PERKIN 1 COMMUNICATION

Ring-fused *gem*-dibromocyclopropanes as precursors to enantiomerically pure D- and L-series 3-deoxy- and 2-amino-2,3-dideoxyaldohexose derivatives

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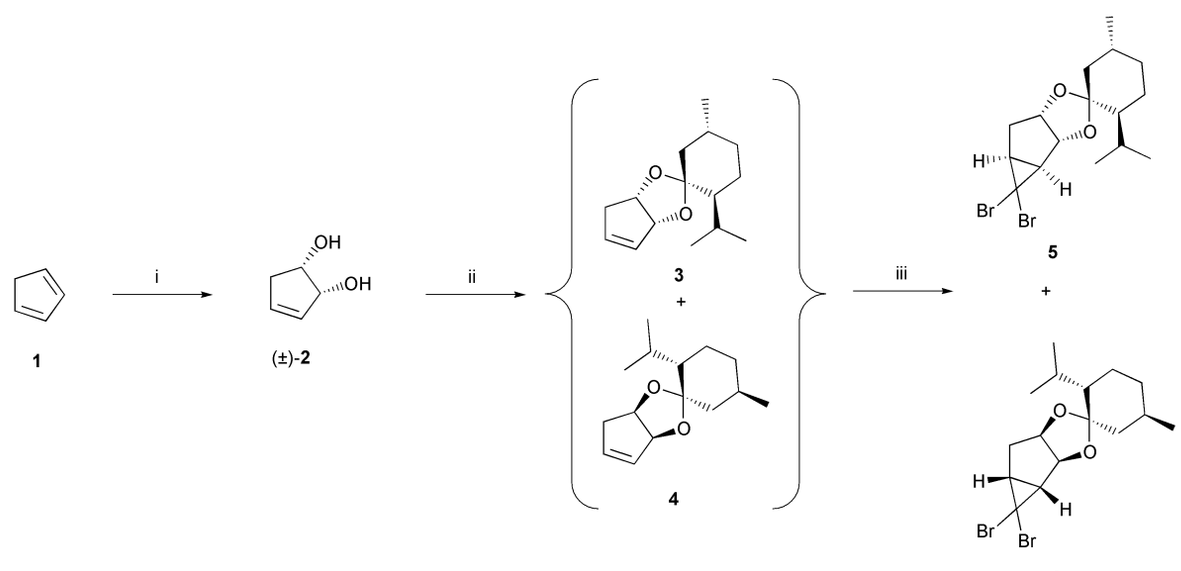
The readily available *gem*-dibromocyclopropanes 5 and 6 undergo silver(I)-promoted electrocyclic ring-opening and the resulting π-allyl cations trapped with a range of nucleophiles to give mixtures of cyclohexenyl bromides such as 7–9 and 17–19, respectively. Subjection of certain of these products to ozonolytic cleavage followed by reduction protocols then affords differentially protected and enantiopure D- and L-series 3-deoxy- and 2-amino-2,3-dideoxyaldohexoses.

3-Deoxyaldohexoses and 2-amino-2,3-dideoxyaldohexoses are of significance because of their occurrence as substructures within more complex carbohydrates and/or their potential as biochemical tools for use in the study of a variety of biochemical transformations.[1] Furthermore, compounds such as 2-amino-2,3-dideoxy-D-*arabino*-hexose (2-amino-2,3-dideoxy-D-*manno*-pyranose) have been shown[2] to act as inhibitors of angiogenesis and, therefore, have potential for the treatment of chronic inflamation, diabetic retinopathy, psoriasis and rheumatoid arthritis as well as the suppression of metastases. As such these rare sugars represent attractive synthetic targets and they have most frequently been prepared by traditional methods involving, *inter alia*, selective deoxygenation of common aldohexoses[3] or desulfurisation of related thiosugars.[4] Fischer–Kiliani chain extension of 2-deoxyaldopentoses has also been employed[5] together with enzymatic processes involving aldolases.[6] A rather versatile approach has been pursued by Vogel and co-workers using non-carbohydrate derived "naked sugars" as synthons for the preparation of a wide-variety of D- and L-forms of various monosaccharides including members of the title classes of compound.[1,7] It is against this background that we now describe new and flexible methods for the synthesis of enantiomerically pure D- and L-series 3-deoxyaldohexoses and 2-amino-2,3-dideoxyaldohexoses from ring-fused *gem*-dibromocyclopropanes. The present work also serves to highlight the value of menthanediyls[8] as protecting groups for *cis*-vicinal diols and as auxiliaries for effecting the resolution of racemic mixtures of such diols.

The pivotal early stages of the present work are outlined in Scheme 1 and involve formation of the previously reported[9] *cis*-1,2-diol (±)-**2** *via* lead tetraacetate-mediated dihydroxylation of freshly cracked cyclopentadiene (**1**). Treatment of compound (±)-**2** with (−)-menthone (*p*-menthan-3-one) and catalytic amounts of toluene-*p*-sulfonic acid (*p*-TsOH) in refluxing pentane resulted in the smooth formation of the corresponding menthanediyls **3**†‡ and **4** (81% combined yield) which were not readily separable by conventional means. As a consequence this mixture of diastereoisomers was subjected to reaction with dibromocarbene (generated under phase-transfer conditions) and in this manner the cyclopropanes **5** {$[a]_D = -10$ (*c* 1.0)§} and **6** {$[a]_D = -30$ (*c* 1.1)} were obtained (98% combined yield) and these could be separated from one another by careful gravity column chromatography involving gradient elution techniques. The assignment of the illustrated structures to compounds **5** and **6** follows from



Scheme 1 *Reagents and conditions*: (i) $Pb(OCOMe)_4$ (0.68 mol equiv.), $MeCO_2H$, H_2O, 0–18 °C, 1 h then K_2CO_3, MeOH, 18 °C, 2 h; (ii) (−)-menthone (1.2 mol equiv.), *p*-TsOH (trace), pentane, 36 °C, 48 h then DBU (1.1 mol equiv. wrt *p*-TsOH); (iii) $CHBr_3$, 50% aq. NaOH, C_6H_6, TEBAC, 0–18 °C, 48 h (TEBAC = triethylbenzylammonium chloride).

