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# Total synthesis of (±)-β-microbiotene, (±)-microbiotol, (±)-cyclocuparanol and (±)-β-cuparenones

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Total synthesis of (±)-β-microbiotene, (±)-microbiotol, (±)-cyclocuparanol and their epimers along with (±)-β-cuparenone has been described. A combination of orthoester Claisen rearrangement, an acid catalysed rearrangement of a diazoketone for the generation of bicyclo[4.2.1]nonanedione, a retro-Claisen condensation and an intramolecular diazoketone cyclopropanation reaction have been employed for the construction of three contiguous quaternary atoms present in cyclocuparanes.

**Keywords**: Sesquiterpene synthesis, cyclocuparanes, cuparenes, cyclopropanation, rearrangement, diazo ketones

**IPC: Int.Cl.[8] C07C**

The tricyclic sesquiterpenes[1] cyclocuparanes contains a 4-methyl-1-(1,2,2-trimethylcyclopentyl)bicyclo-[3.1.0]hexane **1** carbon framework incorporating three contiguous quaternary carbon atoms, whose first members grimaldone and microbiotol were reported[2,3] in 1975 and 1981, respectively. Isolation of cyclocuparanol **2**, originally referred as cyclopropanecuparanol, along with its epimer, was first reported in 1984 by Asakawa and co-workers[4] from *Marchantia polymorpha* and *Marchantia paleacea* Bertol. var *diptera* (Mont) Hatt. Recently, Rycroft and co-workers[5] reported the presence of cyclocuparanol **2** in the liverwort *Cryptothallus mirabilis*. The gross structure of cyclocuparanol **2** was elucidated using spectral data and was supported by the acid catalysed conversion of cyclocuparanol **2** into three *ent*-cuparenes **3**, **4** and **5**. The structure of grimaldone **6**, isolated from the Central European liverwort *Mannia fragrans*, was elucidated by Rycroft and co-workers[6] in 1988 based on the spectral data and single crystal X-ray diffraction analysis. Structure of microbiotol **7**, isolated[3] from the ether extract of the needles of *Microbiota decussata*, was established by Tkachev and co-workers[7] in 1991 on the basis of NMR spectral data and molecular mechanics calculations, and established the absolute configuration by its conversion to (*R*)-cuparene (+)-**5**. Microbiotol **7**, isolated from the plant source, is antipodal to cyclocuparanol **2** and grimaldone **6**, isolated from the liverworts[8]. In 1998, Konig and co-workers[9] reported, in addition to grimaldone **6**, isolation of three more cyclocuparane sesquiterpenes, α-microbiotene **8**, β-microbiotene **9** and isogrimaldone **10** from the essential oil of *Mannia fragrance* collected from Altmuhl valley (**Chart I**).

Presence of an interesting carbon framework incorporating three contiguous quaternary carbon atoms made cyclocuparanes challenging synthetic targets. Even though structure of the first cyclocuparane was established in 1984, there is no report on the synthesis of cyclocuparanes in the literature prior to the initiation of the present work[10]. In continuation of the interest on the synthesis of sesquiterpenes containing multiple contiguous quaternary carbon atoms[11,12], herein are described the details of the first total synthesis[10b] of β-microbiotene **9**, microbiotol **7** and cyclocuparanol **2** and their epimers along with β-cuparenone.

Retrosynthetic analysis (**Scheme I**) readily identified the norcyclocuparanone **11** as the appropriate precursor for the synthesis of cyclocuparanes **2**, **7** and **9**. It was contemplated that an intramolecular cyclopropanation reaction of the diazo ketone derived from the γ,δ-unsaturated acid **12** could generate the norcyclocuparanone **11**. The bicyclo[4.2.1]nonanedione **13** was conceived as a probable precursor for

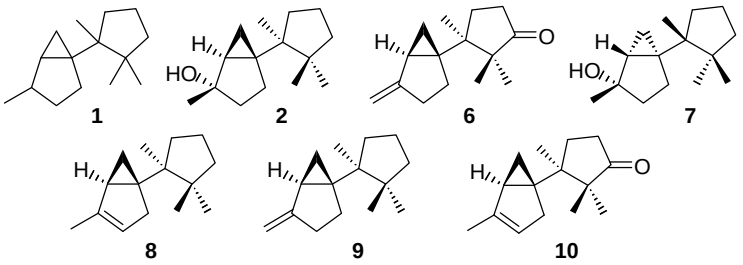
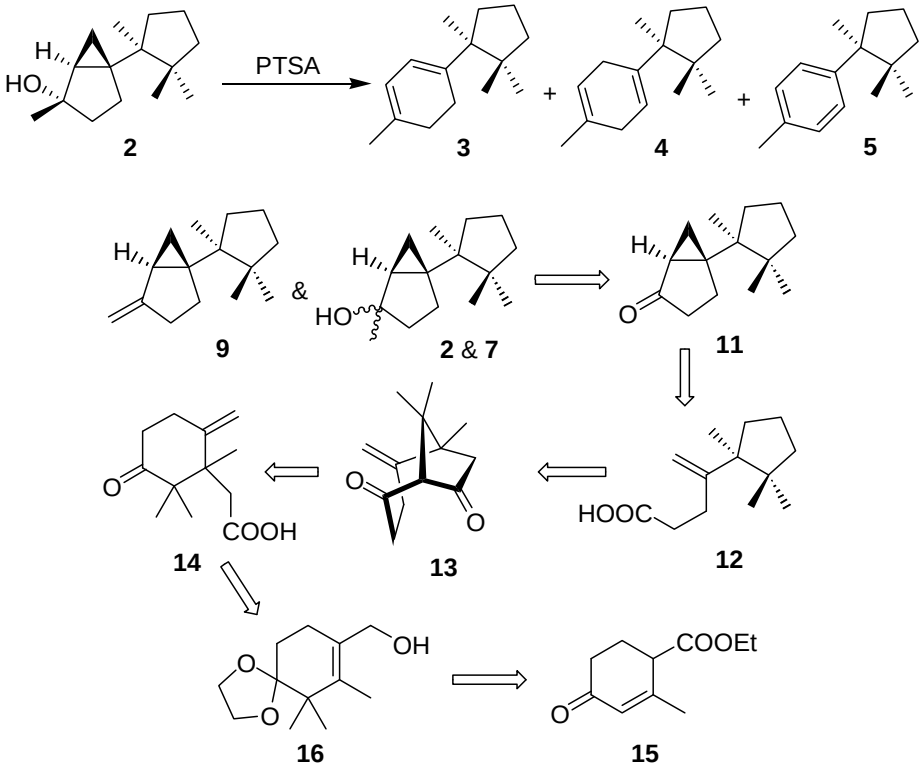


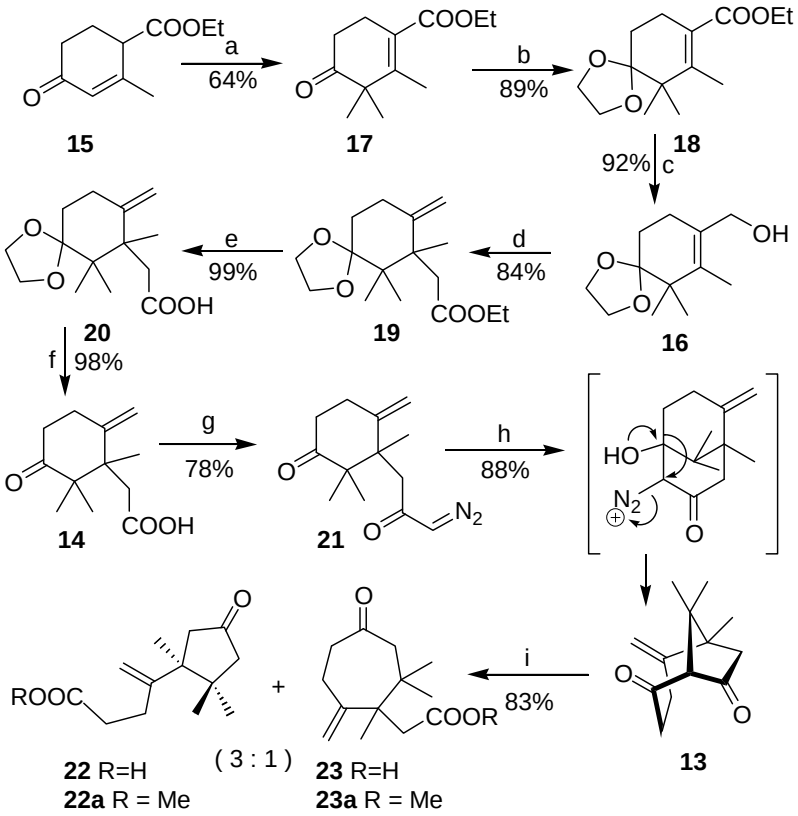

**Chart I**




**Scheme I**

the generation of the γ,δ-unsaturated acid **12** *via* regioselective retro-Claisen condensation reaction[13]. For the synthesis of the bicyclo[4.2.1]nonane-2,8-dione **13**, the keto acid **14** was identified as the requisite precursor, which could be obtained from Hagemann's ester **15** *via* the Claisen rearrangement of the allyl alcohol **16**.

