# Synthesis of (±)-Isocelorbicol

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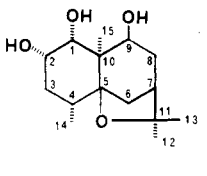
The synthesis of (±)-isocelorbicol (1), a naturally occurring sesquiterpene of the agarofuran group, has been carried out in several steps from 9-keto-α-agarofuran (7). Stereoselective reduction of 7, followed by protection of the hydroxyl group and allylic oxidation gave 9β-benzoyloxy-2-keto-α-agarofuran (13). Hydroxylation of 13, followed by reduction with $NaBH_4$·$CeCl_3$ afforded a mixture of 1β,2α- and 1β,2β-diols (20 and 16, respectively). Diol 20 was regioselectively converted to the 2α-acetate 21, which could also be obtained by reaction of the methanesulfonate of diol 16 with cesium acetate. Oxidation of acetate 21 to ketone 24 followed by stereoselective reduction to 1α-ol 25, hydrogenation, and hydrolysis gave a mixture of isocelorbicol (1) and its 4-epimer (26).

The plants of the family Celastraceae have proven to be a rich source of chemically and biologically interesting natural products. Although the tumor inhibitory compounds of the maytansine[1] and triptolide[2] groups have attracted a great deal of attention, the most characteristic class of compounds produced by these plants are polyhydroxy sesquiterpenes based on an agarofuran skeleton. These polyhydroxyagarofurans range in complexity from a relatively simple triol, isocelorbicol (1),[3] to complex polyols such as euonyminol (2).[4] Many of these polyhydroxylated sesquiterpenes occur in nature as ester alkaloids, in which the nitrogen is contained in a nicotinic acid or substituted nicotinic acid residue.[5] We wish to report at this time the synthesis of (±)-isocelorbicol (1), which constitutes the first reported synthesis of a member of this group of natural products.



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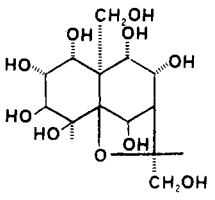

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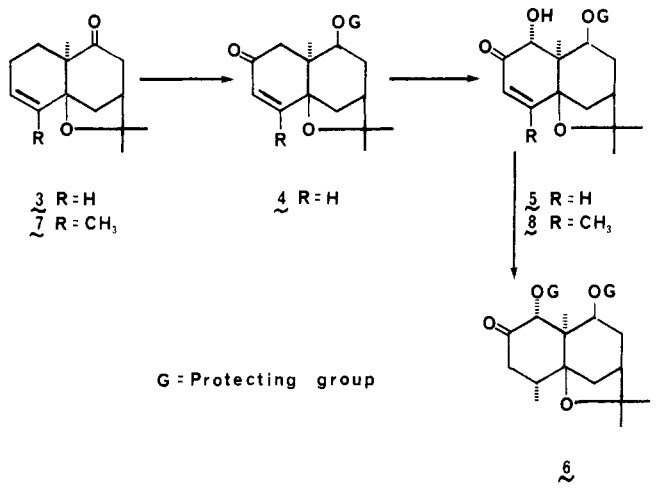
Our initial synthetic design, outlined in Scheme I, was to employ a 14-nor-9-keto-α-agarofuran (3)[6] as starting material. It was anticipated that addition of an organometallic to a suitably protected derivative of hydroxyenone 5, prepared from 3 via enone 4, would proceed by stereoelectronically favored axial attack to afford ketone 6. This approach was abandoned, due to poor yields in the preparation of ketone 3[6] and the failure of enone 4 (G = Ac) to afford conjugate addition products with several organocuprates.[7] Since 9-keto-α-agarofuran (7) could be prepared in considerably better yield than the 14-nor analogue,[6] an alternative approach was developed by employing this ketone as starting material and using a quasi-axial substituent at C-2 to thwart the known propensity for α-agarofuran to undergo reduction to give a β-methyl group at C-4.[8]

Scheme I




In the initial stages of the synthesis (Scheme II) the sterically hindered and strongly hydrogen-bonded hydroxyl group in 9β-hydroxy-α-agarofuran (9)[9] was converted to a nonenolizable ester, benzoate 12, by the method of Kaiser and Woodruff.[10,11] Oxidation to enone 13 could be effected by using the $CrO_3$·$py_2$ complex,[12] however better yields and far more tractable reaction mixtures were obtained by using the chromium trioxide–3,5-dimethylpyrazole complex.[13]

Attempted oxidation of the enolate of 13 by Vedejs' method[14] failed, however, oxidation of *tert*-butyldimethylsilyl enol ether 14[15] gave hydroxyenone 15 in a modest overall yield of 22%. It was subsequently found that this conversion could be effected in considerably

(1) Kupchan, S. M.; Komoda, Y.; Court, W. A.; Thomas, G. J.; Smith, P. M.; Gilmore, C. J.; Haltiwanger, R. C.; Bryan, R. F. *J. Am. Chem. Soc.* **1972**, *94*, 1354.
(2) Kupchan, S. M.; Court, W. A.; Dailey, R. G.; Gilmore, C. J.; Bryan, R. F. *J. Am. Chem. Soc.* **1972**, *94*, 7194.
(3) Smith, C. R.; Miller, R. W.; Weisleder, D.; Rohweder, W. K.; Eickman, N.; Clardy, J. *J. Org. Chem.* **1976**, *41*, 3264.
(4) Shizuri, Y.; Wada, K.; Sugiura, K.; Yamada, K.; Hirata, Y. *Tetrahedron* **1973**, *29*, 1773.
(5) Smith, R. A. In "The Alkaloids"; Manske, R. H. F., Ed.; Academic Press: New York, 1977; Vol 16, pp 215–248. Smith reviews the chemistry of this group of ester alkaloids and the sesquiterpenes obtained from then on hydrolysis.
(6) Huffman, J. W.; Hillenbrand, G. F. *Tetrahedron Suppl.* **1981**, *9*, 269. For a detailed investigation of the preparation of ketone 3 see Huffman, J. W.; Desai, R. C. *J. Org. Chem.* **1982**, *47*, 3254.
(7) Huffman, J. W.; Desai, R. C., unpublished work.
(8) Thomas, A. F.; Ozainne, M. *Tetrahedron Lett.* **1976**, 1717.
(9) Huffman, J. W.; Desai, R. C.; LaPrade J. E. *J. Org. Chem.* **1983**, *48*, 1474.
(10) Kaiser, E. M.; Woodruff, R. A. *J. Org. Chem.* **1970**, *35*, 1198.
(11) Initially, alcohol 9 was converted to acetate 10 by using 4-(dimethylamino)pyridine–acetic anhydride. (Hofle, G.; Steglich, W.; Vorbruggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569. Daily, O. D.; Fuchs, P. L. *J. Org. Chem.* **1980**, *45*, 216. Daily and Fuchs describe the experimental procedures used for the esterification of 9.) Oxidation to enone 11 was carried out by the procedure used for the oxidation of 12 to 13. Attempted hydroxylation of 11 at C-1 failed, apparently due to competitive enolization of the acetate.
(12) Dauben, W. G.; Lorber, M.; Fullerton, D. S. *J. Org. Chem.* **1969**, *34*, 3587.
(13) Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 2057.
(14) (a) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188. (b) Vedejs, E. *J. Am. Chem. Soc.* **1974**, *96*, 5944.
(15) Rubottom, G. M.; Gruber, J. M. *J. Org. Chem.* **1978**, *43*, 1599.

