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Unexpected Incorporation of Bromine at a Non-anomeric Position during the Synthesis of an O²-Glycosylated Diazeniumdiolate

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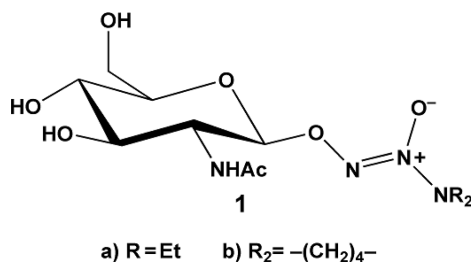
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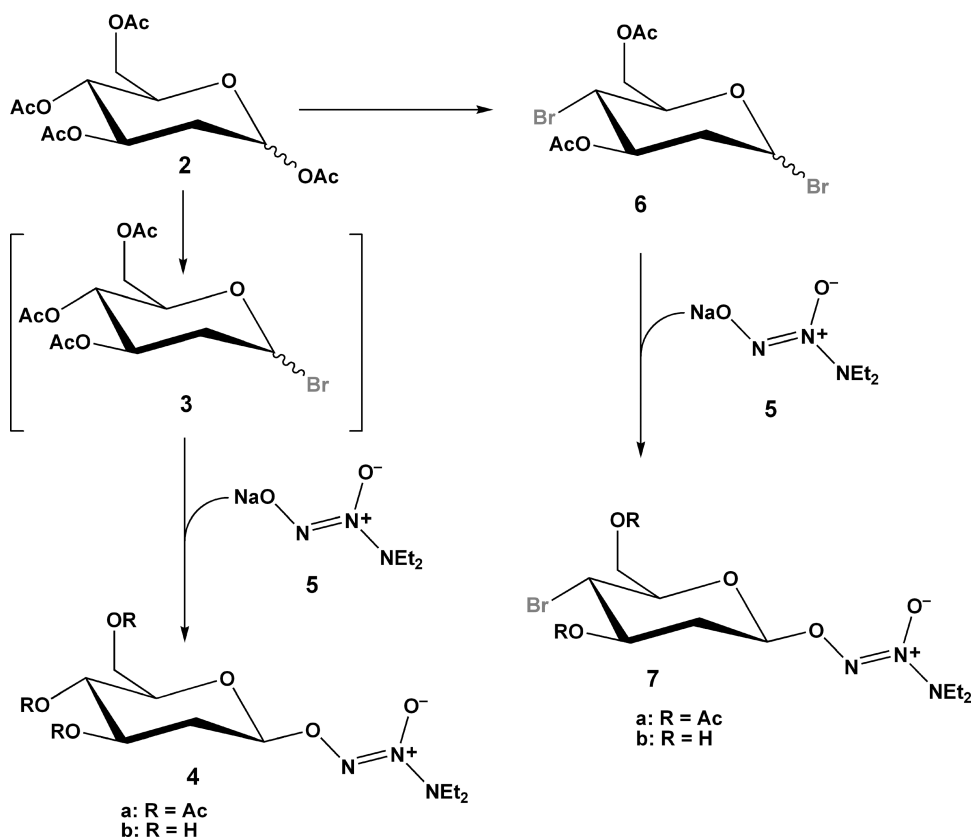
We recently reported that the novel NO-releasing O²-glycosylated diazeniumdiolates of structure **1** showed promising anti-parasitic activity against *Leishmania major*.¹ While preparing some 2-deoxyglucose analogs for lead optimization, we have observed the facile displacement of acetate by bromide from the 4-position of peracetylated 2-deoxyglucose **2**, as shown in *Scheme 1*, providing a convenient synthesis of 4-brominated 2,4-dideoxyglucose derivatives that would otherwise be difficult to access by currently preferred, directed synthetic routes.



In an effort to prepare compound **4a**, peracetylated 2-deoxyglucose **2** was treated with HBr in glacial acetic acid. A tar assumed to be bromide **3** was formed and immediately

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Scheme 1

reacted with diazeniumdiolate salt **5** to generate a product expected to be **4a**. However, this easily crystallized, sharp-melting product was characterized by elemental analysis values that were vastly different from our expectation. Further examination revealed the presence of only two methyl singlets in the proton NMR, and mass spectrometry pointed to the presence of a bromine atom in the molecular ion isotopic cluster. Detailed analysis of the ¹H NMR spectral properties showed that the halide had replaced the C4 acetoxy group with retention of configuration. Further work-up afforded **7a** in 38% yield. The product **7a** was deacetylated with methoxide in methanol to produce **7b**. An alternate bromination procedure using BiBr₃ and trimethylsilyl bromide gave 4- α -bromo-2,4-dideoxyglucosyl bromide diacetate **6**, presumably the same glycosylating agent produced in the HBr/HOAc reaction. The reaction with BiBr₃ was rapid, efficient, and gave a higher yield of **6** than the HBr procedure.

