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The first enantioselective synthesis of (−)-microbiotol and (+)-β-microbiotene

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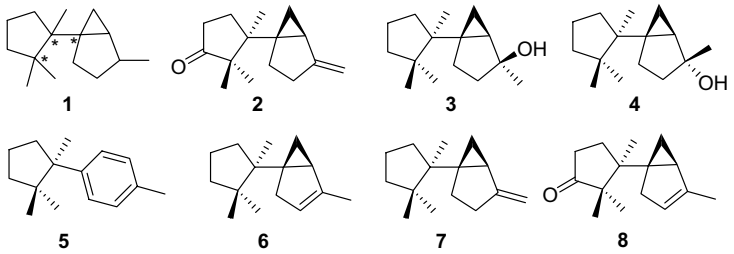
Abstract—The first enantioselective total synthesis of (−)-microbiotol and (+)-β-microbiotene, sesquiterpenes containing three neighboring quaternary carbon atoms belonging to the cyclocuparane group, starting from cyclogeraniol employing a Sharpless–Katsuki asymmetric epoxidation, a boron trifluoride etherate mediated epoxide rearrangement and an intramolecular diazo ketone cyclopropanation as key steps, is described.

1. Introduction

The cyclocuparane group is a small class of tricyclic sesquiterpenes, containing a 4-methyl-1-(1,2,2-trimethylcyclopentyl)bicyclo[3.1.0]hexane **1** carbon framework comprising of three contiguous quaternary carbon atoms. Even though the first two members of this class of sesquiterpenes, grimaldone **2** and microbiotol **3** were isolated in 1975 and 1981, their structures were only elucidated in 1988 and 1991, respectively.[1,2] Isolation of cyclocuparanol **4** was first reported in 1984 by Asakawa et al.[3] from *Marchantia polymorpha* and *Marchantia paleacea* Bertol. var *diptera* (Mont) Hatt., and was the first one to be established to contain the cyclocuparane carbon framework. Isolation of microbiotol **3** was first reported by Raldugin et al. in 1981, from the ether extract of the needles of *Microbiota decussata*, an evergreen bush, which grows on the Sikhote–Alin mountain ridge, while the structure was established by Trachev et al.[2] in 1991 on the basis of spectral data and molecular mechanics calculations in conjunction with conformational analysis by NMR. The absolute configuration of microbiotol **3** was established via its chemical transformation to (*R*)-cuparene (+)-**5**. It is worth noting that microbiotol **3**, isolated from the plant source is antipodal to cyclocuparanol **4** and grimaldone **2**, isolated from the liverworts. In 1998, Konig et al.[4] reported the isolation of three more cyclocuparane sesquiterpenes, α-microbiotene **6**, β-microbiotene **7**, and isogrimaldone **8**, in addition to grimaldone **2** from the essential oil of *Mannia fragrance*. The presence of a 1,2,2-trimethylcyclopentyl substituted bicyclo[3.1.0]-hexane carbon framework containing three contiguous quaternary carbon atoms made the cyclocuparanes challenging synthetic targets.[5] Herein, we report the first enantioselective total synthesis of (−)-microbiotol **3** and (+)-β-microbiotene **7**.



