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STEREOSELECTIVE TOTAL SYNTHESIS OF (±)-ISOCELORBICOL

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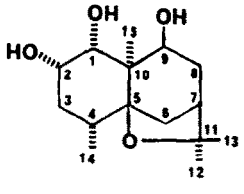
Abstract A completely stereoselective total synthesis of the naturally occurring polyhydroxyagarofuran, (±)-isocelorbicol (1) is described. The readily available α-agarofuran derivative 3 was converted to 3β-hydroxy-9-keto-β-agarofuran (6) by epoxidation followed by rearrangement with strong base. Diimide reduction gave exclusively the required 4α-methyldihydroagarofuran (7), which was converted to the 2-dehydroagarofuran (8). Stereoselective LAH reduction and protection of the 9β-ol followed by epoxidation afforded 2β,3β-oxide 11. This epoxide was converted to allylic alcohol 12 via reaction with phenylselenide and selenoxide elimination. Osmium tetraoxide oxidation of alcohol 12 gave exclusively the 1α,2α,3β-triol (13), which after protection as the acetonide, Barton deoxygenation and hydrolysis of the protecting groups afforded (±)-isocelorbicol. The overall yield for the 15 steps was 3.2%.

The plants of the family Celastraceae have proven to be a rich source of a variety of chemically and biologically interesting natural products. Although the tumor inhibitory compounds of the maytansine[1] and triptolide groups[2] have attracted a great deal of recent attention, the most characteristic class of compounds produced by these plants are polyhydroxy sesquiterpenes which contain a dihydroagarofuran skeleton. These polyols range in complexity from the relatively simple triol, isocelorbicol (1)[3] to very complex substances such an euonyminol (2)[4]. Many of these hydroxylated sesquiterpenes occur in nature as ester alkaloids in which the nitrogen is contained in nicotinic or substituted nicotinic acid residues.[5]

No member of this group of natural products has been shown to possess biological activity, although several ester alkaloids based on these sesquiterpenes have been isolated from Catha edulis (khat), a stimulant narcotic used in the Middle East and parts of Africa.[6] As the first phase of a synthetic program which had as an ultimate goal the synthesis of one or more of the ester alkaloids of khat, we chose as a synthetic target isocelorbicol (1).[7]



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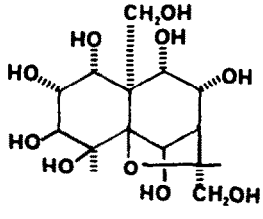

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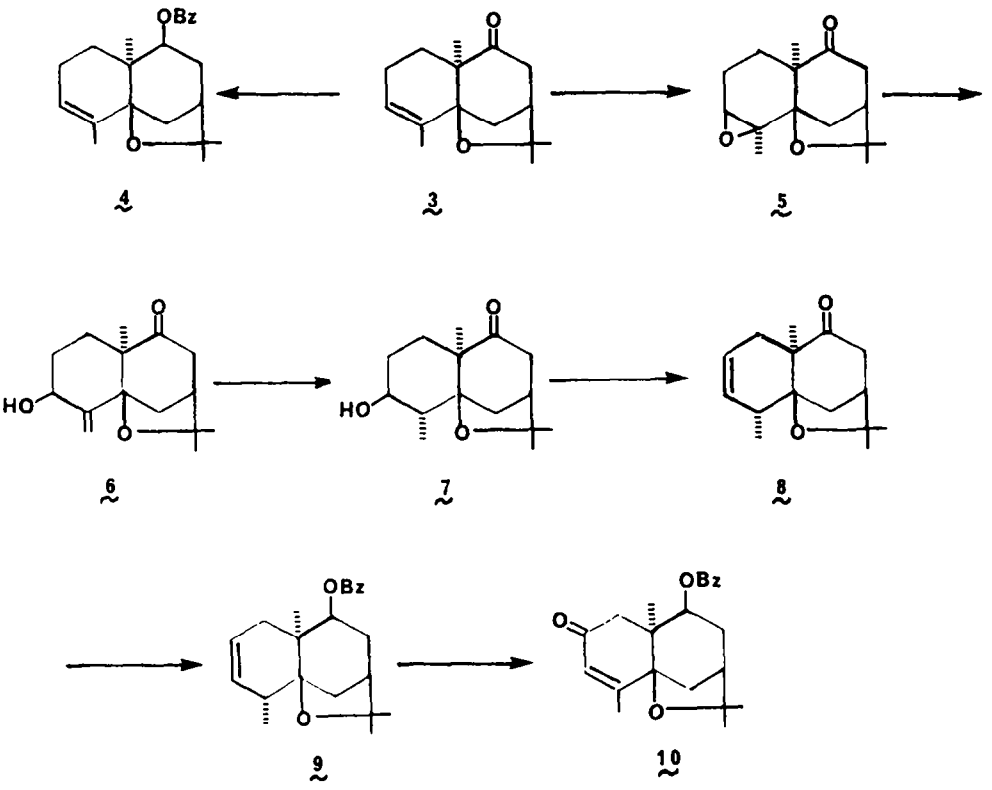
Although isocelorbicol is one of the least structurally complex polyhydroxyagarofurans, it still presents a considerable synthetic challenge. This challenge is due primarily to the fact that isocelorbicol contains a trans-decahydronaphthalene skeleton with seven substituents, six of which are axial. In an earlier, not entirely stereoselective approach to triol 1[8], the synthesis started with 9-keto-α-agarofuran (3, Scheme I), a compound which is easily prepared in a few steps from hydroxycarvone and ethyl vinyl ketone.[9] Although it was possible to stereoselectively generate the axial hydroxyl group at C-9, some

problems were encountered in obtaining the desired stereochemistry of the vicinal diol at C-1 and C-2. The final step in this earlier synthesis was the reduction of the double bond which proceeded in poor yield and gave the undesired 4β-methyl isomer as the major product.[8] In order to circumvent these problems, the synthesis was redesigned to introduce the correct stereochemistry at C-4 at an early stage and generate the 1α,2α-diol in subsequent steps.