Accordingly, sequence was initiated with Hagemann's ester[14] **15** (**Scheme II**). Reaction of the Hagemann's ester **15** with two equivalents of sodium hydride in THF at 0°C followed by reaction with 2.5 equivalents of methyl iodide at -100°C for 1.5 hr furnished γ,γ-dimethyl Hagemann's ester **17** in 64% yield, whose structure was established from its spectral data. Reaction of the ester **17** with ethylene glycol and a catalytic amount of *p*-TSA in refluxing benzene with Dean-Stark water trap furnished the ketal ester **18** in 89% yield. Regioselective reduction of the ketal ester **18** with LAH in ether at low temperature (-70°C) furnished the allyl alcohol **16**, in 92% yield, whose structure has been firmly established from its spectral data. Johnson's ortho ester Claisen rearrangement[15] of the allyl alcohol **16** with triethyl orthoacetate and a catalytic amount of propionic acid in a sealed tube at 180°C for 7 days furnished the γ,δ-unsaturated ester **19** in 84% yield. Reaction of the ketal ester **19** with 5% sodium hydroxide in refluxing aqueous methanol furnished the ketal acid **20**, which on treatment with 3*N* aqueous HCl in THF at RT furnished the keto acid **14** in 97% yield. Reaction of the keto acid **14** with oxalyl chloride in benzene



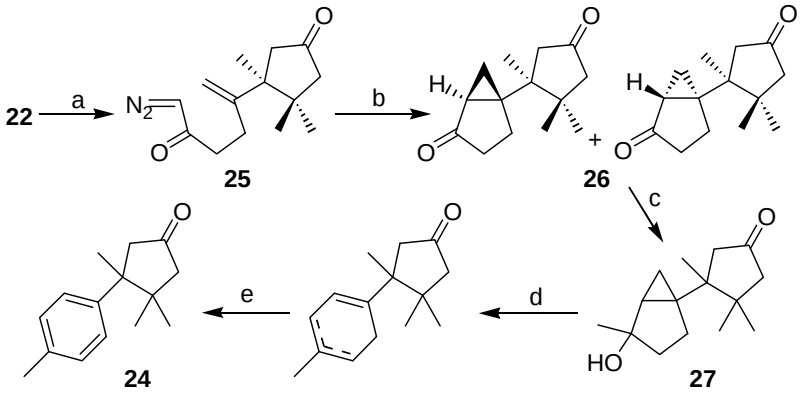

Reagents: (a) NaH, THF, MeI; (b) $(CH_2OH)_2$, $C_6H_6$, PTSA; (c) LAH, $Et_2O$; (d) $CH_3C(OEt)_3$, $EtCO_2H$, Δ; (e) NaOH, MeOH-$H_2O$; (f) 3*N* HCl, THF; (g) $(COCl)_2$, $C_6H_6$; $CH_2N_2$, $Et_2O$; (h) $BF_3.Et_2O$, $CH_2Cl_2$; (i) NaOH, MeOH-$H_2O$; $CH_2N_2$, $Et_2O$.

**Scheme II**

at RT, followed by treatment of the resultant acid chloride with an excess of ethereal solution of diazomethane at RT furnished the diazo ketone **21**. Reaction[16] of the diazo ketone **21** with boron trifluoride diethyl etherate in methylene chloride at 0°C for 45 min furnished the bicyclo[4.2.1]nonane-2,8-dione **13**, in 88% yield, in a highly regio-selective manner, whose structure was established from its spectral data.

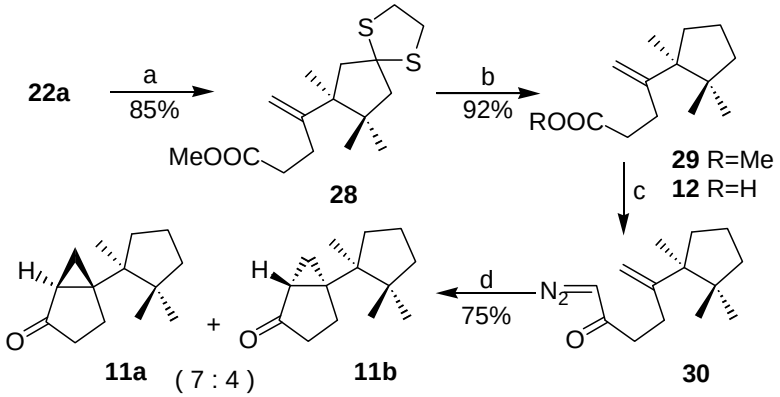
Next, attention was focused on the conversion of the dione **13** into the γ,δ-unsaturated acid **12** *via* retro-Claisen condensation and deoxygenation sequence. Thus, reaction of the bicyclic dione **13** with 10% aqueous sodium hydroxide and methanol in a sealed tube at 120°C for 8 hr furnished a 3:1 mixture of the keto acids **22** and **23**, which on esterification with an excess of ethereal solution of diazomethane furnished a 3:1 mixture of keto esters **22a** and **23a** in 83% yield. The keto esters **22a** and **23a** were separated by column chromatography on silica gel and the structures were established from their spectral data.

First as a model study, it was contemplated to convert the keto ester **22a** into β-cuparenone[17] **24** (**Scheme III**). Thus, hydrolysis of the keto ester **22a** with 5% sodium hydroxide in refluxing aqueous methanol furnished quantitatively the keto acid **22**. Treatment of the keto acid **22** with an excess of oxalyl chloride in benzene at RT followed by treatment of the resultant acid chloride with an excess of ethereal solution of diazomethane furnished the diazo ketone **25**. Intramolecular cyclopropanation reaction[18] of the diazo ketone **25** with copper powder and anhydrous copper sulphate in refluxing cyclohexane furnished, as anticipated, a 3:2 diastereomeric mixture of the norcyclocuparanedione **26**. No attempt was made to separate the diastereomers as both will lead to β-cuparenone **24**. Reaction of the tricyclic dione **26** with methylmagnesium iodide in ether at 0°C furnished a diastereomeric mixture of the hydroxy ketone **27** in a regioselective manner. Presence of a carbonyl absorption band at 1730 $cm^{-1}$ due to cyclopentanone in the IR spectrum revealed the regioselectivity of the




Reagents: (a) $(COCl)_2$, $C_6H_6$; $CH_2N_2$, $Et_2O$; (b) Cu, $CuSO_4$, *c*-$C_6H_{12}$; 70% (2 steps) (c) MeMgI, $Et_2O$, 50%; (d) *p*-TSA, $CH_2Cl_2$; (e) DDQ, $C_6H_6$, 51% (2 steps).

**Scheme III**




Reagents: (a) $(CH_2SH)_2$, $BF_3.Et_2O$, $C_6H_6$; (b) Raney Ni, EtOH; NaOH; (c) $(COCl)_2$, $C_6H_6$; $CH_2N_2$, $Et_2O$; (d) Cu, $CuSO_4$, *c*-$C_6H_{12}$.

**Scheme IV**

reaction. Reaction of the hydroxy ketone **27** with a catalytic amount of *p*-TSA in methylene chloride gave a mixture of the cyclohexadienes, which on treatment with DDQ in refluxing benzene furnished (±)-β-cuparenone **24**. Comparison of the $^1$H NMR spectroscopic data with that reported[19] in the literature confirmed the structure of (±)-β-cuparenone **24**.

After successful completion of the synthesis of β-cuparenone **24**, attention was turned towards the conversion of the ketoester **22a** into the acid **12**, the key intermediate for the synthesis of the cyclocuparanes **2**, **7** and **9** (**Scheme IV**). For the reductive deoxygenation of the keto group in the keto ester **22a**, a two-step methodology *via* the thioketal **28** was employed. Thus, reaction of the ketoester **22a** with ethanedithiol and boron trifluoride diethyl etherate in benzene for 15 min furnished the thioketal **28** in 85% yield. Desulfurisation of the thioketal **28** with an excess of Raney nickel in refluxing ethanol furnished the ester **29** in 92% yield.

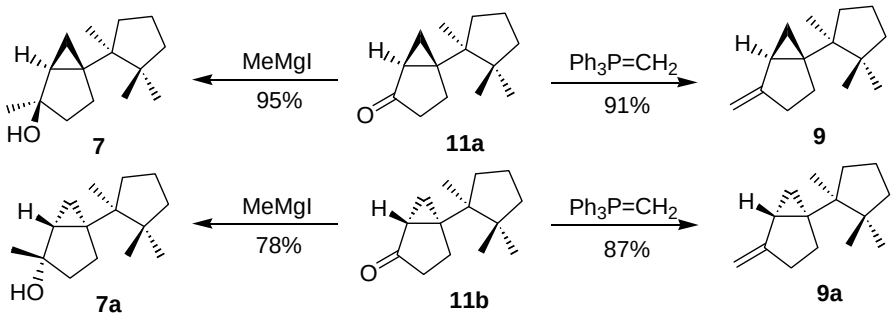
Hydrolysis of the ester **29** with 10% aqueous sodium hydroxide in refluxing methanol quantitatively furnished the acid **12**. Reaction of the acid **12** with oxalyl chloride in benzene at RT followed by treatment of the resultant acid chloride with an excess of ethereal solution of diazomethane furnished the diazo ketone **30**. Intramolecular cyclopropanation reaction of the diazo ketone **30** with a mixture of copper powder and anhydrous copper sulphate in refluxing cyclohexane (tungsten lamp) for 5 hr furnished a 7:4 diastereomeric mixture of the norcyclocuparanones **11a** and **11b** in 75% yield, which were separated by careful column chromatography over silica gel. Presence of the molecular ion peak at *m/z* 206 ($C_{14}H_{22}O$) in the mass spectrum and presence of a carbonyl absorption band at 1720 cm$^{-1}$ due to the ketone group and disappearance of bands due to diazo and exomethylene groups in the IR spectrum revealed the formation of the tricyclic ketones **11a** and **11b**. The $^1$H and $^{13}$C NMR spectra of

the two tricyclic ketones **11a** and **11b** are very similar indicating their diastereomeric nature. From the spectral data, however, it was not possible to distinguish the stereostructures of the ketones **11a** and **11b**, and were assigned tentatively. Final conformation of stereostructures of the ketones **11a** and **11b** were obtained by conversion of the major ketone **11a** into the cyclocuparanes **2**, **7** and **9**.