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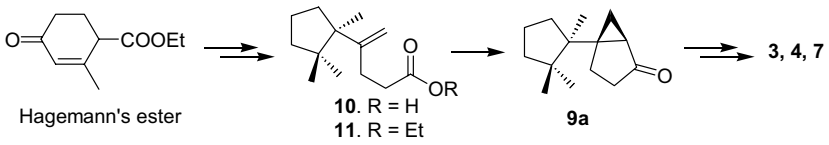
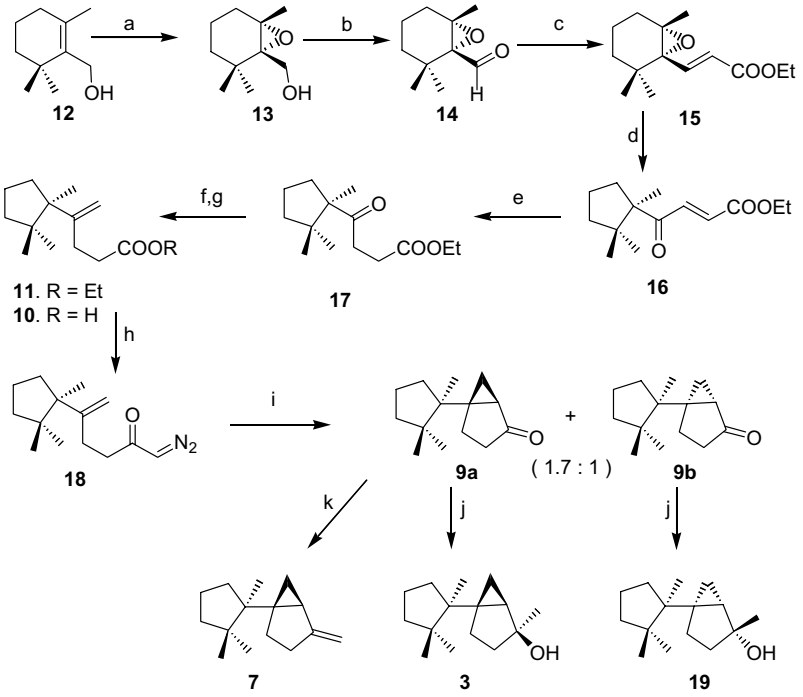


2. Results and discussion

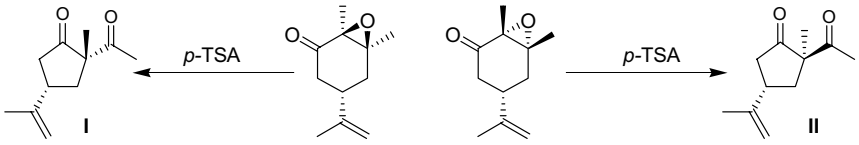
Recently, we have reported[5b] the synthesis of racemic cyclocuparanes **3**, **4**, and **7** by employing the tricyclic ketone **9a** as the key precursor, which was obtained from Hagemann's ester via intramolecular cyclopropanation of the diazo ketone derived from acid **10**. Hence, a methodology was conceived for the enantioselective generation of ester **11** starting from the readily available cyclogeraniol **12**.

The sequence is depicted in Scheme 1. Katsuki–Sharpless asymmetric epoxidation of cyclogeraniol **12** using (+)-diethyl tartrate following the reported procedure[6] generated the (1*S*,6*S*)-epoxide (−)-**13**, $[\alpha]_D^{25} = -26.5$ (*c* 1.1, $CHCl_3$), with an enantiomeric excess of 95%. Oxidation of the primary alcohol in **13** with phosphorus pentoxide–dimethyl sulfoxide and triethylamine[7] furnished the epoxyaldehyde **14**, $[\alpha]_D^{25} = +48.3$ (*c* 1.5, $CHCl_3$), in 48% yield. Horner–Wadsworth–Emmons reaction with triethyl phosphonoacetate and sodium hydride transformed aldehyde **14** into the epoxy propenoate **15** in 77% yield, whose structure was established from its spectral data.[11] For the ring contraction of the six-membered ring in **15**, a Lewis acid mediated rearrangement of epoxide was adopted. Thus, treatment of epoxy ester **15** with boron trifluoride etherate in methylene chloride at −70 °C for 1 h cleanly furnished ketoester **16** in 90% yield.[11] The configuration of the stereogenic center in **16** was assigned as *R* in analogy to the rearrangement of epoxides derived from β-methylcarvone,[8] and finally confirmed by its conversion to (−)-microbiotol **3**. However, the enantiopurity of **16** has been slightly reduced (87%)[9] in comparison to geraniol epoxide **13** as the reaction is not stereospecific and the intermediacy of a carbonium ion in the rearrangement. Hydrogenation of the olefin in ketoester **16** with 10% palladium over carbon as the catalyst in ethanol furnished keto ester **17** in a quantitative yield.[11] Since a conventional Wittig reaction was not successful, ketoester **17** was converted into pentenoate **11** employing the procedure developed by Lombardo.[10] Thus, reaction of ketoester **17** with the reagent prepared from methylene bromide, zinc, and titanium tetrachloride furnished pentenoate **11** in 60% yield.[11] Pentenoate **11** was transformed into microbiotol and β-microbiotene by employing a previously reported[5b] sequence. Thus, hydrolysis of ester **11** with 5% sodium hydroxide in 1:1 methanol–water furnished acid **10**, which was converted into diazo ketone **18** via the corresponding acid chloride. Anhydrous copper sulfate–copper catalyzed intramolecular cyclopropanation of diazo ketone **18** furnished a 1.7:1 mixture of norcyclocuparanones **9a**, $[\alpha]_D^{25} = -25$ (*c* 0.4, $CHCl_3$) and **9b**, $[\alpha]_D^{25} = -11.4$ (*c* 0.7, $CHCl_3$), which were separated by