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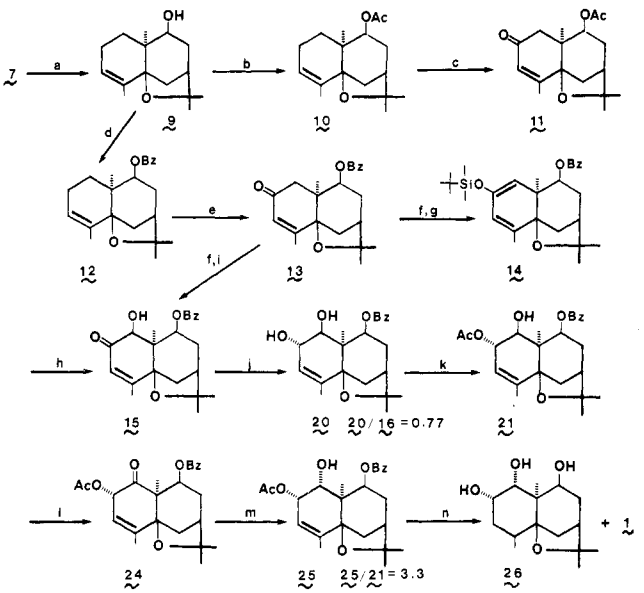
Scheme II[a]



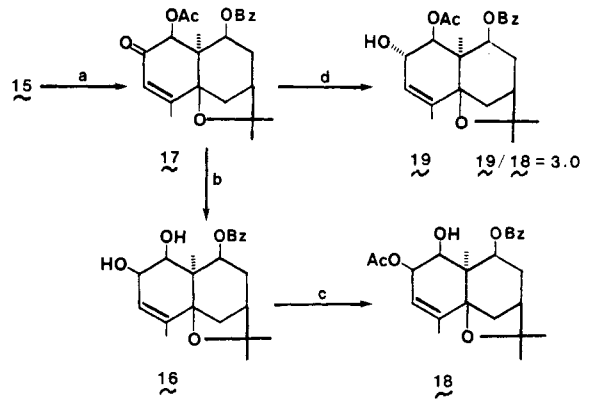
[a] Reagents: a, $LiAlH_4$, $Et_2O$, -10 °C, 5 h, 99%; b, $Ac_2O$, DMAP, $Et_3N$, $CH_2Cl_2$, 25 °C, 48 h, 71%; c, $CrO_3 \cdot py_2$; $CH_2Cl_2$, 0-13 °C, 26 h, 57%; d, *n*-BuLi, THF, 25 °C; PhCOCl, THF, reflux 1 h, 100%; e, $CrO_3$-3,5-dimethylpyrazole, $CH_2Cl_2$, -20 °C, 5 h, 60%; f, LDA (1 equiv), THF, 0 °C, 45 min; g, *t*-$BuMe_2SiCl$, HMPA, THF, 25 °C, 18 h, 44%; h, MCPA, hexanes, 25 °C, 4 h; HCl, THF, 25 °C, 20 h, 50%; i, $(PhCO_2)_2$, THF, -10 °C, 2 h, 50%; j, $NaBH_4$, $CeCl_3 \cdot 7H_2O$, $CH_3OH$, 25 °C, 3 h, 75%; k, $Ac_2O$, pyridine, 25 °C, 24 h, 91%; l, $K_2Cr_2O_7$, $(n\text{-}Bu)_4NHSO_4$, 7 M $H_2SO_4$, $CH_2Cl_2$, 25 °C, 4 h, 55%; m, *t*-$BuNH_2 \cdot BH_3$, $CH_2Cl_2$, 25 °C, 29 h, 73%; n 50% KOH, $CH_3OH$, 25 °C, 3 h; 5% Rh/C, $H_2$, 29%.

better yield (50%) by reaction of the enolate of enone **13** with purified benzoyl peroxide.[16]

Although it had been expected that hydroxylation at C-1 would lead to a compound having the desired natural 1$\alpha$-equatorial stereochemistry, the NMR spectrum of the ketol indicated that it was the 1$\beta$-isomer (**15**), based principally on the observation that the hydroxyl proton appeared as a doublet ($J$ = 6.6 Hz) in deuteriochloroform, indicating strong hydrogen bonding, presumably to the oxygen of the ether bridge.[17] Attempted isomerization to the presumably more stable 1$\alpha$-epimer under acidic or basic conditions gave only recovered ketol or products of gross decomposition.

On the assumption that failure to effect epimerization at C-1 of hydroxy ketone **15** was due to stabilization by hydrogen bonding, efforts were made to convert **15** to a suitable derivative, maintaining the severe interactions with the other axial oxygen substituents but removing the stabilizing influence of the hydrogen bond. Acetylation of **15** could only be achieved by treatment with a catalytic

Scheme III[a]



[a] Reagents: a, $Ac_2O$, $H_2SO_4$, 25 °C, 1 h, 62%; b, L-Selectride, THF, -78 °C, 5 h; 2 M NaOH, 30% $H_2O_2$, 25 °C, 18 h, 67%; c, $Ac_2O$, pyridine, 25 °C, 24 h, 68%; d, $NaBH_4$, EtOH, 0 °C, 2.5 h, 65%.

amount of sulfuric acid in acetic anhydride to give an ester, the NMR spectrum of which showed the shielded ($\delta$ 1.67) singlet characteristic of a 1$\alpha$-acetate in various hydroxyagarofuran derivatives.[18] Since the compound was stable to the strongly acidic conditions of its formation, it was tentatively concluded that esterification had proceeded with epimerization at C-1. However, treatment of the acetate with an aprotic base (NaH–ether) afforded **15**, presumably via hydrolysis during the isolation of the product. In an effort to establish the stereochemistry at C-1, the acetate was reduced with L-Selectride[19] (Aldrich) to a single diol,[20] which formed an acetonide under mild conditions, indicating that the hydroxyl groups were cis. The NMR spectrum of this diol showed *both* hydroxyl protons as doublets in $CDCl_3$ solution (see Experimental Section), indicating that both were strongly hydrogen bonded and that the diol is the 1$\beta$,2$\beta$-isomer (**16**, Scheme III). The ester obtained on acetylation of enone **15** must then be 1$\beta$-acetoxy-9$\beta$-benzoyloxy-2-keto-$\alpha$-agarofuran (**17**). Acetylation of diol **16** under standard conditions gave a monoacetate (**18**) in which the unhindered quasi-equatorial 2$\beta$-hydroxyl is selectively esterified.

