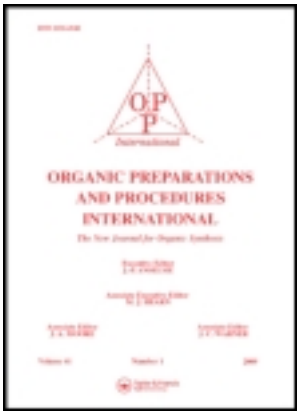

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Syntheses of C-1 Axial Derivatives of l-Menthol

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Syntheses of C-1 Axial Derivatives of L-Menthol

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Derivatives of menthol have interesting ^{1}H NMR spectra and often, complete assignments of the protons and determination of the configuration of substituents on the cyclohexane ring are difficult. As part of a project to investigate the NMR properties of menthol derivatives, several axially substituted menthanes **(3–6)** were prepared and their structures established.[1]

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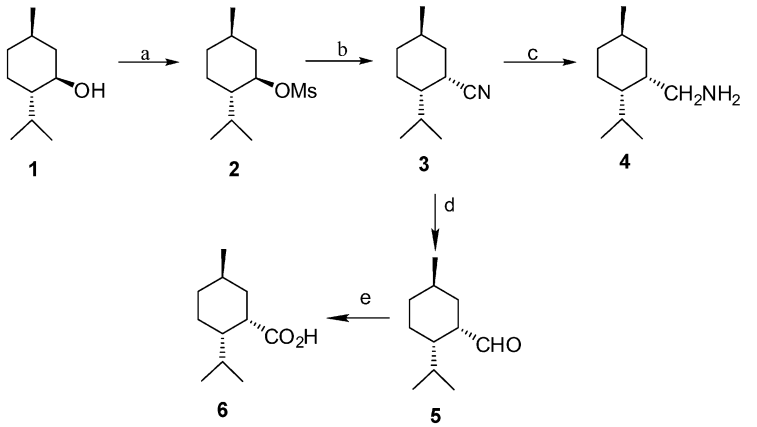
Menthanes containing equatorial substituents at C-1 have found use as chiral auxiliaries.[2–4] Fewer examples of menthol derivatives with axial substituents at C-1 have been synthesized and literature methods have significant difficulties.[5–7] This article describes the improved preparation of the known axial nitrile **3** and the syntheses of three isomerically pure axial compounds **4–6**. The functional groups present on the C-1 substituents are suitable for further elaboration of these compounds as potential chiral auxiliaries.

The axial nitrile **3** had previously been prepared by Adolfsson *et al.* by treatment of L-menthol tosylate[8] with sodium cyanide in DMSO.[9] In our hands, attempts to carry out this procedure on a larger scale proved problematic. The yields were significantly lower than described on scales larger than 2 mmols and the inherent safety concerns of large scale reactions involving excess cyanide in DMSO led to the development of an improved procedure. Extensive investigations of leaving group, solvent, temperature, ratio of cyanide to substrate, and other factors led to the optimized conditions presented here (*Scheme 1*). While the tosylate derivative gave similar results in the substitution reaction, the mesylate derivative[10] gave comparable or better yields in our hands and was more easily prepared in pure form from L-menthol. The change of solvent from DMSO to acetonitrile led to slightly lowered yields but allowed for easier regulation of the temperature at the optimal 80°C and made the reaction inherently safer. Microwave-assisted synthesis was attempted but gave no improvements in yield. A five-fold excess of cyanide, either sodium or potassium cyanide, and one equivalent of 18-crown-6 resulted in the optimal yields, 64% from L-menthol The use of fewer equivalents of cyanide or 18-crown-6 lowered the yield to 40–50% and gave significantly more E1 elimination and rearrangement products. The yields were reproducible on scales ranging from 0.5 to 50 g of mesylate.



a) MsCl, CH_2Cl_2, Et_3N, 99% yield; b) KCN, CH_3CN, 18-crown-6, 64% yield; c) $LiAlH_4$, diethyl ether, 90%; d) Dibal-H, THF, 96% yield; e) Jones reagent, diethyl ether, 66% yield.

