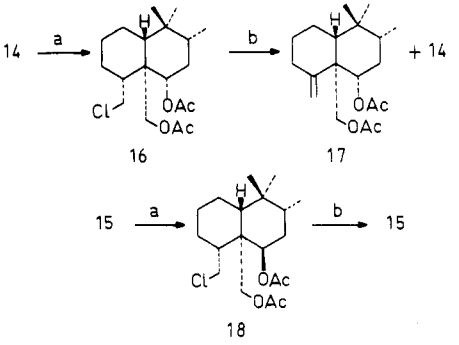
that are inert toward the reactions planned for the completion of ring B, such as reductive aklylation, addition of methyllithium, oxidation, and reduction. At the same time a rapid and selective conversion of these groups into an exocyclic olefin and an acetate must remain possible.

A cyclic ether moiety as in **8** seems to fulfill all these requirements. Octalone **5** was transformed into the dienol ether **6**. The two ester groups were then reduced with lithium aluminum hydride.[10] The diol **7** which resulted after acid hydrolysis of the reduction product was refluxed in hydrochloric acid to afford octalone **8**[11] in 84% overall yield from **5** (Scheme II).

Reductive alkylation of enone **8** with methyl iodide afforded the monoalkylated product **9** in high yield. Ketone **9** was assumed to prosses the *trans*-decalin structure in analogy with the products from similar reductive alkylations.[12]

The method for alkylative carbonyl transposition as developed by Dauben and Michno[13] was used in order to introduce the methyl substituent at C-3 and to oxidize C-1 (Scheme III). Treatment of **9** with bromine in acetic acid, followed by dehydrobromation ($LiBr–Li_2CO_3$ in boiling DMF) gave the α,β-unsaturated ketone **10**. Addition of methyllithium to **10** gave the tertiary allyl alcohol **11**. The stereochemistry at C-3 was not rigorously proven but tentatively assigned on the assumption that β attack of methyllithium had taken place. Oxidation of the allylic alcohol with pyridinium chlorochromate afforded the transposed α,β-unsaturated ketone **12**. The olefinic moiety

Scheme IV[a]



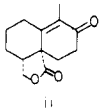
[a] (a) Ac_2O, pyridine hydrochloride, Δ; (b) DBN, Δ.

in **12** was reduced with lithium in ammonia. This reaction was expected to lead to the energetically more favored product,[12] i.e., with the C-3 methyl group in an equatorial position. ^1H NMR, however, showed two different secondary methyl groups in the reduction product in a 1:1 ratio, centered at 0.95 and 0.88 ppm, thus indicating the presence of both the equatorial and the axial C-3 methyls. This epimeric mixture could not be separated by GC or TLC. In contrast, catalytic hydrogenation of **12** with palladium on charcoal gave a single product. Evidence for the stereochemistry at C-3 in the hydrogenated product was found in the values for $J_{2,3}$ in the ^1H NMR spectrum. The C-2 protons display a double doublet at 2.65 ppm with coupling constants of 13 and 13 Hz and a double doublet at 2.13 ppm with coupling constants of 13 and 4 Hz. The values render obvious the equatorial attachment of the C-3 methyl group. Hence catalytic hydrogenation of **12** produces exclusively the desired ketone **13** as a result of addition of hydrogen from the least hindered side of the molecule.

Reduction of **13** with sodium borohydride in 2-propanol at 0 °C gave a 9:1 mixture of the equatorial and axial alcohols, respectively. They were converted into the corresponding acetates by treatment with acetic anhydride/pyridine/4-(dimethylamino)pyridine. These two isomers could easily be separated by column chromatography on silica gel. Acetate **14** was thus obtained in 82% yield and its isomer **15** in 9% yield. On use of the more bulky diisobutylaluminum hydride for the reduction of **13**, the equatorial and axial alcohols were formed in a 94:6 ratio.