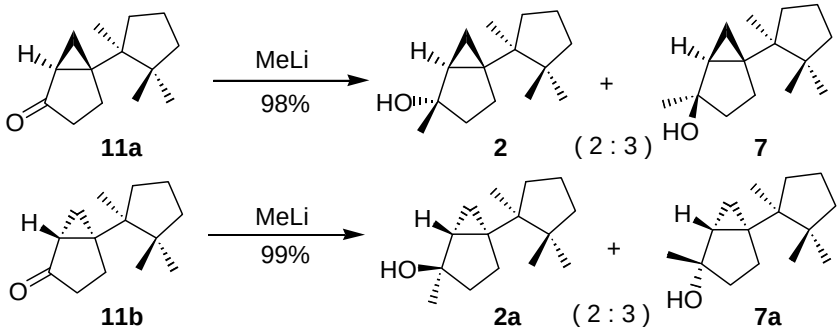
Reaction of the ketone **11a** with an excess of methylenetriphenylphosphorane in benzene at RT for 1 hr furnished (±)-β-microbiotene **9** in 91% yield, **Scheme V**. Similarly, reaction of the ketone **11b** with an excess of methylenetriphenylphosphorane in benzene at RT for 1 hr furnished (±)-5-*epi*-β-microbiotene **9a** in 87% yield. Comparison of the $^1$H NMR spectrum of the synthetic β-microbiotene (±)-**9** in benzene-$d_6$ and the mass spectrum with those of the natural product[9] (+)-**9** unambiguously established the structures of (±)-β-microbiotene **9** and (±)-5-*epi*-β-microbiotene **9a**.

Subsequently, the synthesis of (±)-microbiotol **7** and 5-epimicrobiotol **7a** was addressed. Thus, reaction of the ketone **11a** with an excess of methylmagnesium iodide in ether at 0°C for 3 hr furnished (±)-microbiotol **7**, in 95% yield, in a highly stereoselective manner. Similarly, reaction of the ketone **11b** with an excess of methylmagnesium iodide furnished (±)-5-*epi*-microbiotol **7a**, in 78% yield, in a highly stereoselective manner. Comparison of the $^1$H and $^{13}$C NMR spectra of the synthetic microbiotol (±)-**7** in methanol-$d_4$ with those of (–)-microbiotol **7** isolated from natural source[7], established the structures of (±)-microbiotol **7** and 5-*epi*-microbiotol **7a**. Exclusive formation of microbiotol **7** and 5-*epi*-microbiotol **7a** can be readily explained by the approach of the Grignard reagent from the less hindered *exo* face of the bicyclo[3.1.0]hexanone part of norcyclocuparanones **11a** and **11b**.

For the synthesis of cyclocuparanol **2**, which is epimeric to microbiotol **7** at the carbon bearing hydroxy group, a two-step strategy starting from β-microbiotene **9** was conceived. It was anticipated that stereoselective epoxidation of β-microbiotene **9** generates the *exo*-epoxide *via* approach of the oxygen from the less hindered *exo* face, which could be reductively opened to cyclocuparanol **2**. However, attempts to convert β-microbiotene **9** into the corresponding epoxide were unsuccessful. Finally, it was discovered that addition of methyllithium to the norcyclocuparanones **11** generates a diastereomeric mixture of alcohols, **Scheme VI**. Thus, reaction of the ketone **11a** with an excess of methyllithium in ether at




**Scheme V**




**Scheme VI**

0°C for 2 hr furnished a 2:3 mixture of (±)-cyclocuparanol **2** and (±)-microbiotol **7** in 98% yield, which were separated by column chromatography on silica gel. In a similar manner, reaction of the minor ketone **11b** with an excess of methyllithium furnished a 2:3 mixture of (±)-5-*epi*-cyclocuparanol **2a** and 5-*epi*-microbiotol **7a** in 99% yield, which were separated by column chromatography on silica gel. Comparison of the $^1$H NMR spectrum of (±)-cyclocuparanol **2** obtained in the present study with that of (–)-**2** isolated from the natural source[4,6] unambiguously established the structures of (±)-cyclocuparanol **2** and (±)-5-*epi*-cyclocuparanol **2a**.

In conclusion, the first total synthesis of (±)-β-microbiotene **9**, (±)-microbiotol **7** and (±)-cyclocuparanol **2**, sesquiterpenes containing three contiguous quarternary carbon atoms has been accomplished. A combination of Claisen rearrangement, acid catalysed rearrangement of a diazoketone, a retro-Claisen condensation and an intramolecular diazoketone cyclopropanation reactions were employed for the creation of the three contiguous quaternary carbon atoms.

## Experimental Section

Melting points were recorded using Tempo and Mettler FP1 melting point apparatus in capillary tubes and are uncorrected. IR spectra were recorded on a Perkin-Elmer 781 spectrometer. $^1$H (300 MHz) and $^{13}$C (75 MHz) spectra were recorded on Jeol JNM λ-300 spectrometer. The chemical shifts (δ, ppm) and coupling constants (Hz) are reported in the standard fashion with reference to either internal tetramethylsilane (for $^1$H) or the central line (77.0 ppm) of $CDCl_3$ (for $^{13}$C). In the $^{13}$C NMR spectra, the nature of the carbons (C, CH, $CH_2$ or $CH_3$) was determined by DEPT-135, and are given in parentheses. Mass spectra were recorded using Jeol JMS-DX 303 GCMS instrument using direct inlet mode. Relative intensities are given in parentheses. Acme's silica gel (100-200 mesh) was used for column chromatography (approximately 15-20 g per 1 g of the crude product). All small-scale dry reactions were carried out under inert atmosphere using standard syringe septum technique.

**Ethyl 2,3,3-trimethyl-4-oxocyclohex-1-ene-1-carboxylate 17**. To a magnetically stirred, ice-cold suspension of NaH (60-65% dispersion in oil, 2.285 g, 59.5 mmoles, washed with dry hexane) in anhydrous THF (150 mL) was added Hagemann's ester **15** (5 mL, 5.38 g, 29.71 mmoles) and stirred for 45 min at the same temperature. The reaction mixture was cooled to -100°C, added methyl iodide (4.64 mL, 10.53 g, 74.32 mmoles) and stirred at –100°C for 1.5 hr. The reaction mixture was slowly warmed upto RT and stirred at RT for 7 hr. Solvent was then evaporated under reduced pressure, 3*N* aqueous HCl (20 mL) was added to the residue and extracted with $CH_2Cl_2$ (2 × 25 mL). The combined $CH_2Cl_2$ extract was washed with brine and dried (anhyd. $Na_2SO_4$). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (0:1 to 1:10) as eluent furnished the ester **17** (4 g, 64%) as oil. IR (neat): 1713, 1626 cm$^{-1}$; $^1$H NMR ($CDCl_3$ + $CCl_4$): δ 4.20 (2 H, q, *J* = 7.2 Hz), 2.66 (2 H, br t, *J* = 6.9 Hz), 2.53 (2 H, br t, *J* = 6 Hz), 2.00 (3 H, t, *J* = 1.8 Hz), 1.32 (3 H, t, *J* = 7.2 Hz), 1.23 (6 H, s); $^{13}$C NMR ($CDCl_3$ + $CCl_4$): δ 212.4 (C), 168.2 (C), 149.2 (C), 124.8 (C), 60.3 ($CH_2$), 48.7 (C), 35.7 ($CH_2$), 26.0 ($CH_2$), 23.7 (2 C, $CH_3$), 16.1 ($CH_3$), 14.3 ($CH_3$); MS: *m/z* (%) 210 ($M^+$, $C_{12}H_{18}O_3$, 8), 182 (99), 165 (99), 154 (38), 140 (42), 139 (48), 125 (42), 123 (43), 109 (45), 95 (100), 93 (50).

**Ethyl 4,4-(ethylenedioxy)-2,3,3-trimethylcyclohex-1-ene-1-carboxylate 18**. A magnetically stirred solution of the ester **17** (1 g, 4.76 mmoles), ethylene glycol (1.5 g, 1.35 mL, 24 mmoles) and a catalytic amount of *p*-TSA in dry benzene (35 mL) was refluxed with a Dean-Stark water trap for 5 hr. Benzene was evaporated under reduced pressure, saturated aqueous $NaHCO_3$ solution (5 mL) was added to the residue and extracted with $CH_2Cl_2$ (2 × 10 mL). The combined $CH_2Cl_2$ extract was washed with brine and dried (anhyd. $Na_2SO_4$). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:50 to 1:10) as eluent furnished the ketalester **18** (1.08 g, 89%) as oil. IR (neat): 1712, 1624 cm$^{-1}$; $^1$H NMR ($CDCl_3$ + $CCl_4$): δ 4.18 (2 H, q, *J* = 6.9 Hz), 4.05-3.90 (4 H, m), 2.41 (2 H, q of t, *J* = 6.6 and 2.1 Hz), 1.91 (3 H, t, *J* = 1.8 Hz), 1.75 (2 H, t, *J* = 6.6 Hz), 1.29 (3 H, t, *J* = 6.9 Hz), 1.10 (6 H, s); $^{13}$C NMR ($CDCl_3$ + $CCl_4$): δ 169.2 (C), 148.1 (C), 123.7 (C), 111.4 (C), 64.9 (2 C, $CH_2$), 59.9 ($CH_2$), 44.1 (C), 26.2 ($CH_2$), 25.6 ($CH_2$), 22.1 (2 C, $CH_3$), 16.1 ($CH_3$), 14.4 ($CH_3$); MS: *m/z* (%) 254 ($M^+$, $C_{14}H_{22}O_4$, 20), 209 (25), 168 (26), 140 (22), 137 (30), 134 (22), 109 (27), 99 (20), 95 (30), 87 (94), 86 (100).