Scheme I



The most general approach to dihydroagarofurans with an α-methyl group at C-4 is that of Buchi and Wuest which proceeds by reduction of the exocyclic methylene group of a β-agarofuran.[10] Since 9-keto-α-agarofuran (3) was readily available in quantity,[9] this compound was again chosen as the starting material for the synthesis of isocelorbicol. It was envisioned that ketone 3 could be converted to an appropriate β-agarofuran derivative by sequential epoxidation and base catalyzed rearrangement to an allylic alchol.[11] Initial attempts used as substrate for this sequence 9β-benzoyloxy-α-agarofuran (4)[8]. Although epoxidation proceeded smoothly, rearrangement to the 3β-hydroxy-β-agarofuran derivative using LDA was accompanied by cleavage of the benzoate ester. A variety of other reagents either failed to effect rearrangement of the epoxide or also led to hydrolysis of the ester.[12]

In order to circumvent these problems the epoxidation rearrangement sequence was carried out prior to reduction of the carbonyl group of 3. Epoxidation of 3 under normal conditions (m-chloroperbenzoic acid-CH_2Cl_2) gave poor yields (30%) of β-epoxide 5, apparently due to competing Baeyer-Villiger oxidation. However, when the epoxidation was carried out in the presence of aqueous sodium bicarbonate[13] a 70% yield of pure 5 (Scheme I) was obtained. The NMR spectrum of 5 was in complete agreement with the assigned structure (see Experimental Section). Rearrangement of epoxide 5 (LDA, ether, 25°C) proceeded smoothly to give the 3β-hydroxy-β-agarofuran (6) in 72% yield. Diimide reduction[14] of 6 gave a single saturated alcohol in 90% yield which was assigned structure 7 on the basis of precedent[10] and NMR data. In particular, the secondary methyl group of 7 appears as a doublet (J = 7.9 Hz) at δ 1.07 while in those agarofuran derivatives which have a β-(equatorial)

methyl group at C-4, the methyl group appears at lower field with J = 5.0 to 6.5 Hz.[8]

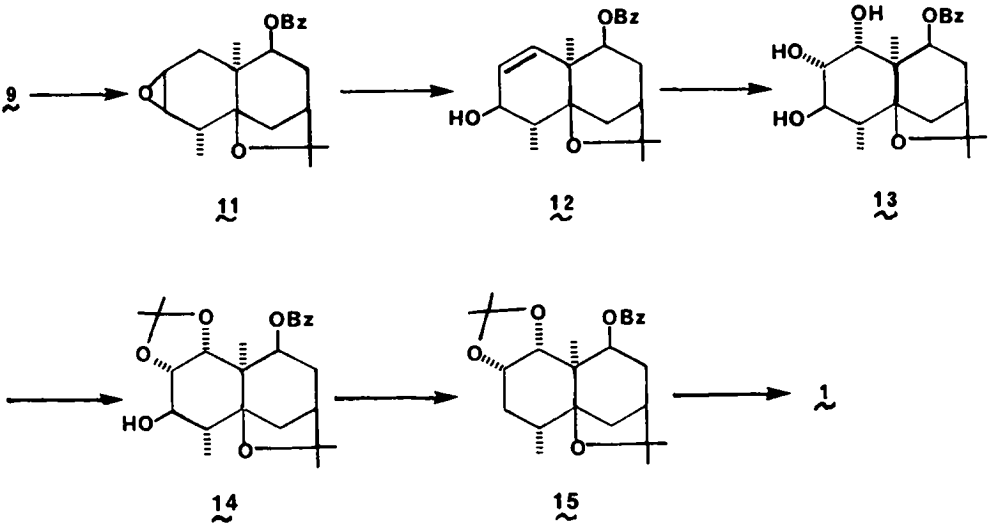
The axial 3β-hydroxyl group was to serve as a device for the ultimate introduction of the vicinal diol present in triol 1. To this end, dehydration of 7 with phosphorus oxychloride-pyridine at reflux gave in 65% yield olefin 8, with no trace of the alternative dehydration product (3). The regioselectivity of this reaction is attributed to two factors: the normal and well known stability of trans-2-octalins relative to the 3-isomer plus the fact that trans-diaxial elimination is predicted to lead to the formation of 8 rather than 3.

At this point, the 9-keto group was stereoselectively reduced ($LiAlH_4$), which by analogy to the previously reported reduction of ketone 3 gave exclusively the required 9β-ol.[15] The hydroxyl group was converted to benzoate ester 9 by the method described previously.[8] The overall yield for the reduction and esterification steps was 93%.