Scheme 1. Reagents, conditions, and yields: (a) Ref. 6; (b) DMSO, P_2O_5, 0 °C, 30 min; Et_3N, 1 h; 48%; (c) $(EtO)_2P(O)CH_2COOEt$, NaH, THF, 8 h, 77%; (d) $BF_3{\cdot}Et_2O$, CH_2Cl_2, −70 °C, 1 h, 90%; (e) H_2 (1 atm), 10% Pd/C, EtOH, 12 h, 99%; (f) $TiCl_4$, CH_2Br_2, Zn, CH_2Cl_2, 0 °C, 1 h, 60%; (g) 5% NaOH, H_2O–MeOH (1:1), reflux, 12 h; (h) $(COCl)_2$, C_6H_6, rt, 2 h; CH_2N_2, Et_2O, 0 °C, 2 h; (i) $CuSO_4$, Cu, *c*-C_6H_{12}, reflux, W-lamp, 5 h, 75%, **11**; (j) MeMgI, Et_2O, 0 °C, 2 h, 75%; (k) $Ph_3P^+CH_3I^-$, NaO^{t}Am, C_6H_6, rt, 2 h, 75%.

silica gel column chromatography. Structures of norketones **9a** and **9b** were established by comparison of the



spectral data with the racemic compounds.[5b] Wittig methylenation of ketone **9a** furnished β-microbiotene **7**, $[\alpha]_D^{25} = +7.4$ (*c* 0.4, $CHCl_3$). On the other hand, addition of methylmagnesium iodide transformed tricyclic ketone **9a** into (−)-microbiotol **3**, $[\alpha]_D^{25} = -11.4$ (*c* 0.8, $CHCl_3$), lit.[2] $[\alpha]_D^{25} = -13$ (*c* 3.08, $CHCl_3$). In a similar manner, addition of methylmagnesium iodide to the tricyclic ketone **9b** furnished epimicrobiotol **19**, $[\alpha]_D^{25} = -24$ (*c* 0.5, $CHCl_3$).

3. Conclusion

In conclusion, we have accomplished the first enantioselective total synthesis of microbiotol **3** and β-microbiotene **7**, cyclocuparane sesquiterpenes containing three contiguous quaternary carbon atoms, employing a Katsuki–Sharpless asymmetric epoxidation of cyclogeraniol, a Lewis acid catalyzed epoxide rearrangement and an intramolecular cyclopropanation of a diazo ketone as key steps.