To confirm these stereochemical assignments, acetate **17** was reduced with sodium borohydride to give a 1:3 mixture of monoacetate **18**, in which reduction is accompanied by acyl migration, and an isomeric acetate, which was tentatively assigned structure **19** as the major product.[21] Sodium borohydride reduction of enone **15** gave

(16) Muller, J. C.; Ourisson, G. *Tetrahedron Lett.* **1972**, 3375. The authors wish to thank Prof. P. Deslongchamps for calling this reaction to their attention. Although this procedure was expected to lead to a 1-benzoate, subsequent work with the 1-acetate derived from ketol **15** indicated that these esters undergo exceedingly rapid hydrolysis (see below). It is assumed that the benzoate is the initial product of this reaction and that it undergoes hydrolysis during the isolation of the reaction products. A small quantity of a material which had an NMR spectrum consistent with a 1,9-dibenzoate structure was obtained from this reaction, however it underwent extensive decomposition on attempted hydrolysis with mild base using conditions which do not affect ketol **15**.

(17) It is well-known that hydroxyl protons normally appear as singlets in deuteriochloroform due to rapid exchange caused by acidic impurities in the solvent. For leading references, see: Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry"; Pergamon Press: Oxford, 1969; pp 299–300, 359.

(18) Kupchan, S. M.; Smith, R. M.; Bryan, R. F. *J. Am. Chem. Soc.* **1970**, *92*, 6667.

(19) Brown, C. A. *J. Am. Chem. Soc.* **1973**, *95*, 4100.

(20) Although the exact mechanism for the loss of the acetate is uncertain, it is probably not a simple reductive cleavage inasmuch as the benzoate withstands these reaction conditions. A more probable explanation is acetyl migration to give a 1-hydroxy-2-acetate, followed by simple hydrolysis during subsequent treatment with alkaline peroxide.

(21) These structural assignments were confirmed by decoupling experiments in which it was found that for acetate **18**, $J_{1,2}$ = 2.9 Hz and $J_{2,3}$ = 1.7 Hz. Assuming a half-chair conformation for this compound with the hydroxyl group strongly hydrogen bonded to the ether oxygen, measurements using Dreiding models show that bond angles, $\phi_{1,2}$ and $\phi_{2,3}$ are 60° and 10°, respectively. Application of the appropriate modifications of the Karplus equation gives calculated values of $J_{1,2}$ = 4.0 Hz and $J_{2,3}$ = 2.7 Hz. The isomeric acetate (**19**) had $J_{1,2}$ = 1.7 Hz and $J_{2,3}$ = 4.2 Hz. The calculated coupling constants, based on $\phi_{1,2}$ = 75° and $\phi_{2,3}$ = 50° are 2.9 Hz and 4.2 Hz, respectively. For calculating $J_{1,2}$ the equation developed by Bothner-By, A. A. and Naar-Colin, C. (*J. Am. Chem. Soc.* **1962**, *84*, 2748) was used. For $J_{2,3}$ that described by Garbisch, E. W. (*Ibid.* **1964**, 86, 5561) was used. The calculated coupling constants for the isomers of **18** and **19** derived from the 1$\alpha$-acetoxy epimer of enone **17** were not compatible with the observed values nor were those of the half-boat conformers of **18** and **19**. For a detailed discussion, see: Hillenbrand, G. F.; PhD Dissertation, Clemson University, 1982.

a mixture of products from which diol **16** could be isolated in 38% yield accompanied by 16% of an isomer with the spectral properties expected for 1β,2α-diol (**20**). Reduction with $NaBH_4$·$CeCl_3$[22] gave 32% of diol **20** and 43% of diol **16**, and as expected, diol **20** was selectively esterified in good yield to give acetate **21**.

The poor stereoselectivity at the reduction stage, combined with an unfavorable ratio of diols **20** to **16**, led us to investigate the conversion of diol **16** to a derivative of diol **20**. Diol **16** was selectively converted to the unstable 2β-mesylate in good yield, prolonged heating of which with cesium propionate in DMF gave the 2-propionate of diol **20** in 69% yield.[23,24] Alternatively, reaction of the mesylate with cesium acetate generated in situ[25] gave acetate **21** in 64% yield. The overall yield of **21** from enone **15** by the combination of the direct route (**15** → **20** → **21**) and that via diol **16** (**15** → **16** → **22** → **21**) is 54%.

Due to the hindered nature and strong hydrogen bonding of the 1-hydroxyl group in **21**, direct epimerization at C-1 did not appear feasible and an approach via reduction of the 1-ketone (**24**) seemed far more attractive. Attempted oxidation of **21** to **24** proved unexpectedly difficult, presumably due to strong hydrogen bonding and 1,3-diaxial interactions of the 1-hydroxyl group with the oxygen atoms at C-5 and C-9.[26] Oxidation of **21** under strongly acidic conditions,[27] which presumably disrupts this hydrogen bonding, gave ketone **24**.

Initial attempts to effect stereoselective reduction of ketone **24** to the 1α-ol using sodium borohydride in various solvents (MeOH, 2-PrOH, DME) afforded complex mixtures of products which included significant quantities of the 1β-ol. Reduction with reasonable stereoselectivity was effected by using the *tert*-butylamine borane complex[28] to give an easily separable 3.3 to 1 mixture of alcohols **25** and **21**.

At this point completion of the synthesis of isocelorbicol (**1**) required the reduction of the $\Delta^3$-olefin and hydrolysis of the ester groups, although not necessarily in that order. It was felt that hydrolysis of **25** to the corresponding triol would afford a polar molecule in which the vicinal diol would associate with the solvent and promote hydrogenation from the β-face and that the α-face of the molecule would be shielded by the quasi-axial substituent at C-2, promoting reduction from the β-face of the molecule. Hydrolysis of both esters of **25** was effected by using 50% methanolic KOH at ambient temperature and the resulting triol was subjected to hydrogenation without prior purification. Reduction using palladium catalysts gave complex mixtures of products, apparently as a result of hydrogenolysis of the allylic carbon–oxygen bonds, while 5% rhodium on alumina at 42 psi gave only recovered starting material. However, reduction using 5% rhodium on carbon for 48 h at 50 psi gave a single dihydro compound, although in mediocre yield. The IR and mass spectra of this compound were essentially indistinguishable from those of natural isocelorbicol (**1**), however the NMR spectrum clearly showed that this material was the 4-epimer of the natural product, triol **26**. In particular the secondary methyl group appeared in the NMR as a doublet at δ 0.91 ($J$ = 6.6 Hz), whereas the axial secondary methyl group in isocelorbicol appears at considerably higher field (δ 1.25, $J$ = 7.2 Hz).[3]