Scheme 1

Originally, we had intended to prepare the axial acid **6** directly by hydrolysis of the nitrile. However, all attempts at carrying out the hydrolysis failed. Thus, the nitrile was reduced to the aldehyde **5** with DIBAL-H in THF, which was then oxidized to the axial

acid **6** with Jones reagent in 63% yield for the two steps. Both compounds are prone to epimerization if subjected to acidic conditions, including silica gel chromatography, but could be chromatographed on florisil, if necessary. Generally, the compounds were obtained in good purity without extensive purification. Finally, a derivative with an sp^3 hybridized carbon at the C-1 position could be prepared by reduction of the nitrile to the corresponding amine **4**. The amine was chosen because of the frequent use of primary amines as chiral auxiliaries. Lithium aluminum hydride reduction of the nitrile proceeded smoothly in diethyl ether, to produce the amine in 90% yield. The free amine is somewhat unstable but its hydrochloride salt can be stored indefinitely. The axial configuration of all compounds was proven by ^{1}H NMR. In all cases, the proton on C-1 is equatorial and is consistently 0.4–0.5 ppm downfield relative to the previously described equatorially substituted compounds.[2–4]

This article has described the efficient preparation of several axially substituted p-menthane derivatives from the inexpensive, commercially available L-(-)-menthol. Each reaction described can be carried out easily in good to excellent yield. The methods are all robust and scalable up to 50 g. While our original interest in these compounds stemmed from their interesting NMR spectral properties, their potential as chiral auxiliaries is currently under investigation in our laboratories.

Experimental Section

All reagents and solvents were of reagent grade and used without further purification unless otherwise specified. THF was dried using an Innovative Technologies PureSolv solvent purification system. TLC was performed on silica gel 60 precoated plates with fluorescent indicator, and compounds were visualized using aqueous vanillin/H_2SO_4 or ethanolic phosphomolybdic acid solutions. Melting points were determined on a Mel-Temp melting point apparatus and are uncorrected. IR spectra were recorded using a Thermo IR100. GC/MS was performed with a Shimadzu QP5050A spectrometer. ^{1}H NMR was obtained at 400 MHz and ^{13}C were obtained at 100 MHz with a JEOL ECX400 spectrometer and referenced to TMS. Optical rotations were measured with a JASCO DIP-370 polarimeter. Elemental analyses were performed by Atlantic Microlabs in Norcross, GA. Compounds **2** and **3** are known and were identical to those reported in the literature.[9–11]

L-Menthol Mesylate (2)

The literature procedure[10] was modified as follows. To a solution of L-menthol (10.0 g, 63.9 mmol) in dichloromethane (125 mL), cooled to 0°C, was added methanesulfonyl chloride (9.2 g, 80.0 mmol) in one portion. The mixture was stirred for 20 minutes, followed by a dropwise addition of triethylamine (8.4 g, 83.0 mmol) to the cold solution. The mixture was stirred for 24 hours at 20°C, whereupon complete consumption of starting material was shown by TLC analysis on SiO_2 using 10% ethyl acetate in hexane as eluent. The mixture was diluted with dichloromethane (250 mL) and washed with water (2 × 100 mL), saturated aq. $NaHCO_3$ (100 mL) and saturated aq. NaCl (50 mL). The organic solution was dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The pale yellow residue was

chromatographed on silica, using 10% ethyl acetate in hexane as eluent to give 15.0 g (99% yield) of a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.81 (d, 3 H, CH_3), 0.82–0.89 (m, 1 H, axial C*H*H), 0.92 (dd, 6 H, 2 CH_3), 1.04 (m, 1 H, axial C*H*H), 1.27 (q, 1 H, axial C*H*H), 1.42 (m, 2 H, axial C*H*H), 1.69 (m, 2 H, equatorial C*H*H and C*H*$(CH_3)_2$), 2.06 (m, 1 H, equatorial C*H*H), 2.26 (m, 1 H, equatorial C*H*H), 3.00 (s, 3 H, SO_2CH_3), 4.53 (td, 1 H, $CHOSO_2$). MS (EI, 70eV): m/z 138 (-OSO_2CH_3).