**4, 4-(Ethylenedioxy)-2, 3, 3-trimethylcyclohex-1-ene-1-methanol 16**. To a magnetically stirred, cold

(-70°C) solution of the ester **18** (1.06 g, 4.165 mmoles) in anhydrous ether (25 mL) was added $LiAlH_4$ (158 mg, 4.165 mmoles) and stirred for 2 hr at the same temperature. Ethyl acetate (2 mL) was then added to consume excess $LiAlH_4$, the reaction was quenched with water (10 mL) and extracted with ether (2 × 10 mL). The combined ether extract was washed with brine and dried (anhyd. $Na_2SO_4$). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:10 to 1:2.5) as eluent furnished the allyl alcohol **16** (0.81 g, 92%) as a white solid. m.p. 71°C. IR (thin film): 3430, 1655 $cm^{-1}$; $^1H$ NMR ($CDCl_3$ + $CCl_4$): δ 4.07 (2 H, s), 4.05-3.90 (4 H, m), 2.27 (2 H, m), 1.76 (2 H, t, *J* = 6.6 Hz), 1.69 (3 H, s), 1.25 (1 H, br s), 1.05 (6 H, s); $^{13}C$ NMR ($CDCl_3$ + $CCl_4$): δ 136.6 (C), 128.6 (C), 112.1 (C), 64.9 (2 C, $CH_2$), 63.4 ($CH_2$), 43.1 (C), 26.8 ($CH_2$), 26.7 ($CH_2$), 22.3 (2 C, $CH_3$), 13.4 ($CH_3$); MS: *m/z* (%) 212 ($M^+$, $C_{12}H_{20}O_3$, 8), 194 (8), 93 (40), 87 (49), 86 (100).

**Ethyl 2-[3,3-(ethylenedioxy)-1,2,2-trimethyl-6-methylenecyclohexyl]acetate 19**. A solution of the allyl alcohol **16** (5 g, 23.6 mmoles), triethyl orthoacetate (17.8 g, 20 mL, 109.1 mmoles) and a catalytic amount of propionic acid (50 μL) was placed in a sealed tube and heated to 180°C for 7 days in an oil bath. The reaction mixture was then cooled, diluted with $CH_2Cl_2$ (25 mL), washed with 1*N* aqueous HCl (5 mL) followed by saturated aqueous $NaHCO_3$ solution (5 mL) and brine, and dried (anhyd. $Na_2SO_4$). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:50 to 1:10) as eluent furnished the ester **19** (5.575 g, 84%) as colourless oil. IR (neat): 1729, 1639, 904 $cm^{-1}$; $^1H$ NMR ($CDCl_3$ + $CCl_4$): δ 4.84 (1 H, br s), 4.68 (1 H, br s), 4.10-3.90 (4 H, m), 3.95-3.75 (2 H, m), 3.48 and 2.14 (2 H, 2 × d, *J* = 12.9 Hz), 2.63 (1 H, m), 2.15 (1 H, m), 1.70-1.50 (2 H, m), 1.19 (3 H, t, *J* = 7.2 Hz), 1.18 (3 H, s), 0.95 (3 H, s), 0.88 (3 H, s); $^{13}C$ NMR ($CDCl_3$ + $CCl_4$): δ 172.5 (C), 150.1 (C), 113.0 (C), 110.6 ($CH_2$), 65.5 ($CH_2$), 63.8 ($CH_2$), 59.5 ($CH_2$), 46.3 (C), 46.2 (C), 40.8 ($CH_2$), 31.8 ($CH_2$), 30.6 ($CH_2$), 21.7 ($CH_3$), 19.0 ($CH_3$), 15.8 ($CH_3$), 14.4 ($CH_3$); MS: *m/z* (%) 282 ($M^+$, $C_{16}H_{26}O_4$, 5), 239 (100), 237 (11), 195 (16), 167 (29), 99 (32).

**2-[1,2,2-Trimethyl-6-methylene-3-oxocyclohexyl]-acetic acid 14**. A magnetically stirred solution of the ketalester **19** (400 mg, 1.42 mmole) in methanol (5 mL) and 10% aqueous NaOH (5 mL, 12.5 mmoles) was refluxed for 12 hr. The reaction mixture was cooled and washed with $CH_2Cl_2$ (2 mL). The aqueous layer was acidified with 3*N* aqueous HCl (4 mL) and then extracted with $CH_2Cl_2$ (3 × 10 mL). The combined $CH_2Cl_2$ extract was washed with brine and dried (anhyd. $Na_2SO_4$). Evaporation of the solvent furnished the ketalacid **20**. A solution of the ketalacid **20** in THF (5 mL) and 3N aqueous HCl (5 mL) was magnetically stirred at RT for 1 hr. The reaction mixture was then diluted with water (1 mL) and extracted with ether (3 × 8 mL). The combined ether extract was washed with brine and dried (anhyd. $Na_2SO_4$). Evaporation of the solvent furnished the keto acid **14** (290 mg, 97% from the ketalester **19**) as a solid, which was purified by recrystallization from hexane. m.p. 127°C. IR (thin film): 3200, 1733, 1705, 1642, 904 $cm^{-1}$; $^1H$ NMR ($CDCl_3$ + $CCl_4$): δ 10.00 (1 H, br s), 5.09 (1 H, s), 4.95 (1 H, s), 2.82-2.25 (6 H, m), 1.29 (3 H, s), 1.07 (3 H, s), 1.03 (3 H, s); $^{13}C$ NMR ($CDCl_3$ + $CCl_4$): δ 214.0 (C), 177.2 (C), 147.0 (C), 113.2 ($CH_2$), 52.5 (C), 47.5 (C), 41.0 ($CH_2$), 37.5 ($CH_2$), 31.6 ($CH_2$), 22.8 ($CH_3$), 17.9 ($CH_3$), 17.7 ($CH_3$); MS: *m/z* (%) 210 ($M^+$, $C_{12}H_{18}O_3$, 25), 151 (82), 135 (25), 125 (40), 123 (60), 122 (86), 121 (60), 109 (50), 108 (55), 107 (65), 93 (44), 41 (100).

**6,9,9-Trimethyl-5-methylenebicyclo[4.2.1]nonane-2,8-dione 13**. A solution of the ketoacid **14** (290 mg, 1.38 mmole) and oxalyl chloride (0.6 mL, 6.9 mmoles) in dry benzene (3 mL) was stirred for 2 hr at RT to furnish the acid chloride, which was taken in ether and added to an ice-cold ethereal solution of diazomethane. The reaction mixture was stirred for 2 hr at RT. Careful evaporation of the solvent and excess diazomethane followed by purification over a silica gel column using ethyl acetate-hexane (1:4 to 1:1) as eluent furnished the diazo ketone **21** (252 mg, 78%) as oil. [IR (neat): 2100, 1700, 1630, 900 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 5.15 (2 H, s), 4.95 (1 H, s), 3.00-2.00 (6 H, m), 1.30 (3 H, s), 1.10 (3 H, s), 0.99 (3 H, s)]. To a magnetically stirred, ice-cold solution of the diazo ketone **21** (252 mg, 1.076 mmoles) in dry $CH_2Cl_2$ (75 mL) was added $BF_3.OEt_2$ (0.067 mL, 0.538 mmoles) and stirred for 45 min at the same temperature. The reaction was quenched with saturated aq. $NaHCO_3$ solution (1 mL) and extracted with $CH_2Cl_2$ (3 × 5 mL). The organic layer was washed with brine and dried (anhyd. $Na_2SO_4$). Evaporation of the solvent and purification over a silica gel column using ethyl acetate-hexane (1:9 to 2:5) as eluent furnished the dione **13** (195 mg, 88%), which was purified by recrystallization from hexane.

m.p. 180°C. IR (thin film): 1735, 1690, 1630, 900 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 5.11 (1 H, s), 4.99 (1 H, s), 3.16 (1 H, s), 2.65 and 2.57 (2 H, 2 × d, *J* = 19.0 Hz), 2.70-2.55 (1 H, m), 2.55-2.35 (3 H, m), 1.34 (3 H, s), 1.16 (3 H, s), 1.02 (3 H, s); $^{13}C$ NMR ($CDCl_3$ + $CCl_4$): δ 210.6 (C), 203.3 (C), 151.5 (C), 114.9 ($CH_2$), 78.3 (CH), 50.9 ($CH_2$), 49.2 (C), 44.1 (C), 42.3 ($CH_2$), 30.4 ($CH_2$), 27.8 ($CH_3$), 20.5 ($CH_3$), 20.4 ($CH_3$); MS: *m/z* (%) 206 ($M^+$, $C_{13}H_{18}O_2$, 7), 123 (33), 83 (100). Anal. Calcd. for $C_{13}H_{18}O_2$ C: 75.69, H: 8.80%; Found, C: 75.40, H: 8.94%.

