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Stereoselective Synthesis of (1*R*,4*R*,6*S*)-6-(Dibromoaluminio)-7-(methoxymethyl)menth-2-ene and further Preparation of *trans*-7-(Methoxymethyl)menth-2-ene Hydroxy- and Oxo-derivatives

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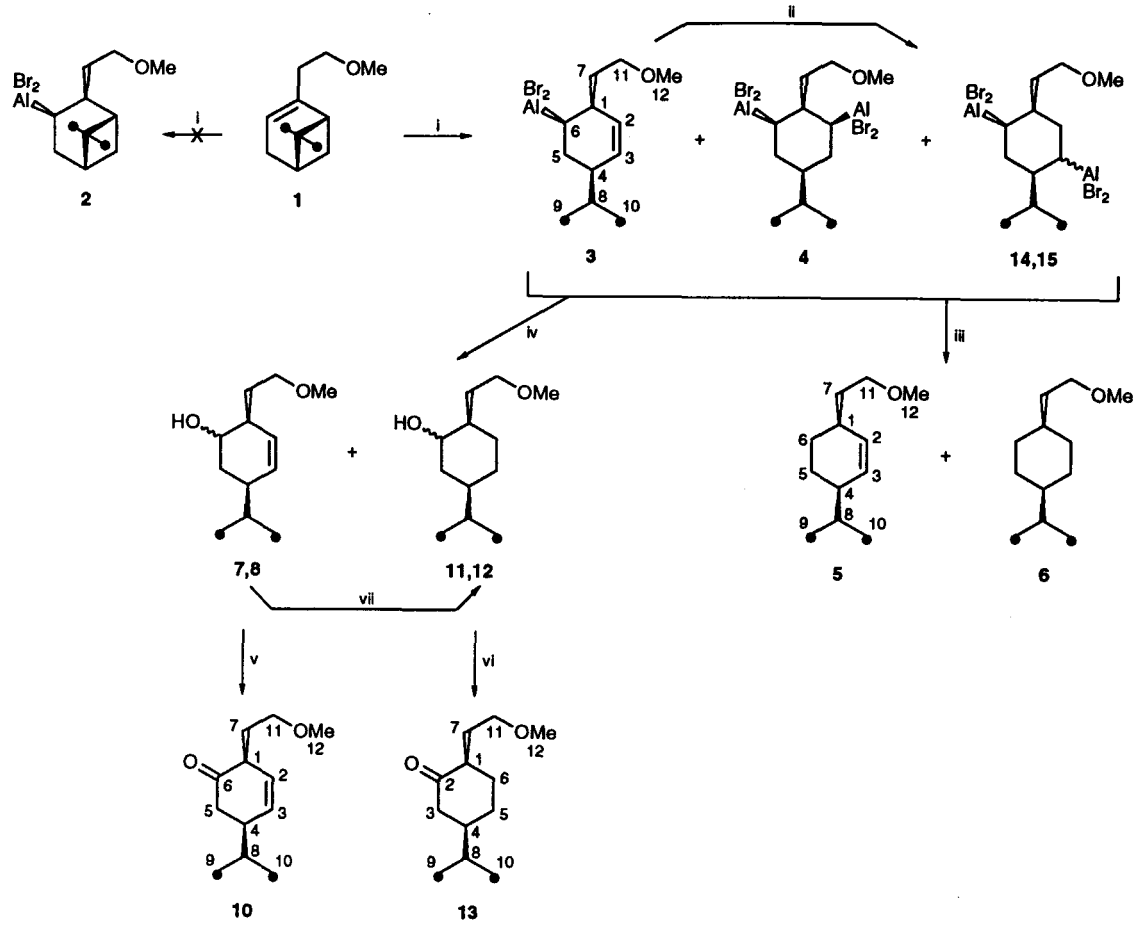
(1*R*,4*R*,6*R*)- and (1*R*,4*R*,6*S*)-7-(Methoxymethyl)menth-2-en-6-ol **7** and **8**, (1*R*,4*R*)-7-(methoxymethyl)menth-2-en-6-one **10**, (1*R*,4*R*)-7-(methoxymethyl)menth-2-ene **5** and their saturated analogues have been synthesized from (1*R*,4*R*,6*S*)-6-(dibromoaluminio)-7-(methoxymethyl)menth-2-ene **3**, prepared under hydroalumination of the methyl ether of 2-{(1*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl}ethanol with the $LiAlH_4 \cdot 3AlBr_3$ system.