The next stage involved the transformation of the cyclic ether moiety in **14**. Ether cleavage by acetyl *p*-toluenesulfonate in refluxing acetonitrile[14] was unsuccessful in that only starting material was recovered from the reaction mixture. On refluxing **14** in acetic anhydride in the presence of pyridine hydrochloride,[15] however, ether cleavage took place, producing **16** in 80% yield. Elimination of hydrogen chloride from this molecule by treatment with diazabicycloundecene (DBU) was unsuccessful, even at 150 °C and prolonged reaction times. The planned reaction could be effectuated by heating **16** in diazabicyclononene (DBN), and the exocyclic olefin **17** was thus formed in 75% yield, alongside a small amount of **14**, resulting from ring closure. The cyclic ether moiety in **15** could be cleaved in the same way as in **14**, producing the chloro diacetate **18**. On treatment of this compound with DBN, the cyclic ether **15** was slowly obtained as the only observable product. In this case the axial acetate at C-1 probably prevents DBN from approaching C-8 as is es-

(10) When the reduction of **6** was carried out with 0.5 molar equiv of lithium aluminum hydride followed by refluxing in hydrochloric acid, lactone **ii** was obtained in a straightforward way in 85% overall yield. The synthesis of **ii** via a different route has recently been reported (Goldsmith, D. J.; John, T. K.; Van Middlesworth, F. *Synth. Commun.* **1980**, *10*, 551).



ii

(11) In a preliminary communication we described the synthesis of **8** together with the transformation of the cyclic ether moiety into an α,β-unsaturated lactone as is found in many clerodanes (Luteijn, J. M.; van Doorn, M.; de Groot, A. *Tetrahedron Lett.* **1980**, 4127).

(12) For a review on this type of reaction, see: Caine, D. *Org. React.* **1976**, *23*, 1.

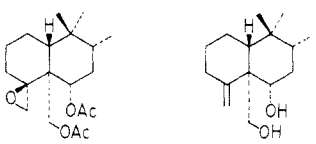
(13) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682.

(14) Karger, M. H.; Mazur, Y. *J. Am. Chem. Soc.* **1968**, *90*, 3878.

(15) Bessière-Chrétien, Y.; Grison, C. *Bull Soc. Chim. Fr.* **1975**, 2499.

sential to the formation of the exocyclic olefin (Scheme IV).

The final step was the epoxidation of the exocyclic olefin in **17**. When **17** was treated with *m*-chloro perbenzoic acid in ether, two isomeric epoxides were formed in a ratio of 1:1. Separation could easily be accomplished by column chromatography. The ^1H NMR spectrum of the first eluted compound showed an AB system (J = 4.5 Hz) representing the epoxide protons with A and B resonating at 2.53 and 2.71 ppm, respectively. In the ^{13}C NMR spectrum the epoxide ring showed signals at 60.7 and 45.6 ppm. The epoxide protons of the second-eluted compound showed an AB pattern with A centered at 2.96 ppm and B at 2.19 ppm with coupling constants of 4 Hz. Furthermore, long-range (W) coupling of the A proton with a proton at C-7 (J = 2 Hz) was observed. In the ^{13}C NMR spectrum the epoxide showed signals at 65.0 and 48.5 ppm. These values strongly suggested that the latter compound possesses structure **3**, the NMR data of the epoxide moiety being similar to those found for ajugarin I. Consequently, the former compound had to be assigned structure **19**. A



19 20

more stereoselective method for the preparation of **3** was achieved via epoxidation of diol **20**. Hydrolysis of diacetate **17** gave **20** which was treated with $VO(acac)_2$–*tert*-butyl hydroperoxide.[16] Subsequent acetylation gave **3** as the single product.

With the synthesis of **3** we have reached our initial goal: the stereospecific synthesis of the decalin portion of ajugarin I and clerodin as a model compound for investigating structure–activity relationships. The stereospecific synthesis of ajugarin I will be the subject of further investigations.[17]

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer 237 spectrometer. UV spectra were obtained on a Perkin-Elmer 550 spectrometer. ^1H NMR spectra were recorded on a Varian EM-390 or a Perkin-Elmer R24B spectrometer with tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded with a Varian XL-100 spectrometer in the pulse FT mode by using $CDCl_3$ as the solvent and tetramethylsilane as the internal standard. Mass spectra and exact mass measurements were obtained with an AEI MS 902 spectrometer. GC/MS Spectra were obtained from a VG Micromass 7070F spectrometer. GC Analyses were carried out on a Hewlett–Packard 5700 A chromatograph. The column used for determining product purity and for monitoring reactions was a 2-m column packed with 3.3% SE-30 on Chromosorb W. All boiling and melting points are uncorrected.