**Methyl 4-[1,5,5-trimethyl-3-oxocyclopentyl]-4-pentenoate 22a and methyl 2-[1,2,2-trimethyl-7-methylene-4-oxocycloheptyl]acetate 23a**. A solution of the dione **13** (430 mg, 2.08 mmoles) in methanol (4.2 mL) and 10% aqueous NaOH (4.2 mL, 10.5 mmole) was placed in a sealed tube and heated to 120°C for 8 hr. The reaction mixture was then cooled, acidified with 3N aqueous HCl (4 mL) and extracted with $CH_2Cl_2$ (3 × 6 mL). The combined $CH_2Cl_2$ extract was washed with brine and dried (anhyd. $Na_2SO_4$). Evaporation of the solvent afforded a 3:1 mixture of the two acids **22** and **23**. To a magnetically stirred ice-cold solution of a 3:1 mixture of the acids **22** and **23** in ether (3 mL) was added an ice-cold ethereal diazomethane solution (excess, prepared from 3 g of *N*-nitroso-*N*-methylurea and 25 mL of 60% aqueous KOH solution and 20 mL of ether) and stirred for 0.5 hr at the same temperature. Careful evaporation of the excess diazomethane and solvent followed by purification of the residue over a silica gel column using ethyl acetate-hexane (1:20 to 1:5) as eluent first furnished the ketoester **22a** (310 mg, 63%) as oil. IR (neat): 1735, 1630, 895 $cm^{-1}$; $^1H$ NMR ($CDCl_3$ + $CCl_4$): δ 4.90 (1 H, s), 4.87 (1 H, s), 3.68 (3 H, s), 2.80 (1 H, d, *J* = 18.0 Hz), 2.55-2.25 (4 H, m), 2.25 and 2.15 (2 H, 2 × d, *J* = 18.6 Hz), 2.09 (1 H, d, *J* = 18.0 Hz), 1.22 (3 H, s), 1.19 (3 H, s), 1.00 (3 H, s); $^{13}C$ NMR ($CDCl_3$ + $CCl_4$): δ 215.9 (C), 172.9 (C), 151.5 (C), 110.3 ($CH_2$), 52.7 ($CH_2$), 50.9 ($CH_2$), 51.5 ($CH_3$), 49.5 (C), 41.2 (C), 33.0 ($CH_2$), 28.6 ($CH_2$), 26.1 ($CH_3$), 24.7 ($CH_3$), 23.2 ($CH_3$); MS: *m/z* (%) 239 (M+1, 10), 182 (45), 155 (28), 154 (32), 139 (40), 123 (35), 122 (30), 109 (40), 95 (100), 94 (60). Further elution of the column with the same solvent furnished the ketoester **23a** (99 mg, 20%) as oil. IR (neat): 1730, 1700, 1625, 900 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 5.00 (1 H, s), 4.90 (1 H, s),, 3.58 (3 H, s, OC*H*$_3$), 2.97 (1 H, d, *J* = 12.9 Hz), 2.93 (1 H, d, *J* = 13.5 Hz), 2.65-2.15 (4 H, m), 2.33 (1 H, d, *J* = 13.5 Hz), 2.11 (1 H, d, *J* = 12.9 Hz), 1.25 (3 H, s), 0.95 (3 H, s), 0.82 (3 H, s); $^{13}C$ NMR ($CDCl_3$): δ 213.0 (C), 172.3 (C), 151.0 (C), 115.9 ($CH_2$), 53.3 ($CH_2$), 51.4 ($CH_3$), 47.6 (C), 43.8 ($CH_2$), 40.2 ($CH_2$), 38.7 (C), 28.6 ($CH_2$), 26.1 ($CH_3$), 23.6 ($CH_3$), 20.1 ($CH_3$); MS: *m/z* (%) 238 ($M^+$, $C_{14}H_{22}O_3$, 1), 182 (27), 123 (100), 109 (21), 95 (26).

**4-[1,5,5-Trimethyl-3-oxocyclopentyl]-4-pentenoic acid 22**. A magnetically stirred solution of the ester **22a** (411 mg, 1.72 mmole) in MeOH (6 mL) and 10% aqueous NaOH (6 mL, 15 mmoles) was refluxed for 12 hr in an oil-bath. The reaction mixture was then cooled, acidified with 3N aqueous HCl (6 mL) and extracted with $CH_2Cl_2$ (3 × 8 mL). The combined $CH_2Cl_2$ extract was washed with brine and dried (anhyd. $Na_2SO_4$). Evaporation of the solvent under reduced pressure furnished the acid **22** (382 mg, 99%) as oil. IR (neat): 3000, 1739, 1713, 1633, 898 $cm^{-1}$; $^1H$ NMR ($CDCl_3$ + $CCl_4$): δ 9.30 (1 H, br s), 4.92 (1 H, s), 4.90 (1 H, s), 2.81 (1 H, d, *J* = 18 Hz), 2.60-2.35 (4 H, m), 2.21 (2 H, AB q, *J* = 18.6 Hz), 2.10 (1 H, d, *J* = 18 Hz), 1.22 (3 H, s), 1.20 (3 H, s), 1.00 (3 H, s); $^{13}C$ NMR ($CDCl_3$ + $CCl_4$): δ 216.1 (C), 178.9 (C), 151.2 (C), 110.5 ($CH_2$), 52.7 ($CH_2$), 50.9 ($CH_2$), 49.5 (C), 41.2 (C), 33.0 ($CH_2$), 28.3 ($CH_2$), 26.1 ($CH_3$), 24.7 ($CH_3$), 23.2 ($CH_3$); MS: *m/z* (%) 224 ($M^+$, $C_{13}H_{20}O_3$, 0.5), 168 (24), 140 (45), 125 (53), 109 (18), 95 (100).

**5-(1, 5, 5-Trimethyl-3-oxocyclopentyl)bicyclo-[3.1.0]hexan-2-ones 26**. A solution of the ketoacid **22** (382 mg, 1.70 mmole) and oxalyl chloride (0.77 mL, 8.93 mmoles) in dry benzene (10 mL) was magnetically stirred for 2 hr at RT. Evaporation of the excess oxalyl chloride and solvent under reduced pressure afforded the acid chloride, which was taken in dry ether (3 mL) and added dropwise to a cold, magnetically stirred ethereal solution of diazomethane (excess, prepared from 7 g of *N*-nitroso-*N*-methylurea and 50 mL of 60% aqueous KOH solution and 30 mL of ether) and the reaction mixture was stirred for 2 hr at RT. Careful evaporation of the excess diazo-methane and solvent on water-bath and purification of the residue over a silica gel column using ethyl acetate-hexane (2:5) as eluent furnished the diazo ketone **25** as yellow oil. IR (neat): 2120, 1740, 1635, 900 $cm^{-1}$. To a magnetically stirred, refluxing (by placing two 100 W tungsten lamps near the reaction flask) suspension of copper powder (0.94 g, 14.9 mmoles) and anhydrous copper sulfate (0.31 g, 1.98 mmole) in dry cyclohexane (80 mL) was added dropwise a solution of the diazo ketone **25**, obtained above, in dry cyclohexane (20 mL) over a period of

45 min and the reaction mixture was refluxed for 5 hr. It was then cooled and copper and copper sulfate were filtered off using a sintered funnel. Evaporation of the solvent under reduced pressure and purification of the residue over a silica gel column using ethyl acetate-hexane (1:20 to 3:10) as eluent furnished a 3:2 diastereomeric mixture of the tricyclic diketones **26** (260 mg, 70% from the ketoacid **22**). IR (neat): 1725 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): Peaks due to the major isomer: δ 2.45-1.90 (8 H, m), 1.70-1.55 (1 H, m), 1.50-1.40 (1 H, m), 1.23 (3 H, s), 1.20 (6 H, s), 1.05-0.80 (1 H, m); Peaks due to the minor isomer: δ 1.26 (3 H, s), 1.20 (3 H, s), 1.11 (3 H, s); $^{13}C$ NMR ($CDCl_3$): Peaks due to the major isomer: δ 216.3 (C), 213.8 (C), 53.3 ($CH_2$), 47.8 ($CH_2$), 44.9 (C), 41.9 (C), 38.8 (C), 33.0 ($CH_2$), 31.6 (CH), 26.0 ($CH_3$), 25.6 ($CH_2$), 24.8 ($CH_3$), 21.9 ($CH_3$), 19.6 ($CH_2$); Peaks due to the minor isomer: δ 216.1 (C), 213.5 (C), 54.6 ($CH_2$), 49.4 ($CH_2$), 44.7 (C), 41.9 (C), 39.1 (C), 34.0 (CH), 33.3 ($CH_2$), 26.3 ($CH_3$), 25.8 ($CH_3$), 25.4 ($CH_2$), 22.3 ($CH_3$), 16.6 ($CH_2$); MS: *m/z* (%) 220 ($M^+$, $C_{14}H_{20}O_2$, 10), 164 (22), 136 (95), 121 (18), 108 (16), 94 (92), 93 (47), 79 (100).

