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First Total Synthesis of (±)-β-Microbiotene, (±)-Microbiotol and (±)-Cyclocuparenol

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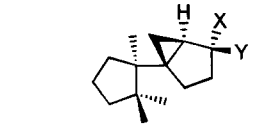
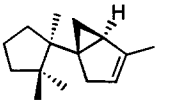
Abstract: First total syntheses of cyclocuparanes mentioned in the title have been achieved starting from Hagemann's ester *via* the bicyclo[4.3.1]nonanedione **8**.

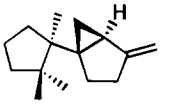
Cyclocuparane sesquiterpenes contain a unique carbon framework, 4-methyl-1-(1,2,2-trimethylcyclopentyl)bicyclo[3.1.0]hexane incorporating three vicinal quaternary carbon atoms. Isolation of the first member of this class of sesquiterpenes, cyclocuparenol **1** (originally referred to as cyclopropane cuparenol) was reported by Asakawa and co-workers in 1984 from the liverwort *Marchantia polymorpha*, and later from the liverwort *Cryptothallus mirabilis*.[1] The structure of microbiotol **2**, isolated in 1981 from the needles of *Microbiota decussata*, was established as the epimer of cyclocuparenol **1** in 1991 by Tkachev and co workers.[2] Recently,[3] Konig and co-workers have reported the isolation of the hydrocarbons α-microbiotene **3** and β-microbiotene **4** from the liverwort *Mannia fragrans*. The presence of three contiguous quaternary carbon atoms and an interesting carbon framework make cyclocuparanes attractive synthetic targets. Herein we report the first total synthesis of (±)-β-microbiotene (**4**), (±)-microbiotol (**2**) and (±)-cyclocuparenol (**1**) starting from Hagemann's ester **5**.



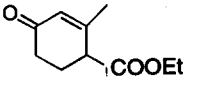
X=OH, Y=Me Cyclocuparenol (**1**)
X=Me, Y=OH Microbiotol (**2**)



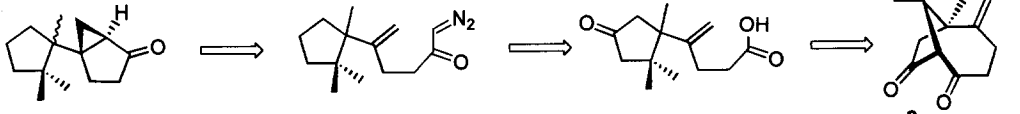
α–Microbiotene (**3**)



β–Microbiotene (**4**)

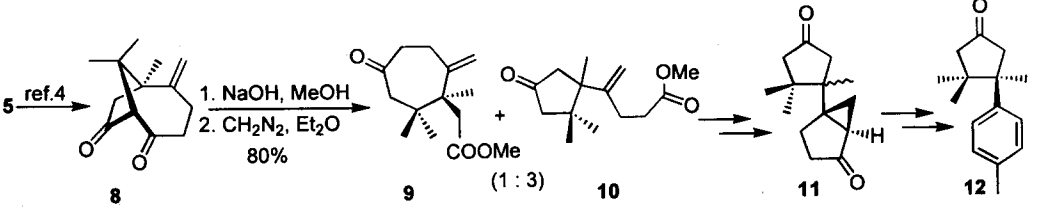


5



7 **6** **8**

An intramolecular diazo ketone cyclopropanation reaction based methodology was conceived for the generation of the bicyclo[3.1.0]hexane system. We have envisaged that intramolecular cyclopropanation of the diazo ketone **6** generates the bicyclo[3.1.0]hexanone **7**, which could serve as a precursor for the target molecules. Recently,[4] we have developed a convenient procedure for the generation of the bicyclo[4.2.1]nonane-2,8-dione **8** starting from Hagemann's ester **5** employing an acid catalysed, highly regioselective intramolecular diazo ketone insertion reaction. We have contemplated that retro Claisen condensation of the bicyclo[4.2.1]nonane-2,8-dione **8** could lead to a keto acid which could be transformed into the diazo ketone **6**. Thus, regioselective cleavage of the dione **8** with sodium hydroxide in methanol followed by esterification of the resulting keto acids with ethereal diazomethane furnished a 1:3 mixture of the keto esters **9** and **10** which were separated by silica gel column



8 **9** (1 : 3) **10** **11** **12**

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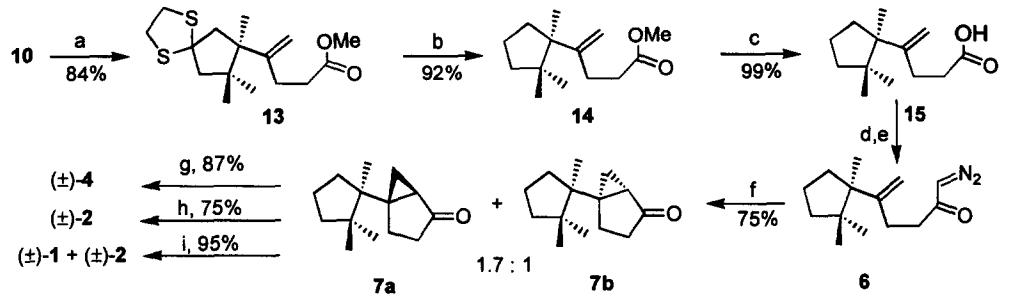
PII: S0040-4039(99)01342-8



