COMMUNICATION

A short and efficient regioselective approach to the C-6 to C-19 segment of bifurcaranes and a formal total synthesis of β-microbiotene, microbiotol and cyclocuparanol

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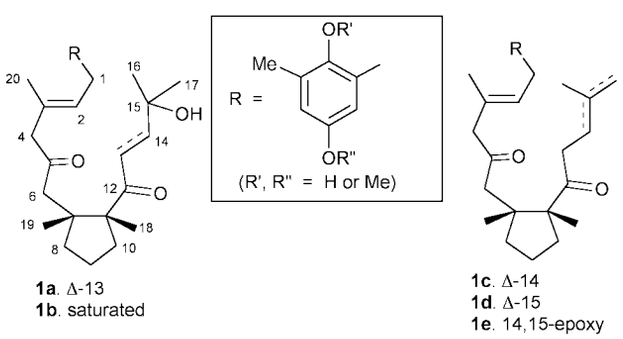
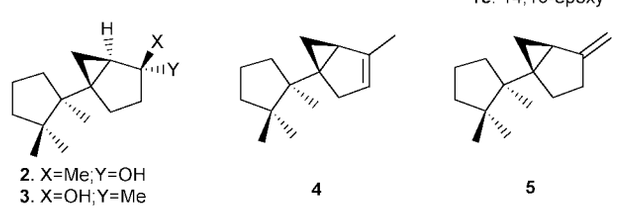
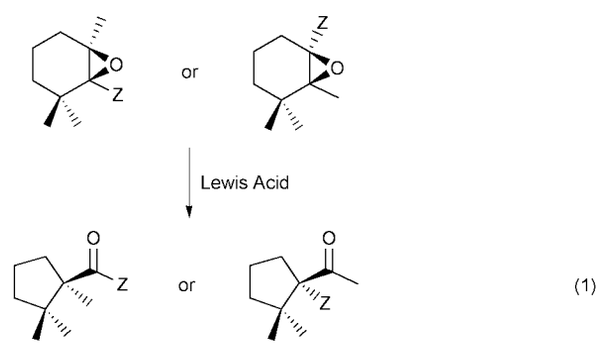
Employing an epoxide rearrangement based ring contraction reaction, a short and efficient regioselective approach to the C-6 to C-19 segment of the toluquinol substituted diterpenes bifurcaranes, and its extension to a formal total synthesis of the sesquiterpenes (±)-β-microbiotene, (±)-microbiotol and (±)-cyclocuparanol are described.

Bifurcaranes (**1a**–**e**) are a small group of methylhydroquinone-substituted monocyclic diterpenes consisting of a cyclopentane ring containing two vicinal quaternary carbon atoms. The first member of this class, bifurcarenone **1a** (R′ = R″ = H) was isolated[1a] from the brown alga *Bifurcaria galapagensis* and found to inhibit the mitotic cell division in the urchin *Strongylocentrotus purpuratus*. Subsequently, bifurcarenone **1a** and its analogues as well as those derived from an intramolecular aldol condensation reaction were isolated from a variety of brown alga belonging to the genus *Cystoseira*.[1] Bifurcaranes were found to exhibit antifungal and antibacterial activities, *e.g.* the mono methyl ether of bifurcarenone **1a** (R′ = H, R″ = Me) was shown to possess antifungal activity against *Botrytis cinerea, Fusarium oxysporum* sp. *mycopersici* and *Verticillium alboatrum*; and antibacterial activity against *Agrobacterium tumefaciens* and *Escherichia coli*.[1e] In addition to the biological properties, presence of two vicinal quaternary carbon atoms in a cyclopentane ring as in the sesquiterpenes cuparanes makes bifurcaranes interesting synthetic targets.[2] In a similar manner, cyclocuparanes cyclocuparenol **2**, microbiotol **3**, α- and β-microbiotenes **4** and **5**, isolated from the liverworts *Marchantia polymorpha, Cryptothallus mirabilis, Microbiota dicussata* and *Mannia fragrans*,[3] containing a 1,2,2-trimethylcyclopentyl group attached to a bicyclo[3.1.0]hexane system and incorporating three contiguous quaternary carbon atoms are interesting synthetic targets.[4] In continuation of our interest in the synthesis of natural products containing contiguous quaternary carbon atoms, herein we describe a short and efficient regioselective approach to the C-6 to C-19 carbon framework of bifurcaranes, and its extension to a formal total synthesis of the cyclocuparanes mentioned in the title.