Robinson Annulation of 2,3-Bis(methoxycarbonyl)-cyclohexanone (4). Preparation of *cis*-5,10-Bis(methoxycarbonyl)-1-methoxy-$\Delta^{1,9}$-octalin-2-one (5). To a stirred solution of **4**[8] (35 g, 0.25 mol) in 500 mL of methanol at 0 °C were added 21 g (0.25 mol) of freshly distilled ethyl vinyl ketone and 10 mL of a 40% solution of benzyltrimethylammonium hydroxide (Triton B) in methanol. The mixture was stirred for 16 h under nitrogen at room temperature. The methanol was removed under reduced pressure, and the residue was dissolved in 500 mL of ether and washed with 6 N hydrochloric acid, 5% aqueous sodium hydroxide, and finally with saturated brine. The ethereal solution was dried (anhydrous magnesium sulfate) and concentrated to afford an oil which crystallized upon standing. Crystallization from ethanol gave **5**: 59.5 g (85%); mp 60–61 °C; IR (KBr) 1730, 1655, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.81 (s, 3 H), 1.4–2.8 (m, 11 H), 3.66 (s, 3 H), 3.69 (s, 3 H); mass spectrum, m/e 280, 220, 161.

Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.56; H, 7.25.

***cis*-5,10-Bis(methoxycarbonyl)-2-methoxy-1-methyl-3,4,5,6,7,10-hexahydronaphthalene (6).** To a mixture of **5** (56 g, 0.20 mol) and trimethyl orthoformate (26 g, 0.25 mol) in 350 mL of absolute methanol was added BF_3–MeOH complex (5 mL of a 14% solution in methanol). After the mixture was stirred for 6 h, triethylamine (2.5 mL) was added, and the methanol was evaporated under reduced pressure. A sample of the resulting light yellow oil (250 mg) was purified by column chromatography on silica gel with ether–hexane (1:1) as eluant to afford 238 mg of a colorless oil: IR (neat) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.72 (s, 3 H), 1.2–2.7 (m, 9 H), 3.52 (s, 3 H), 3.63 (s, 3 H), 3.67 (s, 3 H), 5.57 (m, $W_{1/2}$ = 9 Hz, 1 H); mass spectrum m/e 294, 262, 234, 175; UV (ether) λ_{max} 243 nm; Calcd for $C_{16}H_{22}O_2$ m/e 294.147, found m/e 294.149.

***cis*-5,10-Bis(hydroxymethyl)-1-methyl-$\Delta^{1,9}$-octalin-2-one (7).** The crude **6** (59.7 g) was dissolved in anhydrous ether (250 mL) and added dropwise with stirring to a suspension of lithium aluminum hydride (9.5 g, 0.25 mol) in 150 mL of anhydrous ether. The mixture was refluxed for 1 h, and the excess lithium aluminum hydride was destroyed by the addition of ethyl acetate. Hydrochloric acid (500 mL of a 6 N solution) was added, and the ether was evaporated. The resulting aqueous solution was used without further purification to produce **8**. A sample of 5 mL of the aqueous solution was extracted with methylene chloride. The extract was dried over anhydrous magnesium sulfate and concentrated to afford the diol **7**: 400 mg; IR (neat) 3350, 1650, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2–2.8 (m, 11 H), 1.76 (s, 3 H), 3.4–4.1 (m, 4 H), 4.50 (br, s, 2 H); mass spectrum, m/e 224, 206, 176.

***cis*-5,10-Methanoxy-1-methyl-$\Delta^{1,9}$-octalin-2-one (8).** The aqueous solution of **7** was refluxed under nitrogen for 6 h. During this time a yellow oil separated. After the mixture cooled to room temperature, ether was added, and the aqueous layer was extracted with ether. The combined organic layers were washed with saturated sodium bicarbonate solution and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave an oil which solidified upon standing. Distillation gave **8** (35 g, 84% overall yield) as a white solid: mp 40–41 °C; bp 132–135 °C (0.3 mm); IR (KBr) 1670, 1612 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.79 (s, 3 H), 1.4–2.9 (m, 11 H), 3.69 (d, J = 9 Hz, 1 H), 3.69 (dd, J = 9, 4 Hz, 1 H), 3.92 (d, J = 9 Hz, 1 H), 4.10 (dd, J = 9, 4 Hz, 1 H); ^{13}C NMR δ 197.5 (s), 155.9 (s), 132.2 (s), 73.7 (d), 70.2 (d), 48.3 (d) 47.2 (s), 33.9 (t), 32.5 (t), 28.8 (t), 28.3 (t), 24.0 (t), 11.1 (q); mass spectrum, m/e 206, 176.

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.51; H, 8.74.