The exclusive formation of 4-epiisocelorbicol (**26**) in this reduction could be explained by making the assumption that the quasi-axial 2α-hydroxyl group was selectively binding to the catalyst surface and directing hydrogenation from the α-face.[29] If such an effect was responsible for the high degree of stereoselectivity in the hydrogenation, then reduction of **25**, in which the 2α-hydroxyl is masked as an acetate, would perhaps afford the natural stereochemistry at C-4. In practice, reduction of **25** gave a mixture of products, the NMR spectrum of which indicated that the aromatic ring of the benzoate had been reduced as well as the olefinic double bond. Hydrolysis of the crude reduction product gave a mixture of triol **26** and (±)-isocelorbicol (**1**). By careful chromatography it was possible to obtain synthetic sesquiterpene **1** contaminated with approximately 33% of the 4-epimer. The mass spectrum of this synthetic material was identical with that reported for the natural product.[3] Direct comparison of the NMR spectra of natural and synthetic isocelorbicol indicated that the synthetic material had all of the peaks characteristic of the natural product, including the rather distinctive multiplet associated with the protons at C-1 and C-2. The only difference in the spectra was the presence of small peaks due to triol **26** in the synthetic material. Rechromatography of the mixture of triols **1** and **25** failed to effect separation. Although it might ultimately prove possible to separate this mixture of triols, thereby affording a homogeneous sample of synthetic isocelorbicol, this was not attempted due to the relatively poor chemical yield at the last step, undoubtedly attributable to hydrogenolysis characteristic of the α-agarofuran system,[8] combined with the low stereoselectivity in the hydrogenation step.

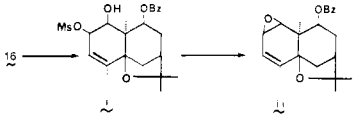
## Experimental Section

Melting points were determined by using a Kofler hot stage and are uncorrected. IR spectra were obtained as neat films between salt plates or as solutions in $CCl_4$ or $CHCl_3$ using a Perkin-Elmer Model 137 spectrophotometer and are reported in reciprocal centrimeters ($cm^{-1}$). NMR spectra were obtained on JEOL FX-90Q, Varian A-60A, or Hitachi Perkin-Elmer Model R-24 spectrometers, using, unless otherwise noted, $CDCl_3$ as solvent. Spectral data are reported in parts per million relative to tetramethylsilane (δ). Elemental analyses were performed by

(22) (a) Luche, J. L.; Gemal, A. L.; Crabbe', P. *J. Chem. Soc., Chem. Commun.* **1978**, 601. (b) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226. (c) Gemal, A. L.; Luche, J. L. *Ibid.* **1981**, *103*, 5454.

(23) Kruizinga, W. H.; Strijtveen, B.; Kellogg, R. M. *J. Org. Chem.* **1981**, *46*, 4321.

(24) Although this appears to be a straightforward $S_N2$ reaction of cesium propionate with mesylate **i**, this is not the case, for if the reaction




is carried out only until the mesylate is consumed a mixture of products is obtained from which epoxide **ii** can be isolated in 32% yield and none of the propionate ester could be detected by TLC. This reaction apparently proceeds by the initial, relatively rapid, formation of epoxide **ii** followed by a slow $S_N2$ reaction of propionate to give the ester by way of normal trans-diaxial opening. The conversion of mesylate **i** to epoxide **ii** is most readily explained in terms of the initial solvolysis of **i** to an allylic cation which is trapped by intramolecular attack of the 1-hydroxyl.

(25) Huffman, J. W.; Desai, R. C. *Synth. Commun.* **1983**, *13*, 553.

(26) Rocek, J.; Westheimer, F. H.; Eschenmoser, A.; Maldovanyi, L.; Schreiber, J. *Helv. Chim. Acta* **1962**, *45*, 2554. Rocek et al. found that the first step in the chromate oxidation of alcohols is the formation of a chromate ester and that in extremely hindered alcohols the rate of this step can be severely retarded. Alcohol **21** is oxidized only very slowly with Jones reagent.

(27) Pletcher, D.; Tait, S. J. D. *Tetrahedron Lett.* **1978**, 1601.

(28) (a) Chang, F. C. *Synth. Commun.* **1981**, *11*, 875. (b) Iida, T.; Chang, F. C. *J. Org. Chem.* **1982**, *47*, 2972. (c) Andrews, G. C.; Drawford, T. C. *Tetrahedron Lett.* **1980**, *21*, 693. Andrews and Drawford describe the reduction of a number of relatively simple ketones with this reagent.

(29) Stork, G.; Kahne, D. E. *J. Am. Chem. Soc.* **1983**, *105*, 1072. Stork and Kahne giving a striking and synthetically useful method of controlling the stereochemistry in catalytic hydrogenations by taking advantage of coordination of hydroxyl groups with an iridium catalyst.

Atlantic Microlab, Inc., Atalanta, GA. Mass spectra were determined at 70 eV by using a Hewlett-Packard 5985B mass spectrometer.

**9β-Benzoyloxy-α-agarofuran (12).** To a stirred solution of 2.37 g (10.0 mmol) of 9β-hydroxy-α-agarofuran (**9**)[9] and a few crystals of 2,2′-bipyridyl in 25 mL of dry THF at room temperature was added dropwise 6.0 mL of 1.67 M *n*-butyllithium in hexane until excess butyllithium was present. After 10 min a solution of 1.48 g (1.05 equiv) of benzoyl chloride in 7.0 mL of dry THF was added. After stirring at ambient temperature for 15 min, the mixture was heated at reflux for 1 h and cooled, and the mixture was poured into saturated aqueous $NaHCO_3$. The mixture was extracted with two portions of ether and the combined ethereal extracts were washed successively with saturated aqueous $NaHCO_3$ and brine. After drying, the solvent was removed at reduced pressure to give 3.40 g (100%) of ester **12** as a crystalline solid which was homogeneous to TLC. Recrystallization from hexanes gave the analytical sample: mp 128–130 °C; IR 1718, 1270 $cm^{-1}$; NMR δ 1.04 (s, 3 H, $CH_3$), 1.31, 1.47, (s, 3 H each, $(CH_3)_2C$—), 1.76 (br s, 3 H, $CH_3$—C=), 5.03, (dd, $J$ = 5.6 Hz, $J$ = 2 Hz, 1 H, —CH—O), 5.55, (m, 1 H, —CH=), 7.32–8.00, (m, 5 H, aromatic CH). Anal. Calcd for $C_{22}H_{28}O_3$: C, 77.64; H, 8.23. Found: C, 77.57; H, 8.31.