Acknowledgements

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8. Reaction of the *anti*- and *syn*-epoxides of β-methylcarvone with *p*-toluenesulfonic acid generated diketones **I** and **II**, respectively, in a highly stereoselective manner (structures of **I** and **II** were confirmed via X-ray crystal analysis of a derivative). Srikrishna, A.; Ramasastry, S. S. V. Unpublished results.
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11. Yields refer to the isolated and chromatographically pure compounds. All the compounds exhibited spectral data (IR, ^1H and ^{13}C NMR, and mass) consistent with their structures. Selected spectral data for ethyl *E*-3-(2,2,6-trimethyl-7-oxabicyclo[4.1.0]heptan-1-yl)prop-2-enoate **15**: $[\alpha]_D^{25} = +86.5$ (*c* 2, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1721, 1653. ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 7.10 (1H, d, *J* 15.6 Hz), 5.95 (1H, d, *J* 15.6 Hz), 4.17 (2H, q, *J* 7.2 Hz), 2.10–1.80 (1H, m), 1.73 (1H, t of d, *J* 15.0 and 5.7 Hz), 1.55–1.35 (3H, m), 1.31 (3H, t, *J* 7.2 Hz), 1.53 (6H, s), 1.13–1.10 (1H, m), 0.94 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 165.7 (C), 144.0 (CH), 124.5 (CH), 70.3 (C), 65.3 (C), 60.1 (CH_2), 35.8 (CH_2), 33.6 (C), 30.0 (CH_2), 26.0 (CH_3), 26.1 (CH_3), 20.9 (CH_3), 17.1 (CH_2), 14.5 (CH_3). HRMS: *m/z* Calcd for $C_{14}H_{22}O_3Na$ (M+Na): 261.1467. Found: 261.1466. For ethyl *E*-4-oxo-4-(1,2,2-trimethylcyclopentyl)but-2-enoate **16**: $[\alpha]_D^{25} = -1.3$ (*c* 1.5, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1725, 1689, 1631. ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 7.38 (1H, d, *J* 15.5 Hz), 6.65 (1H, d, *J* 15.5 Hz), 4.25 (2H, q, *J* 6.9 Hz), 2.52–2.38 (1H, m), 1.85–1.60 (3H, m), 1.60–1.40 (2H, m), 1.34 (3H, t, *J* 6.9 Hz), 1.20 (3H, s), 1.10 (3H, s), 0.86 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 202.8 (C), 165.5 (C), 137.6 (CH), 130.4 (CH), 61.1 (CH_2), 59.2 (C), 44.4 (C), 40.6 (CH_2), 34.4 (CH_2), 25.5 (CH_3), 24.7 (CH_3), 20.3 (CH_3), 19.8 (CH_2), 14.3 (CH_3). Mass: *m/z* ($C_{14}H_{22}O_3$) 238 (M^+, 3), 193 (9), 169 (10), 128 (62), 111 (66). For ethyl 4-oxo-4-(1,2,2-trimethylcyclopentyl)butanoate **17**: $[\alpha]_D^{25} = -23.1$ (*c* 1.3, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1736, 1699. ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 4.04 (2H, q, *J* 7.2 Hz), 2.80–2.50 (2H, m), 2.50–2.25 (3H, m), 1.80–1.30 (5H, m), 1.20 (3H, t, *J* 7.2 Hz), 1.08 (3H, s), 1.02 (3H, s), 0.78 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 212. 2 (C), 172.4 (C), 60.2 (CH_2), 59.2 (C), 44.3 (C), 40.2 (CH_2), 35.3 (CH_2), 34.7 (CH_2), 28.0 (CH_2), 25.6 (CH_3), 24.5 (CH_3), 21.0 (CH_3), 19.7 (CH_2), 14.4 (CH_3). Mass: *m/z* 195 (M^+−OEt, 12), 171 (9), 151 (8), 131 (20), 129 (30), 125 (75), 111 (80). HRMS: *m/z* Calcd for $C_{14}H_{24}O_3Na$ (M+Na): 263.1623. Found: 263.1620. For ethyl 4-(1,2,2-trimethylcyclopentyl)pent-4-enoate **11**: $[\alpha]_D^{25} = -18.6$ (*c* 0.7, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1738, 1631, 891. ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 4.88 (1H, s), 4.75 (1H, s), 4.12 (2H, q, *J* 7.2 Hz), 2.50–2.30 (4H, m), 2.30–2.10 (1H, m), 1.75–1.55 (4H, m), 1.55–1.40 (1H, m), 1.26 (3H, t, *J* 7.2 Hz), 1.04 (6H, s), 0.80 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 173.1 (C), 153.7 (C), 109.1 (CH_2), 60.2 (CH_2), 51.9 (C), 43.7 (C), 40.4 (CH_2), 36.9 (CH_2), 33.6 (CH_2), 28.5 (CH_2), 26.5 (CH_3), 24.8 (CH_3), 23.0 (CH_3), 19.3 (CH_2), 14.4 (CH_3). Mass: *m/z* 238 (M^+, 5), 182 (14), 169 (22), 149 (15), 137 (20), 123 (63), 109 (66), 95 (100). HRMS: *m/z* Calcd for $C_{15}H_{26}O_2Na$ (M+Na): 261.1830. Found: 261.1832.