The initial strategy for for the introduction of an oxygen substituent at C-1 was the allylic oxidation of olefin 9 with the chromic acid-3,5-dimethylpyrazole complex[16] Although it was anticipated that this procedure would afford at least some of the desired 1-ketone, the only product which could be isolated was enone 10 which had been an intermediate in our earlier synthesis of isocelorbicol.[8]

Since it was apparent that direct oxidation of 9 was not a viable approach, the epoxidation-allylic alcohol sequence used for the conversion of 3 to 5 was explored as a means of preparing a 1-olefin which could be converted to the required cis-diol (Scheme II).

Scheme II



Oxidation of olefin 9 with m-chloroperbenzoic acid-CH_2Cl_2 proceeded smoothly to give a single epoxide in 60% yield. The β-face of olefin 9 is considerably less hindered than the α face and it was predicted that the product of oxidation would be epoxide 11 (Scheme II). This assumption was confirmed by the 200 MHz NMR spectrum which showed H-3 as a doublet (J =3.96 Hz) which is consistent with a slightly flattened half-chair conformation for ring-A in which the dihedral angle between H-3 and H-4 is close to 90° (J ≃ 0 Hz). For this conformation the angle between the axial proton at C-1 and H-2 is again close to 90°, while the angle between the equatorial proton and H-2 is 15°-20°, giving rise to a coupling constant in the range of 4.5 Hz. H-2 of 11 appears as a rather broad doublet of doublets with $J_{1e,2}$ = 4.28 Hz. These data are entirely consistent with structure 11, but are not consistent with those of the isomeric α-epoxide.[17]

Initial attempts to effect the isomerization of epoxide 11 to allylic alcohol 12 were carried out using a strong, hindered base (LDA), but the major product of the reaction was again the result of cleavage of the benzoate ester. The same net conversion was carried out by trans-diaxial opening of the epoxide using sodium phenylselenide in refluxing ethanol to give the 2β-phenylselenide in 44% yield (56%) conversion, based on 20% recovery of the starting epoxide).

In accordance with precedent, oxidative selenoxide elimination gave the desired allylic alcohol (12). However, in the absence of diisopropylamine, very mediocre yields of 12 were obtained. A common side reaction in selenoxide eliminations is subsequent reaction of benzeneselenic acid with the product olefin.[18] This undesired side reaction may be suppressed by the addition of a hindered secondary amine.[19] When the selenoxide elimination was carried out using m-chloroperoxybenzoic acid in the presence of diisopropylamine allylic alcohol 12 was obtained in 87% yield, the NMR spectrum of which was in agreement with the assigned structure (see Experimental Section).

It was anticipated that oxidation of allylic alcohol 12 with osmium tetraoxide would afford a mixture of the desired 1α,2α,3β-triol (13) and the 1β,2β-isomer. However, in practice, reaction of alcohol 12 with one equivalent of osmium tetraoxide gave a single triol in 66% yield. That this was the desired stereoisomer (13) was clear from the NMR spectrum in which the axial secondary methyl signal has been shifted downfield to δ 1.31. This compares favorably with the reported chemical shift of δ 1.27 which is reported for isocelorbicol (1).[5]

This fortuitous result was interesting in the light of various literature precedents regarding the stereochemical course of the osmylation reaction. Goldsmith and Sakano suggested that osmylations are relatively insensitive to steric factors[20] while Kishi found that in 3-methyl or hydroxycyclohexene osmylation occurs preferentially trans to the allylic substituent.[21] A similar effect in which stereoselectivity was aided by a homoallylic methylimino group was noted by Johnson.[22] In a variety of acyclic systems in which steric constraints render one diastereotopic face of the double bond more accessible than the other, osmylation occurs preferentially from the more accessible face.[23] Danishefsky has recently suggested that at least in acyclic systems the stereochemistry of osmylation is governed by stereoelectronic effects in which hydroxylation is favored by an allylic oxygen atom which is orthogonal to a cationoid carbon.[24] However, subsequent to the submission of the preliminary communication describing our synthesis of 1,[7] Vedejs and McClure described a series of osmylations which indicate that directive effects in these reactions are predominantly steric in origin.[25]

Examination of models of allylic alcohol 12 clearly indicates that the α-face of this molecule is significantly more hindered than the β-face, and that on purely steric grounds the β-diol would be predicted to be the major product. We believe that in allylic alcohol 12, the stereoelectronic effects of the quasi-axial 3β-hydroxyl group are responsible for the very high stereoselectivity of the hydroxylation. This is, of course, contrary to the conclusions reached by Vedejs[25] and it is clear that additional investigation of the factors governing the stereochemical course of osmylations is needed.

Prior to removal of the 3β-hydroxyl, the 1α,2α-diol group of 13 was protected as the acetonide (14). Treatment of 13 with 2,2-dimethoxypropane-camphorsulfonic acid[4] gave a single acetonide in 87% yield. The observation that this reaction affords only one acetonide provides additional evidence in support of the structure of triol 13 since it would be anticipated that a 1β,2β,3β-triol should afford a mixture of two acetonides.