Diazeniumdiolates generate up to two moles of NO upon hydrolysis under various conditions. Replacement of the C4 acetoxy group of compound **4b** by bromine had little effect (only about three-fold) on hydrolysis rates at pH values of 14, 7.4, and 3.8–4.6 (Table 1), a key predictor of anti-leishmanial activity.¹

In conclusion, we have discovered a novel and simple BiBr₃/TMS bromide-mediated preparation of compound **6**, an extremely useful intermediate in the preparation of the

Table 1
Half-lives of Hydrolysis at 37°C for Diazeniumdiolated Glycosides
of Structure Et₂NN(O)=NOR

R	pH		
	14 ^a	7.4 ^b	3.8–4.6
β -(4- α -Bromo)-2,4-dideoxy-D-glucosyl (7b)	72 min	1.5 days	1.8 days ^c
β -(2-Deoxy)-D-glucosyl (4b) ¹	23 min	0.5 days	1.2 days ^d

^a) 1.0 M NaOH.

^b) 0.1 M phosphate.

^c) 0.95 M citrate at pH 4.6.

^d) 0.05 M citrate at pH 3.8.

2-deoxy sugars primed for further functionality at C4. In particular, compounds **7a** and **7b** offer an electrophilic center at C4, making it potentially useful for further reaction with nucleophiles, including peptide chains or additional saccharides.

Experimental Section

Starting materials were purchased from Aldrich Chemical Co. (Milwaukee, WI). NMR spectra were obtained in chloroform-*d* or deuterium oxide on a Varian UNITY INOVA spectrometer; chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane or 3-(trimethylsilyl)propionic-2,2,3,3-*d*₄ acid, sodium salt. Ultraviolet (UV) spectra were recorded on an Agilent model 8453 or a Hewlett-Packard model 8451A diode array spectrophotometer. ESI-MS analysis was performed on a Finnigan LCQ DECA ion trap mass spectrometer. Elemental analyses were performed by Atlantic Microlab, Inc. (Norcross, GA) and Midwest Microlab (Indianapolis, IN).

*Isolation of O*²-(3,6-Di-O-acetyl-4-[α -bromo]-2,4-dideoxy- β -D-glucopyranosyl) 1-(*N,N*-Diethylamino)diazen-1-ium-1,2-diolate (**7a**) (JS-33–45) from Deoxyglucose Tetraacetate **2** with HBr in glacial Acetic Acid

2-Deoxy-D-glucose (Sigma-Aldrich) was acylated with acetic anhydride and pyridine using the general method of Wolfrom and Thompson.² The spectral properties of the product, **2**, matched those in the published report. A solution of 6.0 g (0.018 mol) of **2** in 12 mL of 30% HBr/acetic acid at 0°C was allowed to warm to room temperature and stirred for 20 hours. The reaction mixture was diluted with 200 mL of dichloromethane and washed with water. The organic layer was washed three times with aqueous 5% sodium bicarbonate solution, dried over sodium sulfate, and filtered through a layer of anhydrous magnesium sulfate. Evaporation of the solvent gave 3.60 g of **6** as a black tar. A 2.35 g portion of the crude product **6** was dissolved in 25 mL of tetrahydrofuran. The resulting solution was added dropwise to a cold slurry of 1.1 g (0.007 mol) of **5**³ in 20 mL of dimethyl sulfoxide containing 200 mg of anhydrous sodium carbonate. After stirring at room temperature under nitrogen for 72 hours, the solution was diluted with 200 mL of ether and filtered