1,1-Dimethyl-5α,10α-methanoxymethano-*trans*-decalin-2-one (9). A solution of **8** (4.12 g, 20 mmol) in tetrahydrofuran (75 mL, freshly distilled from benzophenone–sodium) and water (360 mg, 20 mmol) was added dropwise under nitrogen to a stirred solution of lithium (560 mg, 80 mmol) in ammonia (250 mL, distilled from sodium). The mixture was stirred for 15 min, and then methyl iodide (15 g, 105 mmol) was added. After 15 min, 10 g of ammonium chloride was added. The ammonia was allowed to evaporate, and the residue was treated with ether and water. The ether layer was separated, and the aqueous layer was washed with ether. The combined ether layers were washed with saturated brine and dried over anhydrous magnesium sulfate. Evaporation of the solvent afforded an oil. Column chromatography on silica gel with ether–hexane (1:1) afforded **9** (4.14 g, 94%) which crystallized upon standing: mp 71–73 °C; IR (neat) 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (s, 3 H), 1.07 (s, 3 H), 1.2–2.8 (m, 12 H), 3.41 (d, J = 8 Hz, 1 H), 3.80 (dd J = 8, 4 Hz, 1 H), 3.83 (s, 2 H); mass spectrum, m/e 222, 123.

Anal. Calcd for $C_{14}H_{22}O_2$; C, 75.63; H, 9.97. Found: C, 75.71; H, 9.78.

1,1-Dimethyl-5α,10α-methanoxymethano-Δ^3-*trans*-octalin-2-one (10). Ketone **9** (3.5 g, 15.9 mmol) in acetic acid (25 mL) was treated dropwise with a solution of Br_2 (2.55 g, 15.9 mmol) in ether (15 mL) at room temperature. Dilution with water and

(16) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136.

(17) See also: Luteijn, J. M.; de Groot, A. *Tetrahedron Lett.* **1981**, 789.

extraction with ether gave the crude 3β-bromo-1,1-dimethyl-5α,10α-(methanoxymethano)-*trans*-decalin-2-one as an oil: 4.50 g; IR ($CHCl_3$) 1722 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (s, 3 H), 1.19 (s, 3 H), 1.3–2.2 (m, 9 H), 2.26 (dd, J = 13, 6 Hz, 1 H), 3.48 (d, J = 8 Hz, 1 H), 3.95 (dd, J = 9, 4 Hz, 1 H) 4.00 (s, 2 H), 5.05 (dd, J = 13, 6 Hz, 1 H); mass spectrum, m/e 302–300, 221. The crude bromo ketone (4.50 g) was dissolved in DMF and heated at 160 °C with LiBr (1.5 g) and Li_2CO_3 (1.5 g) for 6 h under nitrogen. The mixture was poured into water and extracted with ether. The extract was washed with brine and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a light yellow oil. Column chromatography on silica gel with ether–hexane (1:1) as the eluant afforded **10**: 3.3 g (94%); mp 64–65 °C; IR (neat) 1670, 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (s, 3 H), 1.15 (s, 3 H), 1.2–2.3 (m, 8 H), 3.57 (d, J = 8 Hz, 1 H), 3.71 (d, J = 8 Hz, 1 H), 4.02 (dd, J = 9, 4 Hz, 1 H), 4.12 (d, J = 9 Hz, 1 H), 5.87 (d, J = 10 Hz, 1 H), 6.90 (d, J = 10 Hz, 1 H); mass spectrum, m/e 220, 175, 147.

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.50; H, 9.10.

5α,10α-Methanoxymethano-1,1,2β-trimethyl-Δ³-*trans*-octalin-2α-ol (11). To a stirred solution of **10** (2.25 g, 10.5 mmol) in 20 mL of anhydrous ether at −78 °C was added under nitrogen an ethereal solution of methyllithium (11.2 mmol, 8 mL of a 1.40 M solution in ether). The mixture was allowed to warm to room temperature and quenched with 15 mL of water. The ether layer was separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with brine and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave **11** as a colorless oil: 2.44 g (97%); IR (neat) 3420 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.75 (s, 3 H), 0.90 (s, 3 H), 1.0–2.0 (m, 8 H), 1.18 (s, 3 H), 2.12 (br, 1 H), 3.42 (d, J = 8 Hz, 1 H), 3.61 (d, J = 8 Hz, 1 H), 3.93 (dd, J = 8, 4 Hz, 1 H), 3.98 (d, J = 8 Hz, 1 H), 5.37 (d, J = 10 Hz, 1 H), 5.70 (d, J = 10 Hz, 1 H); mass spectrum, m/e 236, 221, 218, 203; Calcd for $C_{15}H_{24}O_2$ m/e 236.178, found m/e 236.179.