Acetonide 14 was uneventfully converted to isocelorbicol derivative 15 in 82% yield by the Barton deoxygenation sequence.[26] Conversion of 15 to (±)-isocelorbicol in 86% yield was accomplished by hydrolysis of the 9-benzoate using methanolic barium hydroxide, followed by cleavage of the acetonide with aqueous acid. The NMR, solution IR and mass spectra of synthetic triol 1 were identical to those of the natural product.

This synthesis of (±)-isocelorbicol from 9-keto-α-agarofuran (3) proceeds in 15 steps

and an overall yield of 3.2%. The synthesis is noteworthy in that each step is completely stereoselective.

EXPERIMENTAL SECTION

Melting points were determined using a Kofler hot stage and are uncorrected. Infrared spectra were obtained as neat films between salt plates, as potassium bromide pellets, or as solutions in chloroform using Perkin-Elmer Model 1310 or Nicolet Model 5DX spectrophotometers, and are reported in reciprocal centimeters. NMR spectra were recorded on a Varian EM-360 (60 MHz), Hitachi Perkin-Elmer R-24 (60 MHz), JEOL FX-90Q (90 MHz) or Nicolet Model 293A (200 MHz) spectrometers using deuteriochloroform, unless otherwise noted, as the solvent. NMR spectral data are presented in parts per million (δ) relative to tetramethylsilane as internal standard. Mass spectral analyses were performed on a Hewlett-Packard 5985 Gas Chromatograph/Mass Spectrometer at 70 eV (direct insertion) and the data tabulated as m/e (intensity expressed as percent of base peak). Elemental analyses were carried out by Atlantic Microlab, Inc., Atlanta, Georgia. Analytical thin-layer chromatography was performed on EM Silica gel 60 G_{254} plastic plates (0.2mm) and/or Eastman Chromogram Sheet (Kodak) No. 13179, silica gel plastic plates (100μ). Compounds were visualized by iodine vapor or under UV-light. Column chromatography was carried out using Woelm silica gel (60-200) using hexanes-ethyl acetate mixtures (gradient elution). Ether and tetrahydrofuran (THF) were distilled from sodium-benzophenone ketyl; benzene and toluene from sodium wire, and diisopropylamine, dichloromethane, dimethylformamide, hexamethylphosphoric triamide (HMPA) from calcium hydride, all under an atmosphere of nitrogen. Commercially available (Aldrich) solutions of methyllithium in ether and n-butyllithium in hexane were titrated with 1,3-diphenyl-2-propanone tosylhydrazone as indicator prior to use.

3β,4β-Epoxy-9-keto-α-agarofuran (5). To a well-stirred mixture of 0.56 g (2.39 mmol) of 9-keto-α-agarofuran[9] (3) in 30 mL of CH_2Cl_2 and 7.0 mL of 0.5M aqueous $NaHCO_3$ was added, in small portions, 0.51 g (2.4 mmol) of 85% m-chloroperoxybenzoic acid over a period of 30 min. The mixture was allowed to stir at room temperature for 6 h. The organic layer was separated and washed successively with saturated aqueous $NaHCO_3$, water and brine. After drying over anhydrous K_2CO_3, the solvent was distilled off to furnish the crude epoxide. After chromatographic purification, 0.41 g (70%) of pure 5 was obtained which on recrystallization from hexanes-ethyl acetate yielded crystals of analytical purity, mp 99-100°C: IR (KBr) 2950, 1700, 1435, 1375, 1250, 1115, 1020, 885 cm^{-1}; NMR: δ 1.02, 1.20, 1.32, 1.38, (s, 3H each, CH_3), 3.01 (br s, 1H); MS 250 (m^+) Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86, Found: C, 71.80, H, 8.91.

3β-Hydroxy-9-keto-β-agarofuran (6). To a freshly prepared solution of 4.45 g (44 mmol) of LDA in 25 mL of hexane and 15 mL of ether at 0°C, under nitrogen, was added a solution of 2.20 g (8.8 mmol) of epoxide 5 in 20 mL of ether and the reaction mixture was stirred at room temperature for 6 h. The reaction was quenched by the dropwise addition of 10 mL of 5% aqueous HCl and the mixture was stirred for 15 min. The organic layer was separated, and the aqueous portion was washed with ether. The combined organic phases were washed with water and brine, and dried over $MgSO_4$. On removal of the solvent under reduced pressure 1.60 g (72%) of alcohol 6 was obtained. Chromatographic purification followed by recrystallization from hexanes-ethyl acetate afforded crystals of analytical purity, mp 122-123°C. IR (KBr): 3460, 2920, 1700, 1435, 1140, 1100, 100, 875 cm^{-1}; NMR: δ 1.00 (s, 3H), 1.23 (s, 6H), 4.22 (d, 1H, 9.62 Hz), 4.37 (d, 1H, 9.59 Hz), 5.01, 5.18 (br s, 1H each); MS: 250 (m^+) Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86; Found: C, 71.80; H, 8.93.