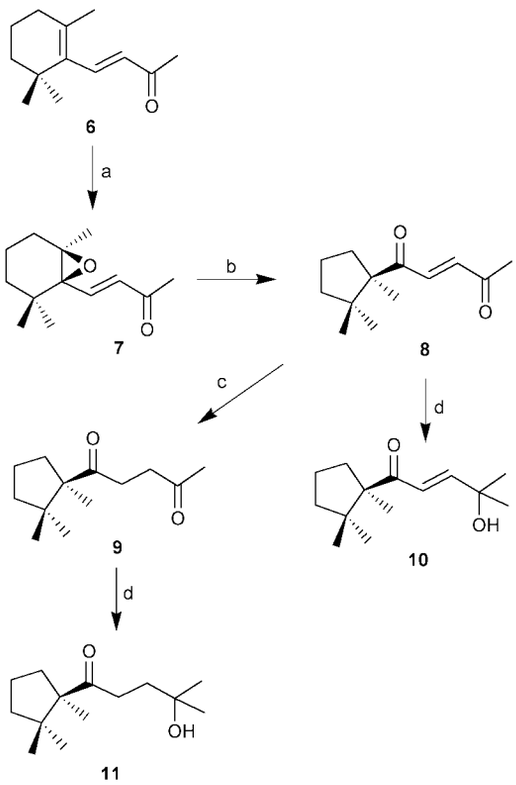
It was anticipated that the Lewis acid catalysed rearrangement of an epoxide derived from a trimethylcyclohexene could generate a 1,2,2-trimethylcyclopentyl ketone selectively [eqn. (1)] if the substituent Z on the epoxy carbon was an electron



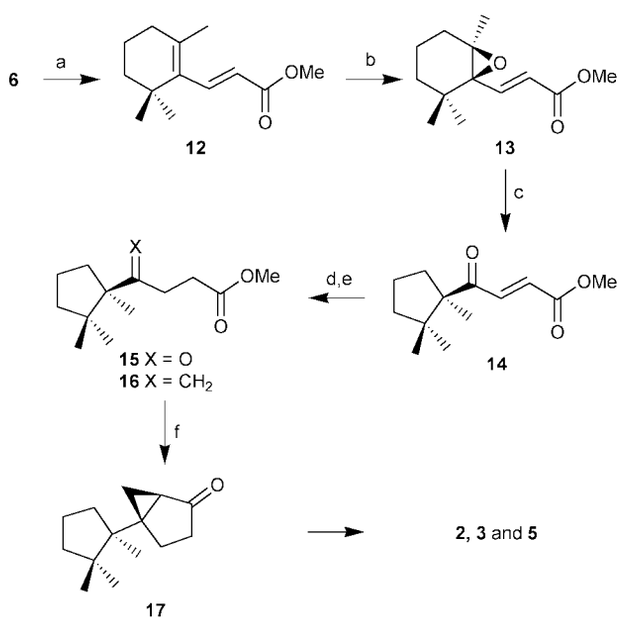
(1)

withdrawing group.[5] The 1,3,3-trimethylcyclohexene system present in the readily available β-ionone **6** was exploited. The sequence is depicted in Scheme 1. To begin with, reaction of β-ionone **6** with *m*-chloroperbenzoic acid (MCPBA) regiospecifically generated the epoxide **7** in 90% yield. For the key step, boron trifluoride–diethyl ether was chosen as the Lewis acid. Treatment of a 0.5 M methylene chloride solution of the epoxide **7** with three equivalents of boron trifluoride–diethyl ether at −70 °C for one hour, cleanly furnished the ring contracted product, enedione **8**, in 94% yield, in a highly regioselective manner.[6] A catalytic hydrogenation reaction transformed the enedione **8** into the dione **9**. Regiocontrolled Grignard reaction of the diones **8** and **9** with methylmagnesium iodide at 0 °C furnished the keto alcohols **10**† and **11**, which contain the C-6 to C-19 carbon framework of bifurcaranes **1a** and **1b**. Replacement of one of the tertiary methyl groups in the starting material **6** by a suitable side chain, *e.g.* an allyl group, will lead to compounds suitable for further elaboration to bifurcaranes. The structures of the compounds **10** and **11** were established from their spectral data (^{1}H and ^{13}C NMR spectra) in comparison with the bifurcaranes.

After successfully demonstrating the applicability of the epoxide rearrangement for the generation of the C-6 to C-19 of bifurcaranes, the methodology has been extended to the formal total synthesis of the cyclocuparanes mentioned in the title, Scheme 2. Thus, bromoform reaction on β-ionone **6** followed by esterification of the resulting acid furnished the ester **12** in 95% yield. Regiospecific epoxidation of the diene ester **12** with MCPBA furnished the epoxide **13**† in 98% yield. Rearrangement of the epoxide **13** with boron trifluoride–diethyl ether furnished, exclusively, the keto ester **14**,† in 90% yield, which on catalytic hydrogenation furnished the keto ester **15** in quantitative yield. Methylenation of the ketone in **15** will lead to the ene ester **16** which has already been transformed[4] into the cyclocuparanes **2**, **3** and **5** *via* intramolecular cyclopropanation



Scheme 1 *Reagents, conditions and yields*: (a) MCPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, 3 h, 90%; (b) $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 °C, 1 h, 94%; (c) H_2, 10% Pd–C, EtOH, 12 h, 100%; (d) MeMgI, Et_2O, 5 min, 65% for **10** and 81% for **11**.