8α,9α-Methanoxymethano-3,4,4-trimethyl-Δ²-*trans*-octalin-1-one (12). To a stirred solution of pyridinium chlorochromate (4.50 g, 21 mmol) in 30 mL of methylene chloride was added a solution of **11** (2.44 g, 10.35 mmol) in 20 mL of methylene chloride. The mixture was stirred for 6 h at room temperature, during which time the solutin became dark brown and a dark polymer separated. The solution was decanted from the black polymer, which in turn was washed with ether. The combined organic layers were washed successively with 2 N aqueous sodium hydroxide, 2 N hydrochloric acid, and saturated sodium bicarbonate solution. Removal of the solvent gave an oil which was purified by column chromatography on silica gel with ether as the eluant to afford **12**: 2.30 g (95%); mp 56–58 °C; IR ($CHCl_3$) 1665, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (s, 3 H), 1.12 (s, 3 H), 1.1–2.4 (m, 8 H), 1.91 (s, 3 H), 3.44 (d, J = 8 Hz, 1 H), 3.76 (d, J = 9 Hz, 1 H), 4.03 (d, J = 9 Hz, 1 H), 4.19 (dd, J = 8, 4 Hz, 1 H), 5.71 (s, 1 H); mass spectrum, m/e 234, 110.

Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46; m/e 234.1620. Found: C, 76.69; H, 9.16; m/e 234.1630.

8α,9α-Methanoxymethano-3α,4,4-trimethyl-*trans*-decalin-1-one (3). A solution of **12** (2.0 g, 8.55 mmol) in 20 mL of methanol and 4 mL of triethylamine was hydrogenated at 40 psi of H_2 with 10% palladium on charcoal as catalyst. After the hydrogen uptake has ceased (4 h), the catalyst was removed by filtration. Evaporation of the solvent gave 1.95 g (97%) of **13** as a colorless oil. The product was shown to be pure by GC: IR (neat) 1697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.77 (s, 3 H), 0.94 (s, 3 H), 0.95 (d, J = 6 Hz, 3 H), 1.1–2.9 (m, 9 H), 2.13 (dd, J = 13, 4 Hz, 1 H), 2.65 (dd, J = 13, 13 Hz, 1 H), 3.35 (d, J = 8 Hz, 1 H), 3.80 (dd, J = 8, 5 Hz, 1 H), 4.00 (d, J = 9 Hz, 1 H), 4.06 (d, J = 9 Hz, 1 H); ^{13}C NMR δ 212.5 (s), 72.7 (t), 69.0 (t), 60.6 (s), 54.1 (d), 45.4 (d), 43.7 (t), 40.3 (d), 37.1 (s), 28.6 (t), 27.3 (q), 25.7 (t), 22.2 (t), 16.6 (q), 15,3 (q); mass spectrum, m/e 236 (M^+);Calcd for $C_{15}H_{24}O_2$ m/e 236.1776, found m/e 236.1785.

Reduction of 12 with Lithium–Ammonia. To a stirred solution of lithium (21 mg, 3 mmol) in ammonia (25 mL, distilled from sodium) were added under notrogen 250 mg (1.07 mmol) of **12** and 49 mg (1.07 mmol) of ethanol in tetrahydrofuran (10 mL, freshly distilled from benzophenone–sodium). The ammonia was allowed to evaporate, and water was added. Extraction with ether followed by the same workup as described for **9** gave an oil (230 mg), which was purified by column chromatography on silica gel with ether–hexane (1:1) as the eluant to afford 200 mg (80%) of a colorless oil. This product was judged to be pure **13** as indicated by GC and TLC. However, ^1H NMR analysis showed the presence of two different secondary methyls at 0.95 and 0.88 ppm in a 1:1 ratio, indicating that a nonstereoselective reduction had taken place.