3β-Hydroxy-4α-methyl-9-ketodihydroagarofuran (7). Method A. A solution of 2.05 g (9.6 mmol) of sodium metaperiodate in 20 mL of water was added dropwise over 3 h to a mixture of 0.48 g (1.92 mmol) of allylic alcohol 6, 3.84 g (76.8 mmol) of hydrazine monohydrate, 3 drops of saturated aqueous $CuSO_4$ and 3 drops of glacial acetic acid, all dissolved in 15 mL of ethanol. Stirring was continued for a period of 6 h, the reaction mixture was poured into water and extracted with ether. The ether extracts were washed with water, brine and dried over anhydrous Na_2SO_4. Removal of the solvent afforded 0.43 g (90%) of 7 which on

recrystallization from hexanes-ethyl acetate yielded pure crystalline material, mp 129-130°C. IR (KBr): 3480, 2920, 1700, 1455, 1120, 990, 870 cm^{-1}; NMR: δ 1.07 (d, 3H, J = 7.91 Hz), 1.17, 1.19, 1.22 (s 3H each), 3.67 (d, 1H, J = 9.68 Hz), 4.31 (d, 1H, J = 9.95 Hz); MS: 252 (m^+) Anal. Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H. 9.59; Found: C, 71.36; H, 9.64.

Method B. To a stirred mixture of 0.337 g (1.35 mmol) of alcohol 6, and 1.5 mL of hydrazine hydrate in 10 mL ethanol was added, dropwise, 1.5 mL of 3% aqueous hydrogen peroxide over a period of 2 h. Stirring was continued at room temperature for 16 h, the mixture was poured into water and the reaction mixture was extracted with two portions of pentane. The pentane extracts were dried over anhydrous Na_2SO_4 and the solvent was distilled off. Recrystallization of the crude alcohol from hexanes gave 0.29 g (85%) of 7 identical to the material desribed in part A above.

2,3-Dehydro-4α-methyl-9-ketodihydroagarofuran (8). To a solution of 1.37 g (5.43 mmol) of alcohol 7 in 25 mL of pyridine was added 2.7 mL of $POCl_3$ and the mixture was heated at reflux for 1 h. After cooling, the reaction mixture was poured into 100 mL of 10% aqueous HCl and extracted with ether. The ether extract was washed with aqueous saturated $NaHCO_3$, water and brine and dried over anhydrous Na_2SO_4. The solvent was removed and the residue purified by chromatography to furnish a highly viscous oil (0.83 g, 65%) which defied attempts at crystallization. IR (film): 2960, 1700, 1465, 1350, 1130, 1005, 715 cm^{-1}; NMR: δ 1.13 (d 3H, J = 7.81 Hz), 1.20 (s, 6H), 1.25 (s, 3H), 5.63 (d, 2H, J = 2.93 Hz); MS (m/e): 234 (13), 219 (29), 210 (45), 198 (11), 174 (29), 173 (29).

2,3-Dehydro-4α-methyl-9β-hydroxydihydroagarofuran. To a stirred suspension of 0.153 g (4.0 mmol) of $LiAlH_4$ in 25 mL of ether was added, under nitrogen at -50°C, a solution of 0.80 g (3.41 mmol) of ketone 8 in 20 mL of ether. After stirring at -50°C for 5 h, the reaction mixture was allowed to warm to room temperature and stirring was continued for an additional 18 h. After the destruction of the unreacted lithium aluminum hydride, the reaction mixture was filtered and the residue digested with three 15 mL portions of hot THF and the filtrate collected. The combined filtrates were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to yield 0.790 g (98%) of alcohol as a white solid. Recrystallization from hexanes-ethyl acetate gave the analytical sample, mp 73-74°C. IR (film): 3420, 2910, 1450, 1375, 1140, 715 cm^{-1}; NMR: δ 1.05 (s, 3H), 1.09 (d, 3H, J = 7.81 Hz), 1.25, 1.52 (s, 3H each), 3.43 (m, 1H), 5.61 (m, 2H); MS: 236 (m^+); Anal. Calcd. for $C_{15}H_{24}O_2$: C, 76.23; H, 10.23; Found: C, 76.08; H, 10.28.

2,3-Dehydro-4α-methyl-9β-benzoyloxydihydroagarofuran (9). To a stirred solution of 0.60 g (2.58 mmol) of the above 9β-ol and a few crystals of 2,2'-bipyridyl in 10 mL of dry THF, at ambient temperature, was added, dropwise 1.7 mL of 1.6 M n-butyllithium in hexane until the end point was indicated. After 10 min, a solution of 0.38 g (2.17 mmol) of benzoyl chloride in 5 mL of THF was added. After stirring at room temperature for 15 min, the mixture was heated under reflux for 1 h. The cooled reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with ether. The combined ether extracts were washed with aqueous $NaHCO_3$ and brine and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure afforded crude benzoate ester 9. Chromatography gave 0.83 g (95%) of pure 9 which was recrystallized from hexanes-ethyl acetate, mp 114-115°C. IR (KBr): 2940, 1700, 1445, 1370, 1275, 1000, 700 cm^{-1} NMR: δ 1.10, (d, 3H, J = 7.81 Hz), 1.18, 1.28, 1.54 (s, 3H each), 5.13 (d, 1H, J = 5.61 Hz), 5.58 (d, 2H, J = 3.42 Hz), 7.39-8.17 (m, 5 H,), MS: 340 (m^+); Anal. Calcd. for $C_{22}H_8O_3$: C, 77.61; H, 8.29; Found: C, 77.72; H, 8.30.