**2-Methyl-5-[1,5,5-trimethyl-3-oxocyclopentyl]bicyclo[3.1.0]hexan-2-ol 27**. To a magnetically stirred, ice-cold solution of a 3:2 diastereomeric mixture of the diketone **26** (110 mg, 0.5 mmole) in dry ether (12 mL) was added, a solution of MeMgI in ether (1.2 mL, 1.2 mmole) [prepared from magnesium (240 mg, 10 mmoles) and methyl iodide (0.62 mL, 10 mmoles) in dry ether (10 mL)] and stirred for 2 hr at RT. The reaction was then quenched with saturated aqueous $NH_4Cl$ solution (2 mL) and extracted with ether (2 × 3 mL). The combined ether extract was washed with brine and dried (anhyd. $Na_2SO_4$). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:20 to 3:10) as eluent first furnished the unreacted starting material **26** (64 mg). Further elution of the column with the same solvent furnished a diastereomeric mixture of the ketoalcohol **27** (25 mg, 21%, 50% based on the starting material consumed) as oil. IR (neat): 3400, 1730 $cm^{-1}$; $^1H$ NMR ($CDCl_3$ + $CCl_4$): Peaks due to the major isomer: δ 2.35-0.50 (12 H, series of m), 1.34 (3 H, s), 1.16 (3 H, s), 1.15 (3 H, s), 1.14 (3 H, s). $^{13}C$ NMR ($CDCl_3$ + $CCl_4$): Peaks due to the major isomer: δ 216.8 (C), 78.7 (C), 53.5 ($CH_2$), 48.7 ($CH_2$), 44.8 (C), 42.0 (C), 36.8 ($CH_2$), 32.7 (C), 31.9 (2 C, CH and $CH_3$), 28.3 ($CH_2$), 26.1 ($CH_3$), 24.9 ($CH_3$), 21.6 ($CH_3$), 11.3 ($CH_2$); MS: *m/z* (%) 236 ($M^+$, $C_{15}H_{24}O_2$, 1), 137 (83), 123 (51), 119 (36), 109 (77), 95 (40), 94 (57), 93 (50), 43 (100).

**3, 4, 4-Trimethyl-3-(4-methylphenyl)cyclopentanone (β-cuparenone 24)**. A solution of the ketoalcohol **27** (18 mg, 0.076 mmoles) and *p*-TSA (catalytic) in dry $CH_2Cl_2$ (8 mL) was magnetically stirred for 2 hr at RT. The reaction mixture was then washed with saturated aqueous $NaHCO_3$ solution (1 mL) and brine, and dried (anhyd. $Na_2SO_4$). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:50 to 1:25) as eluent furnished a mixture of the cyclohexadienes, which was taken in dry benzene (3 mL) and DDQ (30 mg, 0.13 mmole) was added and refluxed for 4 hr. Evaporation of the solvent under reduced pressure and purification of the residue over a silica gel column using ethyl acetate-hexane (1:30) as eluent furnished β-cuparenone **24** (8 mg, 51%) as oil. IR (neat): 1740, 1510, 810 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 7.19 and 7.10 (4 H, 2 × d, $J$ = 8.4 Hz), 3.13 (1 H, d, $J$ = 17.4 Hz), 2.33 (3 H, s), 2.35-2.15 (3 H, m), 1.42 (3 H, s), 1.22 (3 H, s), 0.72 (3 H, s); $^{13}C$ NMR ($CDCl_3$): δ 218.4 (C), 141.2 (C), 135.8 (C), 128.7 (2 C, CH), 126.5 (2 C, CH), 52.4 ($CH_2$), 50.7 ($CH_2$), 47.8 (C), 41.8 (C), 26.2 ($CH_3$), 24.4 ($CH_3$), 24.1 ($CH_3$), 20.8 ($CH_3$); MS: *m/z* (%) 216 ($M^+$, $C_{15}H_{20}O$, 25), 159 (14), 133 (59), 132 (99), 117 (100), 115 (32), 105 (12), 91 (39).

**Methyl 4-[2,3,3-trimethyl-6,9-dithiaspiro[4.4]non-2-yl]-4-pentenoate 28**. To a magnetically stirred, ice-cold solution of the ketoester **22a** (60 mg, 0.25 mmole) and ethanedithiol (0.085 mL, 1.01 mmole) in dry benzene (2 mL) was added $BF_3.OEt_2$ (0.025 mL, 0.2 mmole) and stirred for 15 min at same temperature. The reaction was carefully quenched with saturated aqueous $NaHCO_3$ solution (2 mL) and extracted with ether (2 × 6 mL). The combined ether extract was washed with brine and dried (anhyd. $Na_2SO_4$). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (2:5) as eluent furnished the thioketal **28** (67 mg, 85%) as oil. IR (neat): 1735, 1630, 890 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 4.87 (1 H, s), 4.77 (1 H, s), 3.68 (3 H, s), 3.45-3.20 (4 H, m), 3.09 (1 H, d, $J$ = 14.1 Hz), 2.57 (1 H, d, $J$ = 15 Hz), 2.55-2.25 (6 H, m), 1.22 (3 H, s), 1.06 (3 H, s), 0.96 (3 H, s); $^{13}C$ NMR ($CDCl_3$): δ 173.7 (C), 152.2 (C), 109.3 ($CH_2$), 64.3 (C), 61.2 ($CH_2$), 57.1 ($CH_2$), 52.9 (C), 51.5 ($CH_3$), 45.0 (C), 40.4 ($CH_2$), 39.9 ($CH_2$), 33.1 ($CH_2$), 28.0 ($CH_2$), 25.2 ($CH_3$), 23.9 ($CH_3$), 23.0 ($CH_3$); MS:

*m/z* (%) 314 ($M^+$, $C_{16}H_{26}O_2S_2$, 7), 258 (100), 230 (50), 198 (40), 159 (35), 145 (40), 125 (35).

**Methyl 4-(1,2,2-trimethylcyclopentyl)-4-pentenoate 29**. A magnetically stirred solution of the thioketal **28** (280 mg, 0.89 mmole) and freshly prepared Raney Ni (excess) in dry ethanol (40 mL) was refluxed in an oil bath for 5 hr. The reaction mixture was then cooled, filtered through a small column of silica gel using $CH_2Cl_2$ (5 mL) as eluent. Evaporation of the solvent under reduced pressure furnished the pentenoate **29** (184 mg, 92%) as oil. IR (neat): 1740, 1630, 890 $cm^{-1}$; $^1H$ NMR ($CDCl_3$ + $CCl_4$): δ 4.88 (1 H, s), 4.75 (1 H, s), 3.67 (3 H, s), 2.56-2.10 (4 H, m), 1.73-1.30 (6 H, m), 1.03 (6 H, s), 0.84 (3 H, s); $^{13}C$ NMR ($CDCl_3$ + $CCl_4$): δ 173.7 (C), 153.7 (C), 109.1 ($CH_2$), 51.9 (C), 51.5 ($CH_3$), 43.7 (C), 40.4 ($CH_2$), 36.9 ($CH_2$), 33.4 ($CH_2$), 28.5 ($CH_2$), 26.4 ($CH_3$), 24.7 ($CH_3$), 22.9 ($CH_3$), 19.3 ($CH_2$); MS: *m/z* (%) 224 ($M^+$, $C_{14}H_{24}O_2$, 7), 155 (48), 123 (62), 109 (69), 107 (40), 95 (100), 82 (99).

**4-(1,2,2-Trimethylcyclopentyl)-4-pentenoic acid 12**. A magnetically stirred solution of the ester **29** (184 mg, 0.82 mmole) in methanol (3.4 mL) and 10% aqueous NaOH (3.4 mL, 8.5 mmoles) was refluxed for 10 hr. The reaction mixture was then cooled, acidified with 3N aqueous HCl (4 mL) and extracted with $CH_2Cl_2$ (3 × 6 mL). The $CH_2Cl_2$ extract was washed with brine and dried (anhyd. $Na_2SO_4$). Evaporation of the solvent furnished the acid **12** (170 mg, 99%) as oil. IR (neat): 3100, 1710, 1630, 893 $cm^{-1}$; $^1H$ NMR ($CDCl_3$ + $CCl_4$): δ 10.00 (1 H, br s), 4.90 (1 H, s), 4.78 (1 H, s), 2.60-2.30 (4 H, m), 2.30-2.10 (1 H, m), 1.70-1.40 (5 H, m), 1.03 (6 H, s), 0.79 (3 H, s); $^{13}C$ NMR ($CDCl_3$ + $CCl_4$): δ 180.0 (C), 153.5 (C), 109.3 ($CH_2$), 52.0 (C), 43.7 (C), 40.4 ($CH_2$), 36.9 ($CH_2$), 33.5 ($CH_2$), 28.2 ($CH_2$), 26.5 ($CH_3$), 24.8 ($CH_3$), 23.0 ($CH_3$), 19.3 ($CH_2$); MS: *m/z* (%) 210 ($M^+$, $C_{13}H_{22}O_2$, 4), 167 (20), 154 (27), 141 (43), 125 (33), 123 (35), 109 (45), 107 (40), 95 (100), 82 (69).