(1S, 2S, 5R)-1-Cyano-2-isopropyl-5-methylcyclohexane (3)

To a solution of the mesylate (3.39 g, 14.5 mmol) in acetonitrile (50 mL) was added potassium cyanide (4.7 g, 72.3 mmol) and 18-crown-6 (3.8 g, 14.5 mmol) and the resulting mixture was heated to reflux for 48 hours. The progress of the reaction was monitored by GC/MS. The mixture was poured into dichloromethane (150 mL). The yellow solution was washed with water (4 × 25 mL) to remove excess cyanide and 18-crown-6. The organic phase was washed with saturated aqueous NaCl (50 mL) and dried over $MgSO_4$. The solution was filtered through silica gel and the solvents removed *in vacuo*. The resulting pale yellow oil was chromatographed on silica with 5% ethyl acetate in hexanes as eluent. A colorless oil was obtained (1.57 g, 65%).

(1S, 2S, 5R)-2-Isopropyl-5-methylcyclohexanecarboxaldehyde (5)

A solution of nitrile **2** (0.893 g, 5.4 mmol) in dry THF under argon was cooled to 0°C. Diisobutyl aluminum hydride (13.5 mL, 1.0 M in toluene, 13.5 mmol) was added dropwise. The resulting solution was stirred at 0°C for 4 hours, then allowed to warm to 25°C, and stirred for an additional 18 hours. GC/MS analysis showed complete consumption of starting material. To quench, 100 mL of diethyl ether and 50 mL of 2% aq. H_2SO_4 were cooled to 0°C. The reaction mixture was added in 6 mL aliquots to the two-phase mixture with stirring between additions. After complete addition, the two-phase mixture was acidified further with 5 mL of 2% aq. H_2SO_4. The organic phase was separated and the aqueous phase was extracted with ether (2 × 100 mL). The organic phases were combined and washed with saturated aq. NaCl (50 mL), then dried over $MgSO_4$, filtered, and the solvents removed *in vacuo*. A colorless oil was isolated (0.88 g, 96%). Due to its instability upon chromatography, this compound was used without further purification. $[\alpha]_D^{20} = -10.9$ (c 0.024, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.80 (d, 3 H, CH_3), 0.82–0.85 (m, 8 H, 2 CH_3 and 2 axial C*H*H), 1.05 (m, 1 H, axial C*H*H), 1.19 (m, 1 H, axial C*H*H), 1.37 (m, 1 H, axial C*H*H), 1.6–1.8 (m, 3 H, equatorial C*H*, C*H*$(CH_3)_2$), 2.0 (dd, 1 H, equatorial C*H*), 2.67 (bs, equatorial C*H*CHO), 9.85 (d, 1 H, C*H*O). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.02, 21.68, 22.61, 27.19, 28.48, 29.79, 35.29, 36.01, 46.29, 48.86, 206.58. MS (EI, 70 eV): m/z 168 (M^+).

(1S, 2S, 5R)-2-Isopropyl-5-methylcyclohexanecarboxylic Acid (6)

To a solution of the aldehyde **2** (0.42 g, 2.5 mmol) in 20 mL of ether and cooled to 0°C was added Jones reagent (5.0 mL) in 1.0 mL portions over 1 hour. After the final addition, the dark green mixture was stirred an additional 10 minutes. The aqueous and organic phases