Oxidation of 2,3-Dehydro-4α-methyl-9β-benzoyloxydihydroagarofuran. To a suspension of 0.75 g (7.5 mmol) of anhydrous chromium trioxide in 5 mL of CH_2Cl_2 at -20°C, was added 0.72 g (0.75 mmol) of 3,5-dimethylpyrazole. After stirring the mixture for 20 min, a solution of 0.17 g (0.5 mmol) of 9 in 5 mL of CH_2Cl_2 was added and the mixture was stirred at -20°C for 15 h. The reaction mixture was quenched with aqueous NaOH and stirred for 1 h. The layers were separated and aqueous layer was washed well with CH_2Cl_2. The combined organic phases were washed with 5% aqueous HCl, saturated aqueous $NaHCO_3$ and brine. After drying and concentrating the extract, a greenish yellow residue was obtained. After

chromatography there was obtained 0.10 g (56%) of enone 10, identical to a sample prepared previously.[8]

2β,3β-Epoxy-4α-methyl-9β-benzoyloxydihydroagarofuran 11. To a solution of 0.978 g (2.7 mmol) of ester 9 in 25 mL of CH_2Cl_2 was added in small portions 0.58 g (2.7 mmol) of m-chloroperoxybenzoic acid, and the mixture was stirred at 25°C for 4 h. The reaction mixture was washed successively with saturated aqueous sodium sulfite, water and brine. After drying over Na_2SO_4, the solvent was removed to give 0.57 g (60%) of crude epoxide 11 which was recrystallized from hexanes-ether, mp 144-145°C. IR (film): 2945, 1705, 1450, 1280, 1110, 750, 720 cm^{-1}; NMR: δ 1.19 (s 3H), 1.22 (d, 3H, J = 8.52 Hz), 1.25, 1.48 (s, 3H each), 2.99 (d, 1H, J = 3.96 Hz), 3.19 (dd, 1H, J = 4.19, 4.28 Hz), 5.06 (d, 1H, J = 7.41 Hz) 7.44-8.12 (m, 5H); MS 356(m^+); Anal. Calcd. for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92; Found: C, 73.90, H, 7.99.

2α-Selenophenyl-3β-hydroxy-4α-methyl-9β-benzoyloxydihydroagarofuran. To a solution of 0.468 g (1.5 mmol) of diphenyldiselenide in 2 mL of absolute ethanol (distilled from magnesium ethoxide just before use) was added in portions 0.22 g (6 mmol) of $NaBH_4$, with stirring under nitrogen, until the bright yellow solution turned colorless. (CAUTION: reduction of the diselenide is exothermic and vigorous hydrogen evolution occurs!) To this solution was added 0.178 g (0.5 mmol) of epoxide 11 and the reaction mixture was heated at reflux for 1.5 h. After cooling, the solvent was removed yielding a sticky yellow residue which was taken up in CH_2Cl_2 and washed with 5% aqueous HCl and water. Drying over anhydrous Na_2SO_4 and removal of the solvent under reduced pressure afforded the crude reaction mixture. Chromatography gave 0.114 g (56%) of hydroxyselenide which was recrystallized from ethyl acetate, mp 173-174°C, and unreacted starting material (11, 0.035 g, 20%). IR (KBr): 3440, 2920, 1700, 1450, 1450, 1280, 1110, 990, 865, 750, 710 cm^{-1}; NMR: δ 1.25, 1.39, 1.41 (s, 3H each,), 1.43 (d, 3H, J = 0.91 Hz), 3.14 (dd, 1H, J = 5.86, 5.58 Hz), 3.72 (m, 1 H), 3.98 (d, 1H J = 9.3 Hz), 7.22-8.10 (m, 5H); MS: 515 (m^+); Anal. Calcd. for $C_{28}H_{34}O_4Se$: C, 65.49; H, 6.67; Found: C, 65.59; H, 6.66.

1,2-Dehydro-3β-hydroxy-4α-methyl-9β-benzoyloxydihydroagarofuran 12. A solution of 0.260 g (0.5 mmol) of β-hydroxyselenide and 0.1 mL of diisopropylamine in 3 mL of CH_2Cl_2 was treated with 0.202 g (10 mmol) of 85% m-chloroperoxybenzoic acid at -78°C for 1 h. Saturated aqueous Na_2CO_3 was added in one portion with vigorous stirring. The layers were separated and the organic layer was washed successively with saturated aqueous Na_2CO_3 and brine. After drying over anhydrous Na_2SO_4, the solvent was removed at reduced pressure. The crude product was purified by chromatography to yield 0.115g (87%) of pure 12 which was recrystallized from hexanes-ethyl acetate, mp 152-153°C. IR (KBr): 3490, 2940, 1700, 1450, 1380, 1280, 1110, 100, 865, 720^{-1}; NMR: δ 1.06 (d, 3 H, J = 7.81 Hz), 1.19, 1.28, 1.33, (s, 3H each), 3.86 (d, 1H, J = 4.64 Hz), 5.05 (d, 1H, J = 4.15 Hz), 5.39 (d, 1H, J = 10.25 Hz), 5.79 (dd, 1H J = 4.39, 5.13 Hz), 7.42-8.01 (m, 5H,); MS: 356 (m^+) Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.13, H, 7.92; Found: C, 74.04; H, 7.93.