into a separatory funnel, washed with water, dried over sodium sulfate, and filtered through a layer of magnesium sulfate. Evaporation of the solvent gave 2.09 g of a brown oil. Purification was carried out on a 25-mm × 300-mm glass column packed with 70 g of silica gel suspended in 10:1 dichloromethane:ethyl acetate. Elution was performed using the same solvent system to give 1.12 g (38% based on 2.35 g of starting material) of **7a** as a colorless crystalline solid, mp 87.8°C. ESI mass spectroscopy confirmed the presence of bromide in the molecule (M^+ 425 and 427); further NMR analysis using COSY and HSQC acquisitions demonstrated that the bromide was at the C-4 equatorial position: UV (EtOH) λ_{\max} (ϵ) 228 nm ($10 \text{ mM}^{-1} \text{ cm}^{-1}$). $^1\text{H NMR}$ (CDCl_3): δ 1.11 (t, 6 H, $J = 7.0 \text{ Hz}$, CH_3CH_2-), 2.09 (s, 3 H, $\text{CH}_3\text{C}=\text{O}$), 2.12 (s, 3 H, $\text{CH}_3\text{C}=\text{O}$), 2.43–2.52 (m, 1 H, H2), 2.71–2.76 (m, 1 H, H2'), 3.18 (q, 4 H, $J = 7.1 \text{ Hz}$, CH_3CH_2-), 3.63–3.67 (m, 1 H, H5), 4.09–4.25 (m, 3 H, H3, H6' and H6), 5.12 (t, 1 H, $J = 9.9 \text{ Hz}$, H4), 5.25 (dd, 1 H, $J = 2.2$ and 10.1 Hz , H1). $^{13}\text{C NMR}$ δ 11.50, 20.65, 20.68, 38.97, 45.26, 48.45, 62.40, 70.78, 74.40, 99.89, 169.30, 170.63.

Anal. Calcd for $\text{C}_{14}\text{H}_{25}\text{BrN}_3\text{O}_7$: C, 39.52; H, 5.69; N, 9.88. Found: C, 39.60; H, 5.67; N, 9.81.

Bromination of 2 via BiBr_3

The general procedure of Montero *et al.*⁴ was used to brominate compound **2**. To a solution of 641 mg (1.93 mmol) of **2** in 10 mL of dichloromethane were added 90 mg (0.2 mmol) of bismuth tribromide (Sigma-Aldrich) and four equivalents (1.03 mL, 8 mmol) of trimethylsilyl bromide under a nitrogen atmosphere. The solution was stirred at room temperature for 2 hours, diluted with dichloromethane, washed with 5% sodium bicarbonate solution, dried over sodium sulfate, and filtered. Evaporation of the solvent gave 551 mg of **6** as a gray-brown oil. The TLC and NMR of this crude product matched the TLC and NMR of the over-brominated compound **6** described in the previous paragraph.

***O*²-[4-(α -Bromo)-2,4-dideoxy- β -D-glucopyranosyl] 1-(*N,N*-diethylamino)diazene-1-ium-1,2-diolate (**7b**) (JS-33–48)**

The general procedure of Wolfram and Thompson⁵ was used in the deacetylation step. A solution of 936 mg (2.2 mmol) of **7a** in 40 mL of methanol was treated with 150 μL of 25% methanolic sodium methoxide and stirred at room temperature. The progress of the hydrolysis was followed on silica-gel TLC using 50:1 dichloromethane:methanol. After 2 hours, 1 g of pre-washed Dowex-50W resin was added to the reaction mixture and stirred for 30 min. Filtration and evaporation of the filtrate gave a colorless solid that was purified on silica gel, eluted with 5:1 dichloromethane:ethyl acetate. Pure **7b** was isolated in 98% yield (738 mg) mp 121–123 °C; UV (EtOH) λ_{\max} (ϵ) 226 nm ($7.9 \text{ mM}^{-1} \text{ cm}^{-1}$). $^1\text{H NMR}$ (D_2O) δ 1.07 (t, 6 H, $J = 7.1 \text{ Hz}$, CH_3CH_2-), 2.27–2.38 (m, 1 H, H2), 2.74–2.80 (m, 1 H, H2'), 3.18 (q, 4 H, $J = 7.1 \text{ Hz}$, CH_3CH_2-), 3.56–3.62 (m, 1 H, H5), 3.70 (t, 1 H, $J = 9.7 \text{ Hz}$, H4), 3.82–3.95 (m, 3 H, H3, H6', and H6), 4.17–4.26 (m, 1 H, H3'), 5.53 (dd, 1 H, $J = 2.2$ and 13.0 Hz , H1). $^{13}\text{C NMR}$ (CDCl_3) δ 11.50, 38.96, 48.37, 51.57, 62.50, 71.74, 77.48, 100.08.

Anal. Calcd for $\text{C}_{10}\text{H}_{20}\text{BrN}_3\text{O}_5 \cdot \frac{1}{4}\text{CH}_2\text{Cl}_2$: C, 33.88; H, 5.69; N, 11.56. Found: C, 33.54; H, 5.57; N, 11.55.