***Scheme 1:* Reagents and Conditions**: *(a) $(CH_2SH)_2$, $BF_3.Et_2O$, C_6H_6, 0 °C, 0.15h; (b) Raney Ni, EtOH, reflux, 3h; (c) 5% NaOH, THF-H_2O, reflux, 12h; (d) $(COCl)_2$, C_6H_6, rt, 2h; (e) CH_2N_2, Et_2O, 0 °C, 2h; (f) Cu-$CuSO_4$, c-C_6H_{12}, reflux, W-lamp, 5h; (g) $Ph_3P^+Me\ I^-$, NaOAm^t, C_6H_6, rt, 2h; (h) MeMgI, Et_2O, 3h; (i) MeLi, Et_2O, 0 °C, 3h.*

chromatography. First, as a model study, the keto ester **10** was transformed into norcyclocuparenedione **11** and β-cuparenone[5] **12**, and the methodology was extended to cyclocuparanes *via* the diazo ketone **6**, Scheme 1. Thus, reaction of the keto ester **10** with 1,2-ethanedithiol and boron trifluoride etherate furnished the thioketal **13**, which on desulfurisation with Raney nickel in refluxing ethanol furnished the ester **14**. Base catalysed hydrolysis of the ester **14** generated the acid **15**, which was transformed into the diazo ketone **6** *via* the corresponding acid chloride. Anhydrous copper sulfate-copper catalysed intramolecular cyclopropanation of the diazo ketone **6** in refluxing cyclohexane furnished, as expected, a 1.7:1 mixture of the norcyclocuparanones **7a** and **7b**, which were separated by silica gel column chromatography. The stereostructures of the ketones **7a** and **7b** were tentatively assigned from their spectral data,[6] and were confirmed by the conversion of **7a** into cyclocuparenes. Wittig methylenation of the ketone **7a** furnished (±)-β-microbiotene **4**, which exhibited the ^1H NMR in C_6D_6 and mass spectra identical to those of the natural compound.[3] Reaction of the ketone **7a** with an excess of methylmagnesium iodide generated (±)-microbiotol **2**, mp. 103 °C, in a highly stereoselective manner *via* the approach of the methyl group from the less hindered *exo* face. The synthetic microbiotol **2** exhibited the ^1H and ^{13}C NMR spectra in CD_3OD identical to those of the natural compound.[2] Whereas reaction of the ketone **7a** with an excess of methyllithium furnished a 1.5:1 mixture of (±)-microbiotol **2** and (±)-cyclocuparenol **1**, which were separated by silica gel column chromatography. The synthetic (±)-cyclocuparenol **1** has also exhibited the ^1H NMR and mass spectra identical to that of the natural compound.[1] In an analogous manner, the same set of reactions on the epimeric ketone **7b** furnished (±)-epi-β-microbiotene, (±)-epimicrobiotol and (±)-epicyclocuparenol.

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References and Notes

1. Asakawa, Y.; Toyota, M.; Bischler, H.; Campbell, E. O.; Hattori, S. *J. Hattori Bot. Lab.* **1984**, *57*, 383; Asakawa, Y.; Tori, M.; Masuya, T.; Grahm, J.-P. *Phytochemistry* **1990**, *29*, 1577; Rycroft, D. S.; Cole, W. J. *J. Chem. Res.(S)* **1998**, 600.
2. Raldugin, V. A.; Storozhenko, V. G.; Resvukhin, A. I.; Pentegova, V. A.; Gorovoj, P. G.; Baranov, V. I. *Khim. Prir. Soedin.* **1981**, 163; Tkachev, A. V.; Shakirov, M. M.; Raldugin, V. A. *J. Nat. Prod.* **1991**, *54*, 849.
3. Melching, S.; Blume, A.; Konig, W. A.; Muhle, H. *Phytochemistry* **1998**, *48*, 661.
4. Srikrishna, A.; Ramachary, D. B. *Tetrahedron Lett.* **1999**, *40*, 1605.
5. Chetty, G. L.; Dev, S. *Tetrahedron Lett.* **1964**, 73; Srikrishna, A.; Krishnan, K. *Tetrahedron* **1992**, *48, 3429.*
6. All the compounds exhibited spectral data consistent with their structures. IR and NMR spectral data for the norcyclocuparenone **7a**: IR (neat): ν_{max}/cm^{-1} 1720. ^1H NMR (300 MHz, $CDCl_3$): δ 2.40-1.95 (4 H, m), 1.80-1.35 (7 H, m), 1.11 (1 H, dd, *J* 5.3 and 3.6 Hz), 1.05 (3 H, s), 1.03 (3 H, s), 1.02 (3 H, s), 0.95-0.8 (1 H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 215.5 (C), 46.9 (C), 44.6 (C), 40.9 (CH_2), 40.2 (C), 33.8 (CH_2), 33.5 (CH_2), 32.2 (CH), 26.0 (CH_3), 25.3 (CH_2), 25.0 (CH_3), 21.7 (CH_3), 20.4 (CH_2), 19.1 (CH_2). For the norepicyclocuparenone **7b**: IR (neat): ν_{max}/cm^{-1} 1715. ^1H NMR (300 MHz, $CDCl_3$): δ 2.30-1.85 (4 H, m), 1.80-1.00 (8 H, m), 1.09 (3 H, s), 1.06 (3 H, s), 0.92 (3 H, s), 0.82 (1 H, dd, *J* 4.7 and 3.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 213.5 (C), 46.7 (C), 44.4 (C), 42.5 (CH_2), 39.7 (C), 36.1 (CH_2), 34.7 (CH), 32.8 (CH_2), 26.5 (CH_3), 26.2 (CH_3), 24.9 (CH_2), 22.8 (CH_3), 18.9 (CH_2), 16.7 (CH_2).