8α,9α-Methanoxymethano-3α,4,4-trimethyl-*trans*-decalin-1α-ol Acetate (14) and 8α,9α-Methanoxymethano-3α,4,4-trimethyl-*trans*-decalin-1β-ol Acetate (15). A solution of sodium borohydride (350 mg, 9.1 mmol) in 2-propanol (5 mL) was added dropwise during 30 min to a stirred solution of ketone **13** (1.90 g 8.0 mmol) in 2-propanol (5 mL) at 0 °C. The solution was stirred for 6 h. Hydrochloric acid (15 mL of a 2 N solution) was added, and most of the 2-propanol was distilled off under reduced pressure. The resulting aqueous layer was extracted with ether. The combined ethereal layers were washed with 10% aqueous sodium bicarbonate solution and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave an oil (1.83 g, 96%) which was shown by ^1H NMR to be a mixture of the 6α- and 6β-hydroxy compounds in a ratio of 9:1, respectively. These two isomers could not be separated by GC or by TLC. This isomeric mixture was treated with pyridine (3 mL), acetic anhydride (3 mL), an 4-(dimethylamino)pyridine (100 mg). After 6 h the pyridine and acetic anhydride were distilled off under reduced pressure. The resulting oily residue was dissolved in methylene chloride (2 mL) and separated by column chromatography on silica gel with ether–hexane as eluant to give **15**: 0.2 g (9%); mp 95–96 °C; IR ($CHCl_3$) 1730, 1234 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.51 (s, 3 H), 0.79 (d, J = 6 Hz, 3 H), 0.92 (s, 3 H), 1.1–1.9 (m, 11 H), 2.08 (s, 3H), 3.32 (d, J = 8 Hz, 1 H), 3.63 (d, J = 9 Hz, 1 H), 3.84 (dd, J = 8, 5 Hz, 1 H), 3.86 (d, J = 9 Hz, 1 H), 4.95 (s, $W_{1/2}$ = 6.5 Hz, 1 H); mass spectrum, m/e 280, 220, 205.

Anal. Calcd for $C_{17}H_{28}O_3$: C, 72.81; H, 10.07. Found: C, 72.69; H, 10.29.

Further elution gave **14**: 1.84 g (82%); mp 87–88 °C; IR ($CHCl_3$) 1728, 1235 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.53 (s, 3 H), 0.84 (d, J = 6.5 Hz, 3 H), 0.88 (s, 3 H), 1.2–1.9 (m, 11 H), 2.06 (s, 3 H), 3.35 (d, J = 9 Hz, 1 H), 3.82 (dd, J = 9, 5 Hz, 1 H), 3.84 (d, J = 9 Hz, 1 H), 3.94 (d, J = 9 Hz, 1 H), 4.80 (dd, J = 13, 4 Hz, 1 H); ^{13}C NMR δ 171.1 (s), 80.5 (d), 74.0 (t), 67.3 (t), 50.9 (s), 50.6 (d), 46.3 (d), 40.7 (d), 36.7 (s), 34.6 (t), 29.9 (t), 27.6 (q), 24.5 (t), 21.7 (q), 21.0 (t), 16.0 (q), 15.3 (q); mass spectrum, m/e 280, 220, 205.

Anal. Calcd for $C_{17}H_{28}O_3$: C, 72.81; H, 10.07. Found: C, 72.96: H, 10.07.

Reduction of 13 with Diisobutylaluminum Hydride. To a solution of **13** (24 mg, 0.1 mmol) in 2 mL of anhydrous ether under nitrogen was added a solution of diisobutylaluminum hydride (0.1 mL of a 25% solution in toluene, 0.18 mmol). The reaction mixture was stirred for 1 h at room temperature. Hydrochloric acid was added (0.5 mL of a 2 N solution), and the organic layer was separated and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was acetylated as described above. GC Analysis of the acetylated products showed the formation of **14** and **15** in a 94:6 ratio, respectively.

9α-(Acetoxymethyl)-8α-(chloromethyl)-3α,4,4-trimethyl-*trans*-decalin-1α-ol Acetate (16). A mixture of **14** (1.68 g, 6.0 mmol), pyridine hydrochloride (4 g, 33 mmol), and acetic anhydride (10 mL) was heated under reflux for 18 h. The acetic anhydride was evaporated under reduced pressure. The resulting dark brown residue was taken up in 3 mL of methylene chloride and chromatographed on silica gel with ether–hexane (1:1) as the eluant to give **16**: 1.72 g (80%); mp 97–98 °C; IR (KBr) 1720, 1230 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.66 (s, 3 H), 0.83 (d, J = 6Hz, 3 H), 0.88 (s, 3 H), 1.2–2.0 (m, 11 H), 2.00 (s, 3 H), 2.04 (s, 3 H), 3.47 (dd, J = 11, 9 Hz, 1 H), 3.96 (dd, J = 11, 3.5 Hz, 1 H), 4.20 (d, J = 13 Hz, 1 H), 4.73 (d, J = 13 Hz, 1 H), 4.75 (dd, J = 12, 4 Hz, 1 H); mass spectrum, m/e 323 (M^+ − Cl), 240–238, 227–225.