**9β-Benzoyloxy-2-keto-α-agarofuran (13).** To a vigorously stirred suspension of 15.01 g (0.15 mol) of dry $CrO_3$ in 125 mL of dry $CH_2Cl_2$ at −25 °C under $N_2$ was added rapidly 14.41 g of dry 3,5-dimethylpyrazole. After 35 min, a solution of 3.40 g (10.01 mmol) of ester **12** in 25 mL of dry $CH_2Cl_2$ was added rapidly dropwise. The mixture was stirred at or below −20 °C for 5 h, 62.5 mL of 5.0 M aqueous NaOH was added, and stirring was continued for an additional 1 h. The layers were separated and the aqueous layer washed with two portions of $CH_2Cl_2$. The combined organic layers were washed successively with three portions of 3 N HCl, saturated aqueous $NaHCO_3$, and brine and dried. The solvent was removed at reduced pressure to give a dark red oil, chromatography of which on neutral alumina (Woelm, activity II) and elution with ethyl acetate–cyclohexane (1:4) gave, after recrystallization from isopropyl alcohol, 2.14 g (60%) of keto ester **13**. The analytical sample, mp 189–191 °C, was crystallized from the same solvent: IR 1705, 1676, 1263 $cm^{-1}$; NMR δ 1.21, (s, 3 H, $CH_3$), 1.40, 1.60 (s, 3 H each, $(CH_3)C$), 2.08, (s, 3 H, $CH_3$—C=), 5.25, (m, 1 H, —CH—O), 6.10, (s, —CH=), 7.65–8.25, (aromatic CH). Anal. Calcd for $C_{21}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.44; H, 7.42.

**1β-Hydroxy-9β-benzoyloxy-2-keto-α-agarofuran (15). A.** To a stirred solution of 0.417 g (1.18 mmol) of keto ester **13** and a crystal of 2,2′-bipyridyl in 2.5 mL of dry THF under $N_2$ at 0 °C, was added sufficient 0.75 M LDA in THF–hexanes to give a persistent color change. After 45 min, a solution of 0.231 g (1.53 mmol) of *tert*-butyldimethylsilyl chloride and 0.27 mL of dry HMPA in 1.5 mL of dry THF was added, and the mixture stirred for 18 h at ambient temperature. After pouring into 10 mL of saturated aqueous $NaHCO_3$, the mixture was extracted with two portions of ether. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine and then dried over anhydrous $Na_2SO_4$. The solvent was removed under reduced pressure to afford an oily residue which was chromatographed on silica gel. Elution with benzene–hexanes (1:1) gave 0.245 g (44%) of silyl enol ether **14** as a glassy solid, the spectral characteristics of which were consistent with the proposed structure.

To a stirred solution of 0.089 g (0.57 mmol) of *m*-chloroperbenzoic acid in 10 mL of hexanes at −15 °C was added 0.220 g (0.52 mmol) of silyl enol ether **14** in 5 mL of hexanes. After 4 h at ambient temperature, the solvent was removed under reduced pressure and replaced by 14 mL of THF, 3 mL of water, and 0.5 mL of concentrated HCl. After stirring 20 h at ambient temperature, the mixture was poured into 50 mL of saturated aqueous $NaHCO_3$ and extracted with two portions of ether. The combined organic layers were dried and the solvent evaporated under reduced pressure to give a semisolid. Chromatography of this material on silica gel, using ether–benzene (1:6) as the eluent, gave 0.105 g (50%) of hydroxy ketone **15**. Recrystallization from hexanes–ethyl acetate gave the analytical sample: mp 182–184 °C; IR 3545, 1709, 1695, 1266 $cm^{-1}$; NMR δ 1.05 (s, 3 H, $CH_3$), 1.37, 1.60, (s, 3 H each, $(CH_3)_2C$), 1.95, (d, $J$ = 1 Hz, 3 H, $CH_3$—C=), 3.83 (d, $J$ = 6.6 Hz, 1 H, CHOH), 5.14 (d, $J$ = 6.6 Hz, OH) 5.36 (d, $J$ = 5.7 Hz, 1 H, —CH—O, Bz), 5.97 (m, 1 H, —CH=), 7.15–8.14 (m, 5 H, aromatic CH). Anal. Calcd for $C_{21}H_{26}O_5$: C, 71.33; H, 7.07. Found: C, 71.52; H, 7.11.

**B.** To a solution of the enolate, generated as described above from 2.00 g (6.17 mmol) of keto ester **13** by using 12.85 mmol of LDA in 50 mL of dry THF under $N_2$ at −10 °C, was added slowly a solution of 8.50 g (35.1 mmol) of purified, dry benzoyl peroxide in 50 mL of dry THF. The reaction mixture was stirred at −10 °C for 2 h and then quenched with a solution of 3.5 g of KI in 20 mL of water and 10 mL of acetic acid. This mixture was stirred at ambient temperature for 12 h, and the aqueous layer was drawn off and extracted with two portions of ether. The combined organic phases were washed with four portions of 1 N $Na_2S_2O_4$ followed by five portions of saturated $NaHCO_3$, water, and brine. After drying the solvent was removed to afford 3.02 g of pale yellow oil. Flash chromatography,[30] on Woelm silica gel using 2:3 ethyl acetate–hexanes, gave 0.62 g (30%) of hydroxy ketone **15** identical with that described in part A. Later fractions afforded 0.706 g of a thick oil which was not homogeneous to TLC. The final fractions afforded 0.518 g (26%) of starting keto ester (**13**). The intermediate fraction was dissolved in 4:1 hexanes–ethyl acetate and rechromatographed on Woelm silica gel. Elution with 7:3 hexanes–ethyl acetate gave first 0.258 g of an amorphous solid, tentatively identified as the 1β-benzoate: NMR 1.18 (s, 3 H, $CH_3$), 1.44, 1.59 (s, 3 H each, $(CH_3)_2O$), 1.59 (br s, 3 H, $CH_3C$=), 5.24 (m, 2 H, CHOBz), 5.80 (br s, 1 H, —CH=), 6.10–8.00 (m, 10 H, aromatic CH). Later fractions eluted with the same solvents gave an additional 0.152 of hydroxy ketone **15**, giving an overall yield of 50% based on starting material consumed.

**1β-Acetoxy-9β-benzoyloxy-2-keto-α-agarofuran (17).** To a stirred solution of 0.355 g (0.96 mmol) of hydroxy ketone **15** in 5.0 mL of acetic anhydride was added one drop of concentrated $H_2SO_4$. After 1 h, the mixture was poured into saturated aqueous sodium bicarbonate, stirred until gas evolution ceased, and then extracted with ether. After drying, the solvent was removed to give a semicrystalline solid, chromatography of which on Woelm silica gel using ether–benzene as eluent afforded 0.244 g (62%) of acetate **17**. Recrystallization from hexanes have the analytical sample: mp 178 °C sublimed; IR 1739, 1709, 1686, 1266 $cm^{-1}$; NMR δ 1.15 (s, 3 H, $CH_3$), 1.38, 1.63 (s, 3 H each, $(CH_3)_2C$), 1.67 (s, 3 H, $CH_3CO$), 2.06 (m, 3 H, $CH_3C$=), 5.17 (br s, 1 H, —CH—OAc), 5.38 (br d, $J$ = 6 Hz, 1 H, —CH—OBz), 5.90 (br s, 1 H, —CH=), 7.43–8.10 (m, 5 H, aromatic CH). Anal. Calcd for $C_{21}H_{26}O_5$: C, 71.33; H, 7.07. Found: C, 71.52; H, 7.11.