**(1*S**,5*S**)-5-[(1*S**)-1,2,2-Trimethylcyclopentyl]-bicyclo[3.1.0]hexan-2-one 11a and (1*R**,5*R**)-5-[(1*S**)-1, 2, 2-Trimethylcyclopentyl]bicyclo[3.1.0]-hexan-2-one 11b**. A solution of the acid **12** (630 mg, 3 mmoles) and oxalyl chloride (1.3 mL, 14.9 mmoles) in dry benzene (15 mL) was magnetically stirred for 2 hr at RT. Evaporation of the excess oxalyl chloride and solvent under reduced pressure furnished the acid chloride, which was taken in ether and added to an ethereal diazomethane solution (excess, prepared from 8 g of *N*-nitroso-*N*-methylurea and 70 mL of 60% aqueous KOH solution and 50 mL of ether) and the reaction mixture was stirred for 2 hr at RT. Solvent and the excess diazomethane were carefully evaporated on a water-bath. Rapid purification of the residue over a silica gel column using ethyl acetate-hexane (1:20 to 3:10) as eluent furnished the diazo ketone **30** (700 mg, 99% from the acid **12**) as yellow oil. [IR (neat): 2103, 1633, 893 $cm^{-1}$]. To a magnetically stirred, refluxing (by placing two 100 W tungsten lamps near the reaction flask) suspension of copper powder (1.54 g, 24.3 mmoles) and anhydrous copper sulfate (517 mg, 3.24 mmoles) in dry cyclohexane (120 mL) was added dropwise a solution of the diazo ketone **30** (700 mg, 2.99 mmoles) in dry cyclohexane (30 mL) over a period of 1 hr and refluxed for 5 hr. The reaction mixture was then cooled and copper and copper sulfate were filtered off using a sintered funnel. Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (0:1 to 1:10) as eluent furnished a 7:4 diastereomeric mixture of the tricyclic ketones **11a** and **11b** (463 mg, 75% from the acid **12**). Careful mixing of the first few fractions of the column furnished the minor ketone **11b** (117 mg), last few fractions furnished the major ketone **11a** (268 mg) and the middle fractions furnished a mixture of the two diastereomers **11a** and **11b** (78 mg). The two ketones **11a** and **11b** were purified by recrystallization from acetonitrile.

For the major ketone **11a**: m.p. 50°C; IR (thin film): 1720 $cm^{-1}$; $^1H$ NMR ($CDCl_3$ + $CCl_4$): δ 2.40-1.90 (4 H, m), 1.80-1.35 (7 H, m), 1.11 (1 H, d of d, *J* = 5.6 and 3.5 Hz), 1.05 (3 H, s), 1.04 (3 H, s), 1.02 (3 H, s), 0.97-0.85 (1 H, m);$^{13}C$ NMR ($CDCl_3$ + $CCl_4$): δ 214.1 (C), 46.9 (C), 44.7 (C), 41.0 ($CH_2$), 39.9 (C), 33.9 ($CH_2$), 33.3 ($CH_2$), 32.0 (CH), 26.2 ($CH_3$), 25.3 ($CH_2$), 25.1 ($CH_3$), 21.8 ($CH_3$), 20.2 ($CH_2$), 19.3 ($CH_2$); MS: *m/z* (%) 206 ($M^+$, $C_{14}H_{22}O$, 5), 191 (12), 136 (75), 123 (50), 121 (50), 119 (47), 109 (45), 107 (40), 95 (45), 94 (42), 93 (75), 79 (80), 69 (100).

For the minor ketone **11b**: m.p. 87°C; IR (thin film): 1720 $cm^{-1}$; $^1H$ NMR ($CDCl_3$ + $CCl_4$): δ 2.35-1.90 (4 H, m), 1.80-1.00 (8 H, m), 1.09 (3 H, s), 1.07 (3 H, s), 0.93 (3 H, s), 0.84 (1 H, d of d, *J* = 4.5 and 3.0 Hz); $^{13}C$ NMR ($CDCl_3$ + $CCl_4$): δ 213.9 (C), 46.7 (C), 44.4 (C), 42.5 ($CH_2$), 39.8 (C), 36.1 ($CH_2$), 34.9 (CH), 32.9 ($CH_2$), 26.5 ($CH_3$), 26.3 ($CH_3$), 25.0 ($CH_2$), 22.8 ($CH_3$), 18.9 ($CH_2$), 16.8 ($CH_2$); MS: *m/z* (%) 206 ($M^+$, $C_{14}H_{22}O$, 11), 191 (21), 149 (20), 137 (30), 136

(92), 123 (75), 121 (76), 109 (45), 107 (50), 96 (50), 95 (60), 94 (52), 93 (100).

**(1*R**,5*S**)-2-Methylene-5-[(1*S**)-1,2,2-trimethylcyclopentyl]bicyclo[3.1.0]hexane (β-microbiotene 9)**. To a magnetically stirred suspension of methyltriphenylphosphonium iodide (260 mg, 0.64 mmole) in dry benzene (2 mL) was added 1*M* solution of $K^+$ $^tAmO^-$ in $^tAmOH$ (0.6 mL, 0.6 mmole) and the resultant yellow coloured solution was stirred for 0.5 hr at RT. To the methylenetriphenylphosphorane thus formed, was added a benzene (1 mL) solution of the major ketone **11a** (20 mg, 0.097 mmoles) and stirred for 1 hr at RT. The reaction was quenched with saturated aqueous $NH_4Cl$ solution (2 mL) and extracted with ether (5 mL). The combined ether extract was washed with brine and dried (anhyd. $Na_2SO_4$). Evaporation of the solvent and purification of the residue over a silica gel column using hexane as eluent furnished β-microbiotene **9** (18 mg, 91%) as a colourless oil. IR (neat): 1650 $cm^{-1}$; $^1H$ NMR ($CDCl_3$ + $CCl_4$): δ 4.73 (1 H, s), 4.54 (1 H, s), 2.25-1.95 (3 H, m), 1.75-1.30 (7 H, m), 1.19 (1 H, d of d, *J* = 6.6 and 5.1 Hz), 0.99 (3 H, s), 0.97 (6 H, s), 0.90 (1 H, m), 0.63 (1 H, d of d, *J* = 5.1 and 4.2 Hz); $^{13}C$ NMR ($CDCl_3$ + $CCl_4$): δ 153.9 (C), 102.0 ($CH_2$), 47.2 (C), 44.9 (C), 41.2 ($CH_2$), 37.6 (C), 34.5 ($CH_2$), 29.7 ($CH_2$), 29.1 ($CH_2$), 28.9 (CH), 26.4 ($CH_3$), 25.2 ($CH_3$), 21.6 ($CH_3$), 19.5 ($CH_2$), 17.0 ($CH_2$); $^1H$ NMR ($C_6D_6$): δ 5.05 (1 H, br s), 4.84 (1 H, br s), 2.20-1.90 (3 H, m), 1.75-1.35 (7 H, m), 1.14 (1 H, d of d, *J* = 8.0 and 6.5 Hz), 1.02 (3 H, s), 0.98 (3 H, s), 0.97 (3 H, s), 0.90-0.80 (1 H, m), 0.61 (1 H, d of d, *J* = 5.1 and 4.1 Hz); $^{13}C$ NMR ($C_6D_6$): δ 154.0 (C), 102.1 ($CH_2$), 47.3 (C), 44.9 (C), 41.4 ($CH_2$), 37.6 (C), 34.6 ($CH_2$), 29.9 ($CH_2$), 29.24 ($CH_2$), 29.19 (CH), 26.3 ($CH_3$), 25.2 ($CH_3$), 21.4 ($CH_3$), 19.7 ($CH_2$), 17.0 ($CH_2$); MS: *m/z* (%) 204 ($M^+$, $C_{15}H_{24}$, 5), 189 (6), 119 (20), 111 (100, $C_5H_6Me_3$), 93 (40, M - $C_5H_6Me_3$), 69 (88).

**(1*S**,5*R**)-2-Methylene-5-[(1*S**)-1,2,2-trimethylcyclopentyl]bicyclo[3.1.0]hexane(5-*epi*-β-microbiotene 9a)**. Wittig reaction of the minor ketone **11b** (21 mg, 0.10 mmole) with methyltriphenylphosphonium iodide (252 mg, 0.62 mmole) and 1*M* solution of $K^+$ $^tAmO^-$ in $^tAmOH$ (0.6 mL, 0.6 mmole) in dry benzene (3 mL) for 2 hr at RT followed by purification, as described for β-microbiotene, furnished 5-*epi*-β-microbiotene **9a** (18 mg, 87%) as a colourless oil. IR (neat): 1650 $cm^{-1}$; $^1H$ NMR ($CDCl_3$ + $CCl_4$): δ 4.76 (1 H, s), 4.58 (1 H, s), 2.20-1.90 (3 H, m), 1.84 (1 H, d of d, *J* = 8.2 and 3.5 Hz), 1.80-1.10 (6 H, m), 1.05 (3 H, s), 1.02 (3 H, s), 0.97 (1 H, d of d, *J* = 7.2 and 6.6 Hz), 0.89 (3 H, s), 0.60 (1 H, d of d, *J* = 8.2 and 4.5 Hz), 0.46 (1 H, d of d, *J* = 4.5 and 3.6 Hz); $^{13}C$ NMR ($CDCl_3$ + $CCl_4$): δ 153.4 (C), 102.4 ($CH_2$), 47.0 (C), 44.7 (C), 42.8 ($CH_2$), 38.6 (C), 36.5 ($CH_2$), 31.4 (CH), 28.72 ($CH_2$), 28.7 ($CH_2$), 26.6 ($CH_3$), 26.0 ($CH_3$), 23.4 ($CH_3$), 19.0 ($CH_2$), 13.7 ($CH_2$); MS: *m/z* (%) 204 ($M^+$, $C_{15}H_{24}$, 5), 189 (8), 119 (22), 111 (100), 93 (38), 69 (89).