Scheme 2 *Reagents, conditions and yields*: (a) NaOH, Br_2, dioxane, 0 °C, 2 h; MeOH, H_2SO_4, reflux, 5 h; 95%; (b) MCPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, 2 h, 98%; (c) $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 °C, 1 h, 90%; (d) H_2, 10% Pd–C, EtOH, 12 h, 100%; (e) $TiCl_4$, CH_2Br_2, Zn, CH_2Cl_2, 0 °C, 2 h, 60%; (f) ref. 4.

of the diazo ketone derived from the keto ester **16** followed by addition of the fifteenth carbon to the resulting norcyclocuparanone **17**. Since conventional Wittig methylenation was not successful, the keto ester **15** was transformed into the ene ester **16** using Lombardo's procedure[7] employing titanium tetrachloride, zinc and methylene bromide. The ester **16** was found to be identical (TLC, IR, ^1H and ^{13}C NMR spectra) with the authentic sample,[4] thus constituting a formal total synthesis of (±)-β-microbiotene **5**, (±)-microbiotol **3** and (±)-cyclocuparanol **2**.

In conclusion, we have developed a short and efficient regioselective approach to the C-6 to C-19 fragment of the marine diterpenoids bifurcaranes employing an epoxide rearrangement based ring contraction as the key step to generate the vicinal quaternary carbon atoms in a regiospecific manner, and extended it to the formal total synthesis of cyclocuparanes β-microbiotene, microbiotol and cyclocuparanol. The brevity and efficiency highlights the importance of the present sequence.

Acknowledgements

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Notes and references

† All the compounds exhibited spectral data consistent with their structure. IR and NMR spectral data for the keto alcohol **10**: ν_{max}/cm^{-1} 3430, 1665, 1610. δ_H (300 MHz, $CDCl_3$ + CCl_4) 6.84 (1 H, d, *J* 15.3 Hz, H-3), 6.62 (1 H, d, *J* 15.3 Hz, H-2), 2.45 (1 H, m), 1.70–1.40 (6 H, m), 1.37 (6 H, s), 1.16 (3 H, s), 1.09 (3 H, s), 0.84 (3 H, s). δ_C (75 MHz, $CDCl_3$+CCl_4) 203.8 (C), 151.7 (CH), 122.7 (CH), 71.1 (C), 59.0 (C), 44.0 (C), 40.6 (CH_2), 34.5 (CH_2), 29.7 (2 C, CH_3), 25.6 (CH_3), 24.7 (CH_3), 20.7 (CH_3), 19.7 (CH_2). For the epoxide **12**: ν_{max}/cm^{-1} 1720, 1650. δ_H (300 MHz, $CDCl_3$ + CCl_4) 7.11 (1 H, d, *J* 15.3 Hz), 5.95 (1 H, d, *J* 15.3 Hz), 3.72 (3 H, s), 1.90–1.65 (2 H, m), 1.50–1.20 (4 H, m), 1.13 (6 H, s), 0.91 (3 H, s). δ_C (75 MHz, $CDCl_3$ + CCl_4) 166.3 (C), 144.4 (CH), 123.9 (CH), 70.4 (C), 65.5 (C), 51.5 (CH_3), 35.7 (CH_2), 33.6 (C), 30.0 (CH_2), 26.1 (CH_3), 26.0 (CH_3), 20.9 (CH_3), 17.1 (CH_2). For keto ester **14**: ν_{max}/cm^{-1}1730, 1690, 1630, 980. δ_H (300 MHz, $CDCl_3$) 7.39 (1 H, d, *J* 15.5 Hz), 6.66 (1 H, d, *J* 15.5 Hz), 3.80 (3 H, s), 2.50–2.35 (1 H, m), 1.80–1.40 (5 H, m), 1.20 (3 H, s), 1.10 (3 H, s), 0.86 (3 H, s). δ_C (75 MHz, $CDCl_3$ + CCl_4) 202.4 (C), 165.8 (C), 137.6 (CH), 129.8 (CH), 59.1 (C), 51.9 (CH_3), 44.3 (C), 40.4 (CH_2), 34.3 (CH_2), 25.4 (CH_3), 24.6 (CH_3), 20.2 (CH_3), 19.7 (CH_2).

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