were separated and the aqueous phase was extracted twice with ether (50 mL). The organic phases were combined and washed twice with water (25 mL) and dried over $MgSO_4$. The dried ethereal solution was filtered through florisil to remove any remaining chromium impurities and the solvent was then removed *in vacuo* to give white crystals (0.306 g, 66%), mp. 65–67°C; $[\alpha]_D^{20} = +3.15$ (c 0.015, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83 (m, 1 H, axial CH), 0.85 (d, 3 H, CH_3), 0.90 (d, 3 H, CH_3), 0.92 (d, 3 H, CH_3), 0.98 (m, 1 H, axial CH), 1.41 (m, 1 H, axial CH), 1.61 (m, 1 H, axial CH), 1.66 (m, 2 H), 1.71 (m, 1 H, equatorial CH), 1.75 (m, 1 H, equatorial CH), 2.00 (dq, 1 H, equatorial CH), 2.90 (bs, 1 H, equatorial CH), 11.0 (bs, 1 H, COOH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.26, 21.50, 22.37, 25.49, 27.44, 30.21, 35.26, 37.97, 41.97, 46.38, 182.13. MS (EI, 70 eV): m/z 184 (M^+).

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.85; H, 11.09.

(1S,2S,5R)-1-(Aminomethyl)-2-isopropyl-5-methylcyclohexane (4)

To a solution of nitrile **2** (0.859 g, 5.19 mmol) in diethyl ether and cooled to 0°C under argon was added dropwise a solution of lithium aluminum hydride (10.4 mL, 0.5 M in glyme, 5.19 mmol) over 15 minutes. The solution was stirred at 0°C for 4 hours and then quenched by the sequential addition of water (0.25 mL), 20% NaOH (0.25 mL) and water (1.0 mL). The mixture was subsequently stirred at 25°C until the salts separated. The mixture was vacuum filtered and the white solids were washed with hexane (25 mL). The combined organic phases were dried over $MgSO_4$ and the solvent removed *in vacuo*. The amine was isolated as a colorless oil (0.795 g, 90%) and converted to its hydrochloride salt, mp. 234–235° (dec.), by addition of conc. HCl (1 mL). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.8–1.0 (m, 12 H, 3 CH_3, 3 axial C*H*H), 1.37 (m, 1 H, axial C*H*H), 1.50 (m, 1 H, C*H*$(CH_3)_2$), 1.68 (m, 3 H, 2 equatorial C*H*H, axial C_5*H*H), 2.42 (bs, 2 H, NH_2), 2.71 (bd, 2 H, CH_2NH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.92, 21.84, 22.83, 25.69, 26.07, 29.44, 35.79, 36.43, 37.90, 38.06, 47.40. MS: (EI, 70 eV): m/z 169 (M^+).

Anal. Calcd. for $C_{11}H_{24}ClN$: C, 64.21; H, 11.76; N, 6.81. Found: C 64.12; H, 11.79; N, 6.57.

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A Practical Synthesis of α-Asarone *via* Iodine-catalyzed Isomerization of α/β-Asarone

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α-Asarone (**1**), isolated from the *Guatteria guameri* plant growing in southeast Mexico, is reported to be an anti-platelet and hypolipidemic agent.[1,2] In addition, it is known to have sedating, neuroleptic, spasmolytic, anti-ulcerogenic and anti-atherogenic activity.[3,4] Due to its low availability from natural sources, several synthetic approaches have been developed for α-asarone (*trans*-isomer, **1**), which involve Grignard, Wittig, Aldol-Grob, Friedel-Crafts reactions.[5–9] However, in the above methods, some of the unwanted toxic β-asarone (*cis*-isomer, **2**) was always formed, along with the desired α-asarone, which is difficult to separate by column chromatography due to similarities in R_f values. β-Asarone can be converted to α-asarone by fusion with KOH in good yield.[10] However, this reaction requires an excess amount of KOH (37 equiv.) and high temperature (200–220°C). Selenium dioxide, which can effectively convert β-asarone to α-asarone,[10] is not a good choice due to its toxicity. A recently developed palladium (II) catalyzed isomerization of *cis*-arylalkenes can also be applied to the preparation of α-asarone,[11,12] however, industrial applications of this reaction on synthesis of α-asarone are challenging because the catalyst is expensive,

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