1α,2α,3β-Trihydroxy-4α-methyl-9β-benzoyloxydihydroagarofuran 13. To a solution of 0.150 g (0.42 mmol) of allylic alcohol 12 in 6 mL of dry pyridine, was added 0.157 (0.42 mmol) of osmium tetraoxide and the reaction mixture was stirred at room temperature for 20 h. To the mixture was added 0.25 g of sodium bisulfite, 3 mL of pyridine and 3 mL of water and the stirring was continued for an additional 3 h. After extraction with six portions of CH_2Cl_2 and drying over anhydrous Na_2SO_4 the solvent was removed under reduced pressure to give 0.110 g (66%) of solid which homogeneous by tlc. Recrystallization from ethanol afforded pure triol 13, mp 237-239°C. IR (KBr): 3420, 3345, 2940, 1700, 1425, 1275, 1110, 1000, 870, 710 cm^{-1}; NMR: δ 1.26 (s, 3H), 1.31 (d 3H J = 8.06 Hz), 1.31, 1.44 (s, 3H each), 3.95 (d, 1H, J = 9.45 Hz), 4.55-4.65 (m, 2H), 5.05 (d, 1H, J = 6.23 Hz), 7.42-8.09 (m, 5H); MS: 390 (m^+); Anal. Calcd. for $C_{22}H_{30}O_6$: C, 67.66; H. 7.75; Found: C, 67.64; H. 7.76.

1α,2α-O-Isopropylidene-3β-hydroxy-4α-methyl-9β-benzoyloxydihydroagarofuran 14. A solution of 0.130 g (0.332 mmol) of triol 13 and 0.008g of (+)-10-camphorsulfonic acid in 10 mL of 2,2-dimethoxypropane was stirred at 50°C for 3 h. After cooling, the solution was

mixed with 20 mL of 10% aqueous $NaHCO_3$ and the resulting mixture was extracted with ethyl acetate. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated to give 0.12 g (87%) of a single acetonide (14) which was recrystallized from ethyl acetate, mp 183-184°C. IR (KBr): 3410, 2910, 1710, 1450, 1375, 1110, 1050, 870 cm^{-1}, NMR: δ 1.04, 1.07 (s, 3H each), 1.20 (d, 3H, J = 7.08 Hz), 1.24, 1.36, 1.42 (s, 3H each), 3.65 (m, 2H), 4.26 (t, 1H, J = 8.54 Hz), 5.05 (d, 1H, J = 8.03 Hz), 7.42-8.12 (m, 5H), MS: 430(1), 415 (10), 413 (18), 412 (690), 275 (27), 233 (20), 217 (21), 191 (64).

1α,2α-O-Isopropylidene-3β-methyldithiocarbonyl-4α-methyl-9β-benzoyloxydihydroagarofuran. To a solution of 0.064 g (0.15 mmol) of 14 in 2 mL of dry THF was added 0.012 g (0.30 mmol) of a 60% oil dispersion of sodium hydride and 0.005 g of imidazole. After stirring the mixture for 2 h at 60°C, 0.03 mL (0.5 mmol) of carbon disulfide was added and stirring continued at 50°C for 1 h. To this mixture was added 0.01 mL (0.16 mmol) of methyl iodide and stirring was continued for 0.5 h at room temperature. The reaction was quenched with 5% aqueous acetic acid and extracted with CH_2Cl_2. After drying over Na_2SO_4 and removal of the solvent the crude xanthate was obtained. Purification was effected by chromatography to give 0.070 g (86%) of pure xanthate. IR (film): 2920, 1710, 1450, 1375, 1270, 1215, 1050, 870 cm^{-1}; NMR: δ 1.00 (s, 3H), 1.12 (d, 3H, J = 7.81 Hz), 1.19, 1.25, 1.35, 1.44 (s, 3H each), 2.57 (s, 3H), 4.53 (m, 2H), 5.07 (d, 1H, J = 8.54 Hz); 6.25 (dd, 1H, J = 9.52, 9.77 Hz), 7.4-8.12 (m, 5 H); MS (m/e): 519 (1.7), 505 (2), 477 (1), 412 (100), 355 (38), 323 (25), 275 (16), 249 (49), 233 (59), 215 (47), 187 (21), 175 (21).

1α,2α-O-Isopropylidene-4α-methyl-9β-benzoyloxydihydroagarofuran (15). To a hot solution of 0.050 g (0.15 mmol) of xanthate in 1 mL of toluene was added slowly a solution of 0.05 g (0.17 mmol) of tri-n-butyltin hydride in 2 mL of toluene using a syringe pump. Heating at reflux was continued for 20 h and the solvent was removed at 50°C at 15 mm pressure. The crude product was chromatographed to give 0.059 g (95%) of pure (tlc) 15. IR (film): 2920, 1700, 1450, 1375, 1280, 1260, 1200, 1015, 865, 710 cm^{-1}; NMR: δ 1.04, 1.09, (s, 3H each), 1.21 (d, 3H, J = 7.08 Hz), 1.24, 1.35, 1.40 (s, 3H each), 4.29-4.85 (m, 2H), 4.99 (d, 1H, J = 7.81 Hz), 7.41-8.15 (m, 5H); MS (m/e): 414 (18), 399 (4), 357 (15), 293 (18), 291 (17), 179 (17), 235 (29), 217 (34), 177 (12), 159 (16), 145 (11), 105 (100).