Anal. Calcd for $C_{19}H_{31}ClO_4$: C, 63.58; H, 8.71. Found: C, 63.31; H, 8.78.

Further elution gave **14**, 210 mg (13%).

9α-(Acetoxymethyl)-8α-(chloromethyl)-3α,4,4-trimethyl-*trans*-decalin-1β-ol Acetate (18). The acetate **15** (150 mg, 0.53 mmol) was refluxed for 18 h in acetic anhydride (2 mL) and

pyridine hydrochloride (0.5 g, 4.2 mmol). Workup as described above afforded **18**: 130 mg (69%); mp 116–118 °C; IR (KBr) 1725, 1230 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.70 (s, 3 H), 0.79 (d, J = 7 Hz, 3 H), 0.93 (s, 3 H), 1.2–2.0 (m, 11 H), 2.03 (s, 3H), 2.13 (s, 3 H), 3.10 (dd, J = 11, 9 Hz, 1 H), 3.62 (dd, J = 11, 2 Hz, 1 H), 4.33 (s, 2 H), 5.20 (s, $W_{1/2}$ = 7 Hz, 1 H); mass spectrum, m/e 323 (M^+ – Cl), 317–315, 258–256, 240–238, 227–225.

Anal. Calcd for $C_{19}H_{31}ClO_4$: C, 63.58; H, 8.71. Found: C, 63.70; H, 8.79.

Attempted Ether Cleavage of 14 by Acetyl *p*-Toluenesulfonate. A mixture of **14** (28 mg, 0.1 mmol) and acetyl *p*-toluenesulfonate (43 mg, 0.2 mmol) in acetonitrile (1 mL) was refluxed overnight. The acetonitrile was evaporated under reduced pressure, and ether and water were added. The ether layer was separated and dried over anhydrous magnesium sulfate. Analysis (GC, TLC, and ^1H NMR) showed only starting material.

9α-(Acetoxymethyl)-8-methylene-3α,4,4-trimethyl-*trans*-decalin-1α-ol Acetate (17). A mixture of **16** (1.3 g, 3.64 mmol) and diazabicyclononene (DBN, 2 mL) was heated at 140 °C under nitrogen for 6 h. The resulting brown reaction mixture was dissolved in 2 mL of methylene chloride and chromatographed on a silica gel column with ether–hexane as the eluant to afford **17** (880 mg, 75%) as a colorless oil which crystallized upon standing; mp 83–84 °C; IR (neat) 1730, 1641, 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.69 (s, 3 H), 0.86 (s, 3 H), 0.87 (d, J = 6 Hz, 3 H), 1.1–2.2 (m, 10 H), 1.93 (s, 3 H), 1.97 (s, 3 H), 4.24 (d, J = 12 Hz, 1 H) 4.47 (s, 1 H), 4.71 (s, 1 H), 4.76 (d, J = 12 Hz, 1 H), 5.10 (dd, J = 11, 5 Hz, 1 H); mass spectrum, m/e 262 (M^+ – 60), 249, 232, 220, 202, 187.

Anal. Calcd for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.90; H, 9.09.

Further elution gave the cyclic ether **14**, 185 mg (18%).

Reaction of 18 with DBN. The chloro diacetate **18** (100 mg, 0.28 mmol) was dissolved in diazacyclononene (DBN, 1 mL) and heated at 140 °C overnight. A workup as described afforded **15** (70 mg, 89%) as the sole product.