Hydroalumination of α-pinene with the $LiAlH_4 \cdot 3AlBr_3$ system is known to give a high yield of (dibromoaluminio)isopinocamphane.[1] A nopol methyl ether **1** that is levorotatory in this case, has a similar structure, but does not lead to the expected 10-(methoxymethyl)(dibromoaluminio)-isopinocamphane **2**. Instead, a product from cyclobutane ring opening, (1*R*,4*R*,6*S*)-6-(dibromoaluminio)-7-(methoxymethyl) menth-2-ene **3**, and a small amount (5–10%) of (6*S*)-(dibromoaluminio)-[(1*S*,2*S*,4*R*)-2-(dibromoaluminio)-7-(methoxymethyl)menthane] **4** were obtained in 94% total



Scheme 1 *Reagents and conditions:* i, $LiAlH_4 \cdot AlBr_3$, C_6H_6, 25 °C, 1 h; ii, $LiAlH_4 \cdot AlBr_3$, C_6H_6, 25 °C, 4 h; iii, H_2O, Et_2O, 0 °C; iv, O_2, THF, 25 °C, 2 h; v, vi, $Na_2Cr_2O_7 \cdot 2H_2O$, H_2SO_4, Et_2O, 25 °C, 2 h; vii, $CoCl_2 \cdot 6H_2O$, $NaBH_4$, EtOH, 25 °C, 140 h.

yield.† Compound **4** was the main product in further hydroalumination of the menthene ring double bond. Hydrolysis of the reaction mixture afforded (1*R*,4*R*)-7-(methoxymethyl)menth-2-ene **5** and *trans*-7-(methoxymethyl)menthane **6** (5–10%) in 84% total yield, while oxidation of the mixture gave a 74% total yield of an equimolar mixture of (1*R*,4*R*,6*R*)- and (1*R*,4*R*,6*S*)-7-(methoxymethyl)menth-2-en-6-ol **7** and **8**, respectively, and a racemic mixture (4–8%) of (1*S*,2*R*,4*R*)-7-(methoxymethyl)menthan-2-ol **11** and its (1*R*,2*S*,4*S*)-isomer.‡ Therefore, the oxidation of **3** occurs with partially-inverted configuration of the chiral centre at C–6, which is due to the lack of stereocontrol effects. Treatment of the mixture of diastereomeric alcohols **7** and **8** with chromic acid[2] afforded (1*R*,4*R*)-7-(methoxymethyl)menth-2-en-6-one **10** in 82% yield.

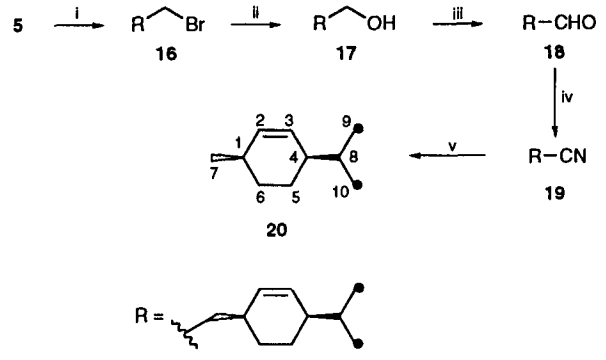
To avoid the partial isomerisation that is often observed during hydrogenation of alkyl-substituted cyclohexenes with such heterogeneous catalysts as Pd or PtO_2,[3,4] a mixture of the unsaturated alcohols **7** and **8** was reduced with the $CoCl_2 \cdot 6H_2O/NaBH_4$ system in ethanol,[5] which led to a mixture of (1*S*,2*R*,4*R*)- and (1*S*,2*S*,4*R*)-7-(methoxymethyl)menthan-2-ol **11** and **12** in 73% yield. The mixture was separated by column chromatography on SiO_2. Oxidation of the latter alcohols with chromic acid afforded (1*S*,4*R*)-7-(methoxymethyl)menthan-2-one **13** in 84% yield.

The use of an additional equivalent of $LiAlH_4 \cdot 3AlBr_3$ promoted exhaustive hydroalumination of the disubstituted double bond in **3** with essentially high regioselectivity, thus affording (6*S*)-(dibromoaluminio)-[(1*S*,2*S*,4*R*)-2-(dibromoaluminio)-7-(methoxymethyl)menthane] **4** as the main product (80%) and a small amount (20%) of (1*R*,2*S*,4*R*,5*R*)- and (1*R*,2*S*,4*R*,5*S*)-2,5-bis(dibromoaluminio)-7-(methoxymethyl)-menthane **14** and **15**, respectively. Further hydrolysis of the reaction mixture leads naturally to a single product, *trans*-7-(methoxymethyl)menthane **6**.

† The methyl ether of 2-{(1*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl}ethanol **1** with $[\alpha]_D^{20} = -35.9°$ (neat) [$-32.6°$ (neat)[12]] was used for the experimental work. *Hydroalumination procedure.* A solution of $LiAlH_4$ (6 mol dm^{-3}; 1 ml, 6 mmol) in diethyl ether was added to benzene (5 ml) with stirring in an argon atmosphere. The bulk of the solvent was removed at 10–15 Torr. Another portion of benzene (30 ml) and a solution of $AlBr_3$ (2.6 mol dm^{-3}; 6.9 ml, 18 mmol) in benzene were added. The mixture was stirred at room temperature for 1 h. A solution of **1** (1.9 g, 10.6 mmol) in benzene (20 ml) was then added dropwise and the mixture was stirred for 1 h. After precipitation of excess $LiAlH_4$, a transparent solution of **3** with an admixture of **4** was decanted, analysed and used for further transformations.