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Syntheses of C-1 Axial Derivatives of L-Menthol

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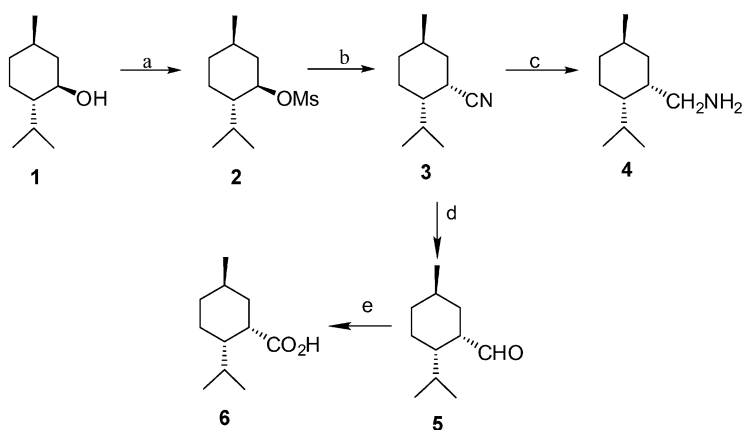
Derivatives of menthol have interesting ^1H NMR spectra and often, complete assignments of the protons and determination of the configuration of substituents on the cyclohexane ring are difficult. As part of a project to investigate the NMR properties of menthol derivatives, several axially substituted 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 tosylate⁸ 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 derivative¹⁰ 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, CH₂Cl₂, Et₃N, 99% yield; b) KCN, CH₃CN, 18-crown-6, 64% yield; c) LiAlH₄, 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 sp³ 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 ¹H 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 pre-coated plates with fluorescent indicator, and compounds were visualized using aqueous vanillin/H₂SO₄ 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. ¹H NMR was obtained at 400 MHz and ¹³C 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 procedure¹⁰ 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 SiO₂ 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. NaHCO₃ (100 mL) and saturated aq. NaCl (50 mL). The organic solution was dried over MgSO₄, 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.

^1H NMR (400 MHz, CDCl_3): δ 0.81 (d, 3 H, CH_3), 0.82–0.89 (m, 1 H, axial *CHH*), 0.92 (dd, 6 H, 2 CH_3), 1.04 (m, 1 H, axial *CHH*), 1.27 (q, 1 H, axial *CHH*), 1.42 (m, 2 H, axial *CHH*), 1.69 (m, 2 H, equatorial *CHH* and $\text{CH}(\text{CH}_3)_2$), 2.06 (m, 1 H, equatorial *CHH*), 2.26 (m, 1 H, equatorial *CHH*), 3.00 (s, 3 H, SO_2CH_3), 4.53 (td, 1 H, CHOSO_2). MS (EI, 70eV): m/z 138 ($-\text{OSO}_2\text{CH}_3$).

(1*S*, 2*S*, 5*R*)-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 \times 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%).

(1*S*, 2*S*, 5*R*)-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 \times 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. $[\alpha]_{\text{D}}^{20} = -10.9$ (c 0.024, CHCl_3). ^1H 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 *CHH*), 1.05 (m, 1 H, axial *CHH*), 1.19 (m, 1 H, axial *CHH*), 1.37 (m, 1 H, axial *CHH*), 1.6–1.8 (m, 3 H, equatorial *CH*, $\text{CH}(\text{CH}_3)_2$), 2.0 (dd, 1 H, equatorial *CH*), 2.67 (bs, equatorial *CHCHO*), 9.85 (d, 1 H, *CHO*). ^{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^+).

(1*S*, 2*S*, 5*R*)-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 MgSO₄. 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, CHCl₃).

¹H NMR (400 MHz, CDCl₃): δ 0.83 (m, 1 H, axial CH), 0.85 (d, 3 H, CH₃), 0.90 (d, 3 H, CH₃), 0.92 (d, 3 H, CH₃), 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). ¹³C NMR (100 MHz, CDCl₃): 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 C₁₁H₂₀O₂: C, 71.70; H, 10.94. Found: C, 71.85; H, 11.09.

(1*S*,2*S*,5*R*)-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 MgSO₄ 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). ¹H NMR (400 MHz, CDCl₃): δ 0.8–1.0 (m, 12 H, 3 CH₃, 3 axial CHH), 1.37 (m, 1 H, axial CHH), 1.50 (m, 1 H, CH(CH₃)₂), 1.68 (m, 3 H, 2 equatorial CHH, axial C₅HH), 2.42 (bs, 2 H, NH₂), 2.71 (bd, 2 H, CH₂NH₂). ¹³C NMR (100 MHz, CDCl₃): 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 C₁₁H₂₄ClN: C, 64.21; H, 11.76; N, 6.81. Found: C 64.12; H, 11.79; N, 6.57.

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