(±)-Isocelorbicol (1). A mixture of 0.040 g (0.10 mmol) of 15 and 10 mL of 0.2M methanolic $Ba(OH)_2$ was heated at reflux for 6 h. The mixture was concentrated almost to dryness and the methanol was replaced by 10 mL of water. This aqueous suspension was centrifuged to remove the barium soap of benzoic acid and the supernatant layer was extracted with $CHCl_3$. After drying over anhydrous Na_2SO_4 and removal of the solvent there was obtained 0.027 g (90%) of the 1α,2α-O-isopropylidene derivative of 1 which was homogeneous to tlc. This crude compound was used in the next step without further purification.

A solution of 0.020 g (0.06 mmol) of this acetonide in 1 mL of THF was treated with 1 mL of aqueous 1N HCl at 25°C for 1 h. The reaction mixture was poured into CH_2Cl_2 and washed successively with saturated aqueous $NaHCO_3$ and brine. Drying over anhydrous Na_2SO_4, followed by removal of the solvent under reduced pressure gave 0.0165 g (95%) of pure (±)-isocelorbicol (1), mp 240-241°C. The spectral properties (NMR, solution IR and MS) were identical to those of the natural product. IR ($CHCl_3$): 3670, 3565, 2900, 1380, 1365, 1135, 1090, 1060, 1010, 955, 860 cm^{-1}; NMR: δ 1.21 (s, 6H), 1.27 (d, 3H, J = 7.91 Hz), 1.48, (s, 3H), 3.19 (d, 1H, J = 11.62 Hz), 3.41 (dd, 1H, J = 5.00, 4.98 Hz), 4.18 (br s, 1H), 4.16 (m, 1H); MS (m/e): 270 (8), 255 (8), 252 (17), 237 (22), 219 (24), 208 (16), 201 (12), 181 (29), 169 (18), 168 (65), 154 (14), 151 (20), 137 (52), 135 (25), 125 (35), 119 (31), 111 (29), 109, (100).

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References

1. Kupchan, S.M.; Komoda, Y.; Court, W.A.; Thomas, G.J.; Smith, P.M.; Gilmore, C.J.; Haltiwanger, R.C.; Bryan, R.S. 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.; Eichman, 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.F.H., Ed.; Academic Press: New York 1977; Vol. 16, pp. 215-248.
6. (a) Baxter, R.C.; Crombie, L.; Simmonds, D.J.; Whiting, D.A.; Braenden, O.J.; Szendrei, K. J. Chem. Soc., Perkin Trans. 1, 1979, 2965. (b) Crombie, L.; Crombie, W.M.L.; Whiting, D.A.; Szendrei, K. Ibid. 1979, 2976. (c) Baxter, R.C.; Crombie, W.M.L.; Crombie., L.; Simmonds, D.J.L Whiting, D.A.; Szendrei, K. Ibid. 1979, 2982.
7. A preliminary communication describing the synthesis has been published: Huffman, J.W.; Raveendranath, P.C. J. Org. Chem. 1986, 51, 2148.
8. Huffman, J.W.; Desai, R.C.; Hillenbrand, G.F. J. Org. Chem. 1984, 49, 982.
9. Huffman, J.W.; Hillenbrand, G.F. Tetrahedron Suppl. 1981, 9, 269.
10. Buchi, G.; Wuest, H. J. Org. Chem. 1979, 44, 546.
11. Crandall, J.K.; Apparu, J. Org. React. (N.Y.) 1983, 29, 345.
12. These preliminary experiments were carried out by Dr. V.D. Winchure.
13. Anderson, W.K.; Veysoglu, T. J. Org. Chem. 1973, 38, 2267.
14. Hoffman, J.M.; Schlessinger, R.H. J. Chem. Soc. Chem. Commun. 1971, 1245.
15. Huffman, J.W.; Desai, R.C.; La Prade, J.E. J. Org. Chem. 1983, 48, 1474.
16. Salmond, W.G.; Barta, M.A.; Havens, J.L. J. Org. Chem. 1978, 43, 2057.
17. Bhacca, N.S.; Williams, D.H. "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, 1964, pp 99-102 discuss the ^{1}H NMR spectra of epoxides in rigid systems.
18. Davis, F.A.; Stringer, O.D.; Billmers, J.M. Tetrahedron Lett. 1983, 24, 1213.
19. Reich, H.J.; Wallowitz, S.; Trend, J.E.; Chow, F.; Wendleborn, D.F. J. Org. Chem. 1978, 43, 1697.
20. Goldsmith, D..J.; Sakano, I. J. Org. Chem. 1976, 41, 2195.
21. Cha, J.K.; Christ, W.J.; Kishi, Y. Tetrahedron Lett. 1983, 24, 3943.
22. Johnson, C.R.; Barbachyn, M.R. J. Am. Chem. Soc. 1984, 106, 2459. For a similar observation in a acyclic system see: Hauser, F.M.; Ellenberger, S.R.; Clardy, J.C.; Bass, L.S. ibid, 1984, 106, 2458.
23. Bartlett, P.A. Tetrahedron, 1980, 36, 3.
24. Danishefsky, S.J.; Larson, E.; Springer, J.P. J. Am. Chem. Soc. 1985, 107, 1274.
25. Vedejs, E.; McClure, C.K. J. Am. Chem. Soc. 1986, 108, 1094.
26. Barton, D.H.R.; McCombie, S.W. J. Chem. Soc., Perkin Trans. 1 1975, 1574.