^1H and ^{13}C NMR spectral assignments confirmed the structures of the resultant compounds. **3**: ^1H NMR (C_6H_6) δ 1.03 and 1.07 (d, 6H, Me, $^3J = 6.9$ Hz), 3.51 (s, 3H, MeO), 5.56 and 5.92 (d, 2H, CH = CH, $^3J = 10.3$ Hz); ^{13}C NMR (C_6D_6) δ 19.60 and 19.85 (q, C–9, 10), 25.55 (d, C–6), 26.02 (t, C–5), 32.01 (d, C–8), 32.98 (t, C–7), 34.62 (d, C–1), 40.54 (d, C–4), 64.12 (q, C–12), 80.51 (t, C–11), 129.52 (d, C–3), 134.02 (d, C–2). **5**: $[\alpha]_D^{20} = -35.2°$ (*c* 14.2 $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 19.26 and 19.58 (q, C–9, 10), 25.66 (t, C–5), 29.90 (t, C–6), 32.31 (d, C–8), 32.22 (d, C–1), 36.49 (t, C–7), 42.23 (d, C–4), 58.42 (q, C–12), 70.70 (t, C–11), 130.50 (d, C–3), 132.12 (d, C–2). **10**: $[\alpha]_D^{20} = -31.3°$ (*c* 6.45 $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 18.93 and 19.18 (q, C–9, 10), 30.70 (t, C–7), 32.27 (d, C–8), 41.48 (t, C–5), 44.17 and 45.18 (d, C–1, 4), 58.31 (q, C–12), 69.93 (t, C–11), 128.91 (d, C–2), 130.44 (d, C–3), 211.8 (s, C–6). **13**: $[\alpha]_D^{20} = +4.1°$ (*c* 9.75 $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 19.14 and 19.43 (q, C–9, 10), 28.66 and 28.91 (t, C–5, 6), 32.57 (d, C–8), 33.03 (t, C–7), 45.52 (t, C–3), 46.57 (d, C–1, 4), 58.28 (q, C–12), 70.27 (t, C–11), 212.6 (s, C–2). **20**: ^{13}C NMR ($CDCl_3$) δ 19.33 and 19.65 (q, C–9, 10), 22.08 (q, C–7), 25.71 (t, C–5), 31.03 (d, C–1), 31.93 (t, C–6), 32.27 (d, C–8), 42.01 (d, C–4), 130.01 (d, C–3), 134.09 (d, C–2).

‡ A mixture of **11** and its enantiomer are the major oxidation products from **4**. Isomeric diols (*ca.* 1%) are also observed.



Scheme 2 *Reagents and conditions:* i, Ph_3PBr_2, PhCl, 125 °C, 4 h; ii, Mg, Et_2O; O_2, Et_2O, 1 h; iii, PCC, CH_2Cl_2, 25 °C, 1.5 h; iv, $NH_2OH \cdot HCl$, Py; Ac_2O, 100 °C, 1.5 h; v, K, HMPTA, Bu'OH, Et_2O, 25 °C, 3 h.

After **3** had been formed, the chiral centres at C–1 and C–4 in the menthene (or menthane) ring were not involved in the subsequent transformations, and any configurational changes in the rest of the chiral centres were under control. Therefore, to determine the absolute configuration and to find the optical purity of **3** as well as of **5**, **7**, **8** and **10–13**, *trans*-7-(methoxymethyl)menth-2-ene underwent further reaction to give *trans*-menth-2-ene, because the configuration of the latter is connected with its rotation sign in a known way.[6]

The ether bond in **6** was cleaved with Ph_3PBr_2 in chlorobenzene,[7] resulting in a 82% yield of *trans*-7-(bromomethyl)menth-2-ene **16** that was transformed into a Grignard reagent. The latter was oxidized with oxygen in an ether[8] to lead to a 56% yield of (*trans*-menth-2-en-7-yl)methanol **17** that was then treated with pyridinium chlorochromate (PCC)[9] to yield 78% of (*trans*-menth-2-en-7-yl)methanal **18**. After treatment of **18** with a mixture of hydroxylamine hydrochloride and pyridine, the resultant oxime was heated *in situ* with acetic anhydride,[10] which afforded (*trans*-menth-2-en-7-yl)cyanide **19** in 74% yield. The latter was decyanated with the K/HMPTA–Bu'OH system,[11] which led to a 80% yield of the target product *trans*-menth-2-ene **20** with $[\alpha]_D^{20} = -38.0°$ (*c* 6.4, $CHCl_3$) corresponding to (1*S*, 4*R*)-menth-2-ene of 35% optical purity ($[\alpha]_D^{20} = -108.0°$ for the pure enantiomer[6]).

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