**1β,2β-Dihydroxy-9β-benzoyloxy-α-agarofuran (16).** To a stirred solution of 0.50 g (0.121 mmol) of keto acetate **17** in 1.2 mL of dry THF under $N_2$ at −78 °C was added in one portion 1.22 mL of a 1.0 M solution of lithium tri-*sec*-butylborohydride (L-Selectride) in the same solvent. After 5 h, the excess hydride was destroyed by the cautious addition of water and the mixture was warmed to 0 °C. To this mixture was then added slowly 2.0 mL of 2.0 M aqueous NaOH and 1.42 mL of 30% hydrogen peroxide and the reaction was stirred at ambient temperature for 18 h. After extraction with three portions of $CHCl_3$ the combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine and dried, and the solvent was removed at reduced pressure to afford a solid residue. Chromatography on Woelm silica gel, using ether–benzene (1:5) as the eluent, gave 0.030 g (67%) of diol **16**. The analytical sample was recrystallized from hexanes–ethyl acetate: mp 186 °C sublimed; IR 3538, 1714, 1271, 1110 $cm^{-1}$; NMR δ 1.04, (s, 3 H, $CH_3$), 1.32, 1.55 (s, 3 H each, $(CH_3)_2C$), 1.83, (m, 3 H, $CH_3$—C=), 3.06, (d, $J$ = 11.4 Hz, 1 H, 1β-OH), 3.75 (m, 1 H, 1α-H), 4.00 (m, 1 H, 2α-H), 4.80 (d, $J$ = 6 Hz, 1 H, 2β-OH), 5.27 (m, 1 H, —CH—OBz), 7.42–8.07 (m, 5 H, aromatic CH). Anal. Calcd for $C_{22}H_{28}O_5$: C, 70.95; H, 7.58. Found: C, 71.12; H, 7.63.

Acetylation of 0.015 g (0.043 mmol) of diol **11** using 0.25 mL of acetic anhydride and 0.50 mL of pyridine at ambient temperature for 24 h afforded 0.11 g (68%) of 2β-acetoxy-1β-hydroxy-9β-benzoyloxy-α-agarofuran (**18**), mp 179–180 °C, after chromatography on silica gel and recrystallization from pentane: IR 3546, 1727, 1267, 1111, 907 $cm^{-1}$; NMR δ 1.10, (s, 3 H, $CH_3$), 1.30, 1.50 (s, 3 H each, $(CH_3)_2C$), 1.75 (m, 3 H, $CH_3$—C=), 2.07,

(30) Still, W. C. Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(s, 3 H, $CH_3CO$), 3.90, (m, 1 H, C*H*OH), 4.90, (d, $J$ = 6 Hz, 1 H, OH), 5.30, (m, 3 H, —CH—OBz, —CH—OAc, —CH=), 7.45–8.10 (m, 5 H, aromatic CH). Anal. Calcd for $C_{24}H_{30}O_6$: C, 69.55; H, 7.30. Found: C, 69.67; H, 7.32.

**Acetonide of 1β,2β-Dihydroxy-9β-benzoyloxy-α-agarofuran.** To a stirred solution of 0.030 g (0.081 mmol) of diol **16** in 0.6 mL of 2,2-dimethoxypropane and 0.2 mL of dry DMF was added 0.020 g (0.086 mmol) of *d*-10-camphorsulfonic acid. The mixture was maintained at 50 °C under $N_2$ for 28 h, and then poured into 10 mL of saturated aqueous $NaHCO_3$ and extracted with three portions of $CHCl_3$. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine. After drying, removal of the solvent under reduced pressure gave a solid, chromatography of which on silica gel using ether–benzene (1:19) as the eluent afforded 0.021 g (63%) of acetonide. The analytical sample was recrystallized from pentane: mp 154–155 °C; IR 1707, 1276, 1112 $cm^{-1}$; NMR 0.73 (s, 3 H, acetonide $CH_3$), 1.05 (s, 3 H, $CH_3$), 1.26, 1.30, 1.57 (s, 3 H each, acetonide $CH_3$ and $(CH_3)_2CO$), 1.80 (m, 3 H, $CH_3$—C=), 4.02 (d, $J$ = 4.3 Hz, 1 H, 1α-H), 4.32 (m, 1 H, 2α-H), 5.33 (d, $J$ = 3 Hz, 1 H, —CH—OBz), 5.36 (m, 1 H, —CH=), 7.37–8.23 (m, 5 H, aromatic CH). Anal. Calcd for $C_{25}H_{32}O_5$: C, 72.79; H, 7.82. Found: C, 72.84; H, 7.28.

**Reduction of 1β-Acetoxy-2-keto-9β-benzoyloxy-α-agarofuran.** To a solution of 0.061 g (0.148 mmol) of keto acetate **17** in 2.0 mL of absolute ethanol at 0 °C was added 0.046 g (1.22 mmol) of $NaBH_4$. The mixture was stirred under $N_2$ for 2.5 h and 0.04 mL of saturated brine was added. After 10 min solid $NH_4Cl$ (ca. 0.5 g) was added cautiously and the mixture was stirred until efferversence ceased. The mixture was poured into 15 mL of saturated aqueous $NaHCO_3$ and extracted twice with ether. The combined extracts were washed with saturated aqueous $NaHCO_3$ and brine and dried, and the solvent was removed under reduced pressure to afford an oil, which was chromatographed on silica gel using ether–benzene mixtures (1:6 to 3:2). The early fractions afforded 0.010 g (16%) of 1β-hydroxy-2β-acetate (**18**) identical in all respects to that obtained earlier, while the later fractions gave 0.033 g (49%) of the isomeric 2α-hydroxy-1β-acetate (**19**) as a crystalline solid: mp 149–151 °C; IR 3765, 3600, 1737, 1282, 873 $cm^{-1}$; NMR δ 1.25 (s, 3 H, $CH_3$), 1.35, 1.67 (s, 3 H each, $(CH_3)_2C$), 1.59 (s, 3 H, $CH_3CO$), 1.89 (m, 3 H, $CH_3$—C=), 4.03 (m, 1 H, —C*H*—OH), 4.95 (br s, 1 H, C*H*OAc), 5.44 (d, $J$ = 7.4 Hz, 1 H, —CH—OBz) 5.69 (m, 1 H, —CH=), 7.41–8.07 (m, 5 H, aromatic CH). Anal. Calcd for $C_{24}H_{30}O_6$: C, 69.55; H, 7.30. Found: C, 69.59; H, 7.30.