**(1*S**,2*R**,5*S**)-2-Methyl-5-[(1*S**)-1,2,2-trimethylcyclopentyl]bicyclo[3.1.0]hexan-2-ol (microbiotol 7)**. To a magnetically stirred, ice-cold solution of the major ketone **11a** (12 mg, 0.057 mmoles) in dry ether (2 mL) was added dropwise a solution of methylmagnesium iodide in ether (1 mL, 0.9 mmole) [prepared from magnesium (240 mg, 10 mmoles) and methyl iodide (0.62 mL, 10 mmoles) in dry ether (11 mL)] and stirred for 3 hr at the same temperature. The reaction mixture was then quenched with saturated aqueous $NH_4Cl$ solution (2 mL) and extracted with ether (3 × 4 mL). The combined ether extract was washed with brine and dried (anhyd. $Na_2SO_4$). Evaporation of the solvent and purification of the residue over a silica gel column using $CH_2Cl_2$-hexane (1:5 to 1:1) as eluent furnished microbiotol **7** (12 mg, 95%) as a white solid, which was purified by recrystallization from acetonitrile. m.p. 103°C (Lit.[7] 116-17°C); IR (KBr): 3297 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.90 (1 H, d of t, *J* = 12.0 and 9.0 Hz), 1.80-1.25 (9 H, m), 1.32 (3 H, s), 1.15-0.80 (3 H, m), 0.98 (3 H, s), 0.98 (3 H, s), 0.97 (3 H, s), 0.60 (1 H, d of d, *J* = 10.5 and 9.0 Hz); $^{13}C$ NMR ($CDCl_3$): δ 79.2 (C), 46.5 (C), 44.5 (C), 41.1 ($CH_2$), 36.8 ($CH_2$), 34.5 ($CH_2$), 33.3 (C), 31.9 (CH), 28.0 ($CH_3$), 27.8 ($CH_2$), 26.1 ($CH_3$), 25.0 ($CH_3$), 21.3 ($CH_3$), 19.3 ($CH_2$), 11.3 ($CH_2$); $^1H$ NMR ($CD_3OD$): δ 2.05-1.85 (1 H, m), 1.75-1.30 (9 H, m), 1.28 (3 H, s), 1.01 (3 H, s), 0.98 (6 H, s), 1.00-0.80 (3 H, m), 0.66 (1 H, d of d, *J* = 5.4 and 3.6 Hz); $^{13}C$ NMR ($CD_3OD$): δ 79.7 (C), 47.7 (C), 45.7 (C), 42.2 ($CH_2$), 37.1 ($CH_2$), 35.7 ($CH_2$), 34.1 (C), 32.6 (CH), 28.8 ($CH_2$), 28.7 ($CH_3$), 26.7 ($CH_3$), 25.6 ($CH_3$), 21.9 ($CH_3$), 20.3 ($CH_2$), 12.5 ($CH_2$); MS: *m/z* (%) 207 (22, $M^+$ - Me, $C_{14}H_{23}O$), 189 (20), 161 (20), 151 (21), 137 (25), 133 (35), 121 (45), 119 (47), 111 (100), 109 (80), 107 (42), 95 (58), 94 (60), 93 (73).

**(1*R**,2*S**,5*R**)-2-Methyl-5-[(1*S**)-1,2,2-trimethylcyclopentyl]bicyclo[3.1.0]hexan-2-ol (5-*epi*microbiotol 7a)**. Grignard reaction of the minor ketone **11b** (20 mg, 0.097 mmoles) in dry ether (3.5 mL) with methylmagnesium iodide in ether (1 mL, 1 mmoles)

for 3 hr at 0°C and purification, as described in the previous reaction, furnished 5-*epi*-microbiotol **7a** (17 mg, 78%) as a white solid. m.p. 85°C. IR (KBr): 3302 $cm^{-1}$; $^1H$ NMR ($CDCl_3$ + $CCl_4$): δ 2.00-1.70 (2 H, m), 1.65-0.95 (10 H, m), 1.37 (3 H, s), 1.01 (3 H, s), 1.00 (3 H, s), 0.91 (3 H, s), 0.46 (1 H, d of d, *J* = 5.0 and 3.5 Hz), 0.38 (1 H, d of d of d, *J* = 7.5, 5.0 and 1.0 Hz); $^{13}C$ NMR ($CDCl_3$ + $CCl_4$): δ 79.1 (C), 46.9 (C), 44.6 (C), 42.5 ($CH_2$), 36.6 ($CH_2$), 36.5 ($CH_2$), 35.0 (C), 34.0 (CH), 28.4 ($CH_2$), 28.3 ($CH_3$), 26.3 ($CH_3$), 25.8 ($CH_3$), 22.9 ($CH_3$), 19.2 ($CH_2$), 9.0 ($CH_2$); MS: *m/z* (%) 222 ($M^+$, $C_{15}H_{26}O$, 1), 207 (20), 189 (15), 151 (22), 137 (28), 123 (35), 121 (39), 119 (35), 111 (100), 109 (54), 103 (40), 95 (58), 94 (70), 93 (70).

**(1*S**,2*S**,5*S**)-2-Methyl-5-[(1*S**)-1,2,2-trimethylcyclopentyl]bicyclo[3.1.0]hexan-2-ol (cyclocuparanol 2) and (1*S**,2*R**,5*S**)-2-methyl-5-[(1*S**)-1,2,2-trimethylcyclopentyl]bicyclo[3.1.0]hexan-2-ol (microbiotol 7)**. To a magnetically stirred ice-cold solution of the major ketone **11a** (21 mg, 0.10 mmole) in dry ether (3 mL) was added a solution of MeLi (1.3 M in ether, 0.47 mL, 0.61 mmole) and stirred for 2 hr at the same temperature. The reaction mixture was quenched with saturated aqueous $NH_4Cl$ solution (3 mL) and extracted with ether (2×5 mL). The combined ether extract was washed with brine and dried (anhyd. $Na_2SO_4$). Evaporation of the solvent and purification of the residue over a silica gel column using $CH_2Cl_2$-hexane (1:5 to 1:1) as eluent first furnished cyclocuparanol **2** (9 mg, 40%) as an oil. IR (neat): 3380 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 2.20-2.00 (1H, m), 1.80-0.85 (12 H, m), 1.30 (3 H, s), 1.05 (3 H, s), 1.00 (3 H, s), 0.95 (3 H, s), 0.20 (1 H, d of d, *J* = 5.1 and 3.6 Hz); $^{13}C$ NMR ($CDCl_3$): δ 80.2, 46.3, 44.6, 41.0, 37.5, 34.6, 34.5, 32.9, 27.7, 26.1, 24.9, 24.7, 21.7, 19.3, 13.9; MS: *m/z* (%) 222 ($M^+$, $C_{15}H_{26}O$, 3), 207 (20), 189 (14), 161 (20), 151 (31), 137 (32), 133 (25), 123 (40), 121 (48), 119 (45), 111 (100), 109 (93), 107 (55), 95 (76), 94 (76). Further elution of the column with the same solvent furnished microbiotol **7** (13 mg, 58%).

**(1*R**,2*R**,5*R**)-2-Methyl-5-[(1*S**)-1,2,2-trimethylcyclopentyl]bicyclo[3.1.0]hexan-2-ol (5-*epi*cyclocuparanol 2a) and (1*R**,2*S**,5*R**)-2-methyl-5-[(1*S**)-1, 2, 2-trimethylcyclopentyl]bicyclo[3.1.0]-hexan-2-ol (5-*epi*microbiotol 7a)**. Reaction of the minor ketone **11b** (23 mg, 0.11 mmole) in dry ether (3 mL) with a solution of MeLi (1.4 *M* in ether, 0.4 mL, 0.56 mmole) for 2 hr, as described in the previous reaction, followed by purification over a silica gel column using $CH_2Cl_2$-hexane (1:1) as eluent furnished 5-*epi*-cyclocuparanol **2a** (10 mg, 40%) as colourless oil. IR (neat): 3380, 910 $cm^{-1}$; $^1H$ NMR ($CDCl_3$ + $CCl_4$): δ 2.20-2.00 (1 H, m), 1.75-1.60 (2 H, m), 1.60-1.35 (7 H, m), 1.28 (3 H, s), 1.30-1.10 (2 H, m), 1.07 (3 H, s), 1.06 (3 H, s), 0.95 (3 H, s), 0.37 (1 H, d of d of d, *J* = 8.4, 5.1 and 1.2 Hz), 0.01 (1 H, d of d, *J* = 5.1 and 3.6 Hz); $^{13}C$ NMR ($CDCl_3$ + $CCl_4$): δ 80.6 (C), 46.7 (C), 44.6 (C), 42.7 ($CH_2$), 36.6 ($CH_2$), 36.5 ($CH_2$), 36.0 (C), 34.6 (CH), 28.0 ($CH_2$), 26.3 ($CH_3$), 26.2 ($CH_3$), 25.6 ($CH_3$), 23.4 ($CH_3$), 19.1 ($CH_2$), 11.2 ($CH_2$); MS: *m/z* (%) 222 ($M^+$, $C_{15}H_{26}O$, 3), 207 (16), 205 (13), 151 (30), 137 (27), 133 (23), 123 (30), 121 (44), 119 (47), 111 (100), 109 (50), 107 (40), 95 (60), 94 (73), 93 (75). Further elution of the column with the same solvent furnished 5-*epi*-microbiotol **7a** (15 mg, 60%).

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