9α-(Acetoxymethyl)-8α,8′-epoxy-3α,4,4-trimethyl-*trans*-decalin-1α-ol Acetate (3) and 9α-(Acetoxymethyl)-8β,8′-epoxy-3α,4,4-trimethyl-*trans*-decalin-1α-ol Acetate (19). To a solution of diacetate **17** (700 mg, 2.18 mmol) in ether (15 mL) was added *m*-chloroperbenzoic acid (2.5 mmol, 570 mg admixed with 30% *m*-chlorobenzoic acid). The solution was allowed to stir for 1 h at room temperature and then washed with 10% aqueous sodium sulfite solution followed by saturated sodium bicarbonate solution. The ethereal solution was dried over anhydrous magnesium sulfate and concentratrated under reduced pressure to afford an oil which was shown by GC to consist of the two isomeric epoxides. Separation of the mixture by column chromatography on silica gel with ether–hexane (4:1) as the eluant gave **19**: 290 mg (40%); mp 139–140 °C; IR ($CHCl_3$) 1725, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.66 (s, 3 H), 0.83 (d, J = 6 Hz, 3 H), 0.90 (s, 3 H), 1.0–1.9 (m, 10 H), 1.93 (s, 3 H), 2.02 (s, 3 H), 2.53 (d, J = 4.5 Hz, 1 H), 2.71 (d, J = 4. 5 Hz, 1 H), 4.28 (d, J = 12 Hz, 1 H), 4.65 (dd, J = 11, 5 Hz, 1 H), 4.81 (d, J = 12 Hz, 1 H); ^{13}C NMR 170.6 (s), 169.7 (s), 72.6 (d), 61.7 (t), 60.7 (s), 55.0 (t), 51.2 (d), 45.6 (s), 39.3 (d), 36.1 (s), 32.6 (t), 31.7 (t), 28.0 (q), 23.4 (t), 21.5 (t), 21.1 (q), 15.9 (q), 15.7 (q); mass spectrum, m/e 323 (M^+ – 15), 308, 295, 265, 223.

Anal. Calcd for $C_{19}H_{30}O_5$: C, 67.43; H, 8.94. Found: C, 67.42; H, 8.66.

Further elution gave **3**: 325 mg (43%); mp 110–111 °C; IR ($CHCl_3$) 1715, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.69 (s, 3 H), 0.86 (d, J = 6 Hz, 3 H), 0.90 (s, 3 H), 1.0–1.9 (m, 10 H), 1.93 (s, 3 H), 2.09 (s, 3 H), 2.19 (d, J = 4 Hz, 1 H), 2.96 (dd, J = 4, 2 Hz, 1 H), 4.35 (d, J = 12 Hz, 1 H), 4.73 (dd, J = 11, 5 Hz, 1 H), 4.81 (d, J = 12 Hz, 1 H); ^{13}C NMR δ 171.0 (s), 170.1 (s), 72.6 (d), 65.0 (s), 61.6 (t), 54.0 (d), 48.5 (t), 45.5 (s), 40.4 (d), 36.2 (s), 33.5 (t), 32.7 (t), 28.5 (q), 25.2 (t), 21.4 (t), 21.2 (q), 15.9 (q), 15.8 (q); mass spectrum, m/e 338, 323, 308, 295, 265, 223.

Anal. Calcd for $C_{19}H_{30}O_5$: C, 67.43; H, 8.94. Found: C, 67.22; H, 8.72.

9α-(Hydroxymethyl)-8-methylene-3α,4,4-trimethyl-3α,4,4-trimethyl-*trans*-decalin-1α-ol (20). Diacetate **17** (110 mg, 0.34 mmol) was dissolved in dry ether (2 mL) and lithium aluminum hydride (50 mg, 1.3 mmol) was added under nitrogen. The mixture was stirred at room temperature for 1 h and water (0.5 mL) and 6 N hydrochloric acid (1 mL) were added. The ether layer was separated, and the water layer was extracted with ether. The combined ethereal extracts were dried over magnesium sulfate and concentrated to afforded **20**: 78 mg (96%); mp 126–128; IR ($CHCl_3$) 3340, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.61 (s, 3 H), 0.83 (s, 3 H), 0.88 (d, J = 6 Hz, 3 H), 1.0–2.3 (*m*, 10 H), 3.26 (br s, 2 H), 4.00 (m, 3 H), 4.96 (s, 1 H), 5.12 (s, 1 H); mass spectrum, m/e 238, 220, 190, 120.

Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.41; H, 10.73.

Stereospecific Epoxidation of Diol 20. To a stirred solution of **20** (60 mg, 0.25 mmol) in methylene chloride (1 mL) was added $VO(acac)_2$ (10 mg) and *tert*-butyl hydroperoxide (0.5 mmol, 55 μL of a 80% solution). The mixture was stirred overnight at room temperature and then chromatographed on a short silica gel column with ether as the eluant. The resulting clear oil was acetylated and worked up as described for **14** to afford **3** (65 mg, 77%) as the only product.

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