**Reduction of 1β-Hydroxy-9β-benzoyloxy-2-keto-α-agarofuran.** To a stirred suspension of 0.620 g (1.67 mmol) of hydroxy ketone **15** and 0.640 g (1.72 mmol) of $CeCl_3 \cdot 7H_2O$ in 30 mL of methanol was added slowly over a period of 5 min 0.262 g (6.89 mmol) of $NaBH_4$. The reaction mixture was stirred under $N_2$ at ambient temperature for 3 h and the excess borohydride decomposed by the addition of acetone. Water was added and the products were isolated by extraction with four portions of ether. The combined extracts were washed with brine and dried, and the solvent removed at reduced pressure to afford a thick oil. Flash chromatography on silica gel[30] and elution with hexanes–ethyl acetate (7:3) gave 0.269 g (43%) of 1β,2β-diol **16**, identical to that described above. Continued elution with the same solvent system gave 0.062 g of a mixture of diol and unreduced ketone. Elution with hexanes–ethyl acetate (1:1) afforded 0.201 g (32%) of 1β,2α-diol **20** as a crystalline solid, mp 74–77 °C, which was homogeneous to TLC and used in the subsequent step without further purification: NMR δ 1.16 (s, 3 H, $CH_3$), 1.33, 1.36 (s, 3 H each, $(CH_3)_2C$), 1.88 (br s, $CH_3C$=), 3.89 (m, 1 H, 1α-H), 4.20 (m, 1 H, 2β-H), 4.86 (d, $J$ = 5.4 Hz, 1β-OH), 5.42 (d, $J$ = 6.3 Hz, 1 H, CHOBz), 5.78 (m, 1 H, —CH=), 7.39–8.14 (m, 5 H, aromatic CH); MS, $m/e$ (relative intensity) 372 (2), 357 (3), 356 (14), 354 (14), 296 (3), 251 (17), 250 (100), 233 (4), 232 (12), 204 (8), 203 (21). Reduction of hydroxy ketone **15** with $NaBH_4$ in ethanol gave a mixture of products from which diol **16** could be obtained in 38% yield and diol **20** in 16% yield.

Reaction of 0.200 g of diol **20** with 0.2 mL of acetic anhydride in 3 mL of pyridine at room temperature for 24 h gave 0.203 g (91%) of the 2α-acetate (**21**), which was homogeneous to TLC: NMR δ 1.11 (s, 3 H, $CH_3$), 1.31, 1.59 (s, 3 H each, $(CH_3)_2C$), 1.88 (br s, 3 H, $CH_3C$=) 1.98 (s, 3 H, $CH_3CO$), 3.82 (m, 1 H, 1α-H), 4.89 (d, $J$ = 6 Hz, OH), 5.13 (m, 1 H, 2β-H), 5.36 (d, $J$ = 6 Hz, CHOBz), 5.71 (m, 1 H, —CH=), 7.10–8.12 (m, 5 H, aromatic CH). The analytical sample, mp 158–160 °C, was recrystallized from methylene chloride–pentane. Anal. Calcd for $C_{24}H_{30}O_6$: C, 69.55; H, 7.30. Found: C, 69.49; H, 7.35.

**2α-((Methylsulfonyl)oxy)-1β-hydroxy-9β-benzoyloxy-α-agarofuran (22).** To a solution of 0.325 g (0.87 mmol) of diol **16** in 6 mL of dry $CH_2Cl_2$ at 0 °C was added 0.08 mL of triethylamine and 0.18 mL of methanesulfonyl chloride. The reaction mixture was stirred at 0–5 °C for 3 h and poured into ice water, and the product was isolated by extraction with ether. After washing with water and 10% aqueous HCl and drying, the solvent was removed with gentle warming to afford 0.366 g (93%) of mesylate **22** as a pale brown oil which was used without further purification.

**2α-Acetoxy-1β-hydroxy-9β-benzoyloxy-α-agarofuran (21).** A solution of 0.307 g (0.71 mmol) of mesylate **22**, obtained from 0.265 g of 1β,2β-diol **16** in 12 mL of dry DMF was added to 0.669 g of freshly prepared cesium acetate[29] and the reaction mixture was stirred under $N_2$ at 5 °C for 36 h. After isolation of the product as described above and flash chromatography[30] on silica gel there was obtained 0.190 g (64%) of hydroxy acetate **21** identical with that described above.

**2α-Acetoxy-1-keto-9β-benzoyloxy-α-agarofuran (24).** A solution of 0.165 g (0.40 mmol) of hydroxy acetate **21** in 10 mL of $CH_2Cl_2$ was added to a solution of 0.076 g of $K_2Cr_2O_7$ and 0.015 g of tetrabutylammonium hydrogen sulfate in 6 mL of 7 M $H_2SO_4$. The reaction mixture was stirred at room temperature for 4 h, the organic phase was separated and the aqueous layer extracted with $CH_2Cl_2$. The combined organic extracts were washed with water and brine and dried, and the solvent was removed at reduced pressure to give a colorless oil. Flash chromatography[30] on silica gel and elution with ethyl acetate–hexanes (1:3) gave first 0.013 g (8%) of recovered hydroxy acetate **21** followed by 0.091 g (55%) of keto acetate **24** as a waxy solid contaminated with approximately 5–10% of unoxidized hydroxy acetate. No suitable solvent for recrystallization could be found. NMR δ 1.21 (s, 3 H, $CH_3$), 1.26 (s, 6 H, $(CH_3)_2C$), 1.88 (m, 3 H, $CH_3C$=), 2.06 (s, 3 H, $CH_3CO$), 5.35 (m, 1 H, 2β-H), 5.66 (m, 1 H, CHOBz), 6.21 (m, 1 H, —CH=), 7.20–8.12 (m, 5 H, aromatic CH).

When 0.095 g (0.22 mmol) of hydroxy acetate **21** in 5 mL of acetone was oxidized using 0.5 mL of Jones reagent for 6 h, there was obtained after flash chromatography[30] 0.046 g (48%) of recovered starting material and 0.028 g of approximately 1:1 mixture of starting material and 1-ketone.

**1α-Hydroxy-2α-acetoxy-9β-benzoyloxy-α-agarofuran (25).** To a stirred solution of 0.138 g (0.33 mmol) of ketone **24** in 10 mL of $CH_2Cl_2$ was added 0.046 g of *tert*-butylamine–borane complex and the reaction mixture was stirred under $N_2$ for 29 h. The reaction was quenched with 5 mL of 2 M HCl and the phases separated. The aqueous layer was extracted with $CH_2Cl_2$ and the combined organic extracts were washed with water and brine. After drying, the solvent was removed at reduced pressure and the residue subjected to flash chromatography on silica gel. Elution with hexanes–ethyl acetate (7:3) gave 0.024 g (17%) of 1β-ol **21**, identical with that described above, followed by 0.077 g (56%) of 1α-ol **25** as a crystalline solid. Recrystallization from pentane–methylene chloride gave the analytical sample: mp 224–226 °C; NMR δ 1.06 (s, 3 H, $CH_3$), 1.34, 1.49 (s, 3 H each, $(CH_3)_2C$), 1.87 (s, 3 H, $CH_3C$=), 2.01 (s, 3 H, $CH_3CO$), 4.67 (m, 1 H, 1β-H), 5.29 (m, 2 H, 2β-H and CHOBz), 5.72 (m, 1 H, —CH=), 7.20–8.20 (m, 5 H, aromatic CH); MS, $m/e$ (relative intensity) 414 (100), 371 (4), 354 (7), 292 (15), 251 (12), 250 (71), 232 (16), 217 (10), 208 (8). Anal. Calcd for $C_{24}H_{26}O_6$: C, 69.56; H, 7.24. Found: C, 69.30; H, 7.35.

**4-Epiisocelorbicol (26).** To 5 mL of 50% methanolic KOH was added 0.046 g (0.11 mmol) of hydroxy acetate **25** and the reaction mixture was stirred at ambient temperature for 3 h. The solvent was removed at reduced pressure with gentle warming and the residue taken up in chloroform. After washing with water and drying, the solvent was removed to give 0.026 g (88%) of triol as a glass, which was homogeneous to TLC and used without further purification: NMR δ 0.98 (s, 3 H, $CH_3$), 1.31, 1.60 (s, 3 H each $(CH_3)_2C$), 1.85 (br s, 3 H, $CH_3C$=), 3.70, 4.35 (m, 3 H, C*H*OH), 5.85 (m, 1 H, —CH=). This material was dissolved in 10 mL of ethanol and hydrogenated at 40 psi using 0.056 g of 5% rhodium on carbon as catalyst. After the catalyst and the solvent

were filtered off, there was obtained a viscous oil, which TLC indicated was a mixture of five compounds. Careful chromatography on silica gel and elution with chloroform–acetone (7:3) gave 0.005 g (19%) of 4-epiisocelorbicol (**26**) as a white solid. Recrystallization from acetone afforded crystals: mp 148–150 °C; NMR $\delta$ 0.91 (d, $J$ = 6.6 Hz, $CH_3CH$), 1.10 (s, 3 H, $CH_3$), 1.21, 1.53 (s, 3 H each, $(CH_3)_2C$), 2.89 (d, $J$ = 10.0 Hz, 9-OH), 3.53 (m, 1 H, 9$\alpha$-H), 4.14 (br s, 2 H, 1$\beta$,2$\beta$-H); MS, $m/e$ (relative intensity) 270 (35), 255 (46), 252 (17), 237 (31), 219 (42), 208 (17), 201 (15), 191 (13), 183 (14), 168 (46).

**(±)-Isocelorbicol (1).** A solution of 0.051 g (0.11 mmol) of hydroxy acetate **25** was hydrogenated as described above and the product hydrolyzed at room temperature by using 6 mL of 0.2 M barium hydroxide as described by Smith et al.[3] Chromatography on silica gel gave first 0.0049 g (17%) of 4-epiisocelorbicol (**26**) identical with that described above and then 0.0035 g (12%) of an approximately 2:1 mixture of (±)-isocelorbicol (**1**) and triol **26**: NMR $\delta$ 1.21 (s, 6 H, $CH_3$), 1.25 (d, $J$ = 7.2 Hz, $CH_3CH$), 1.48 (s, 3 H, $CH_3$), 3.2 (m, 1 H, 9$\alpha$-H), 4.16 (m, 2 H, 1$\beta$-H, 2$\beta$-H); MS, $m/e$ (relative intensity) 270 (30), 255 (31), 252 (18), 237 (26), 219 (31), 208 (18), 183 (11), 168 (51), 154 (15), 151 (27), 137 (50). Careful rechromatography of 0.0062 g of the 2:1 mixture of triols **1** and **26** failed to effect separation.

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**Registry No.** (±)-**1**, 88764-00-5; (±)-**9**, 88764-01-6; (±)-**12**, 88703-19-9; (±)-**13**, 88703-20-2; (±)-**15**, 88703-21-3; (±)-**15** (1$\beta$-benzoate), 88703-22-4; (±)-**16**, 88703-23-5; (±)-**16** (acetonide), 88703-24-6; (±)-**17**, 88703-25-7; (±)-**18**, 88703-26-8; (±)-**19**, 88703-27-9; (±)-**20**, 88764-02-7; (±)-**21**, 88764-03-8; (±)-**22**, 88703-28-0; (±)-**24**, 88703-29-1; (±)-**25**, 88764-04-9; (±)-**26**, 88764-05-0.

# Synthesis and Stereochemical Assignment of (22*R*,24*S*)-, (22*R*,24*R*)-, (22*S*,24*R*)-, and (22*S*,24*S*)-22,24-Dimethylcholesterol

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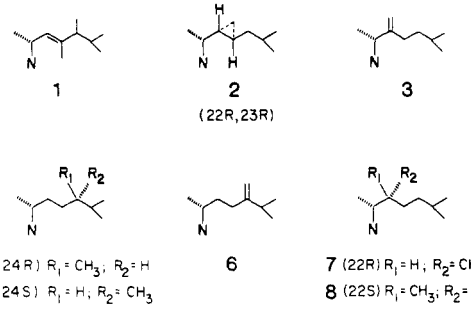
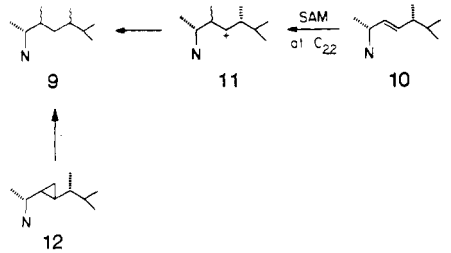
22,24-Dimethylcholesterol, though hitherto unknown, is likely to exist in nature. In order to expedite its recognition, all four isomers have been synthesized and their stereochemistry established. Selective deuterium labeling was used for the assignment of the NMR shifts of the methyl signals at C-22 and C-24.

The existence in the marine environment of 23,24-dimethylcholesterols (e.g., **1**) is well documented.[1-3] The recent isolation from marine organisms of (22*R*,23*R*)-22,23-methylenecholesterol (**2**)[4] and 22-methylenecholesterol (**3**)[5] demonstrates that direct bioalkylation of 22-dehydrocholesterol is possible in nature. Since (24*R*)-24-methylcholesterol (**4**) and its 24*S* epimer (**5**) coexist with 24-methylenecholesterol (**6**)[6] it is likely that (22*R*)-22-methylcholesterol (**7**) and its 22*S* epimer (**8**) may also be naturally occurring. Similarly, it is conceivable that 22,24-dimethylcholesterol (**9**) could also arise in nature by




attack of *S*-adenosylmethionine (SAM) at C-22 of brassicasterol (**10**) followed by loss of a C-22 or C-24 proton from the carbonium ion **11**[7] and subsequent biohydrogenation. Alternatively, enzymatic isomerization of demethylgorgosterol (**12**) followed by biohydrogenation could also lead to such a compound.[8]

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