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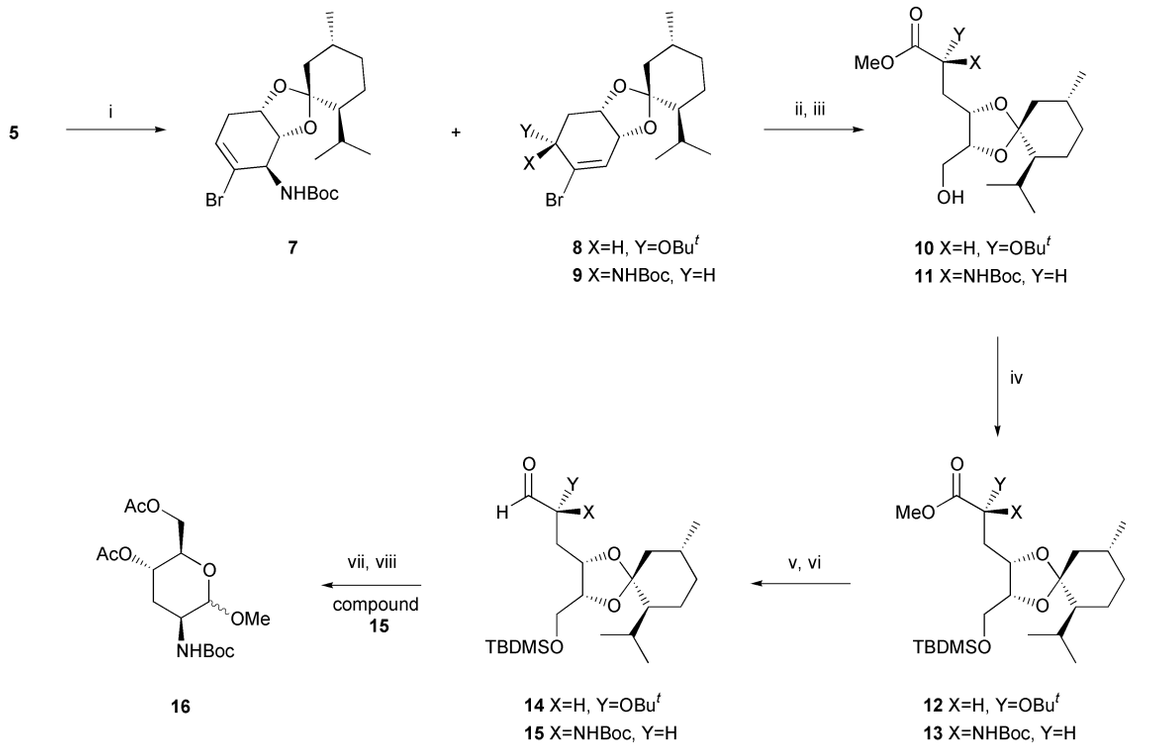


Scheme 2 *Reagents and conditions*: (i) AgOCN (7.0 mol equiv.), Bu^{t}OH, 80 °C, 72 h; (ii) O_3, CH_2Cl_2–MeOH, pyridine (4.0 mol equiv.), −90 °C, 0.2 h; (iii) KI (1.5 mol equiv.), $NaBH_4$ (6.0 mol equiv.), −90–0 °C, 1 h; (iv) TBDMSOTf (1.5 mol equiv.), 2,6-dimethylpyridine, CH_2Cl_2, 0–18 °C, 0.5 h (for **10**→**12**) or TBDMSCl (1.3 mol equiv.), Et_3N (1.8 mol equiv.), DMAP (trace), CH_2Cl_2, 18 °C, 7 h (for **11**→**13**); (v) DIBAL-H (2.0 mol equiv.), CH_2Cl_2, −78–18 °C, 8 h; (vi) Dess–Martin reagent (1.5 mol equiv.), pyridine, CH_2Cl_2, 0–18 °C, 4 h; (vii) 36% HCl (trace) in MeOH, 0–18 °C, 18 h; (viii) Ac_2O (mol equiv.), pyridine, 0–18 °C, 3 h.

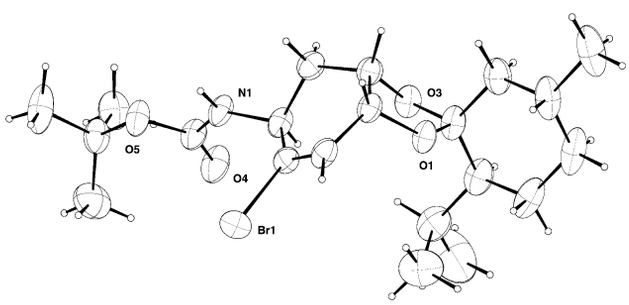


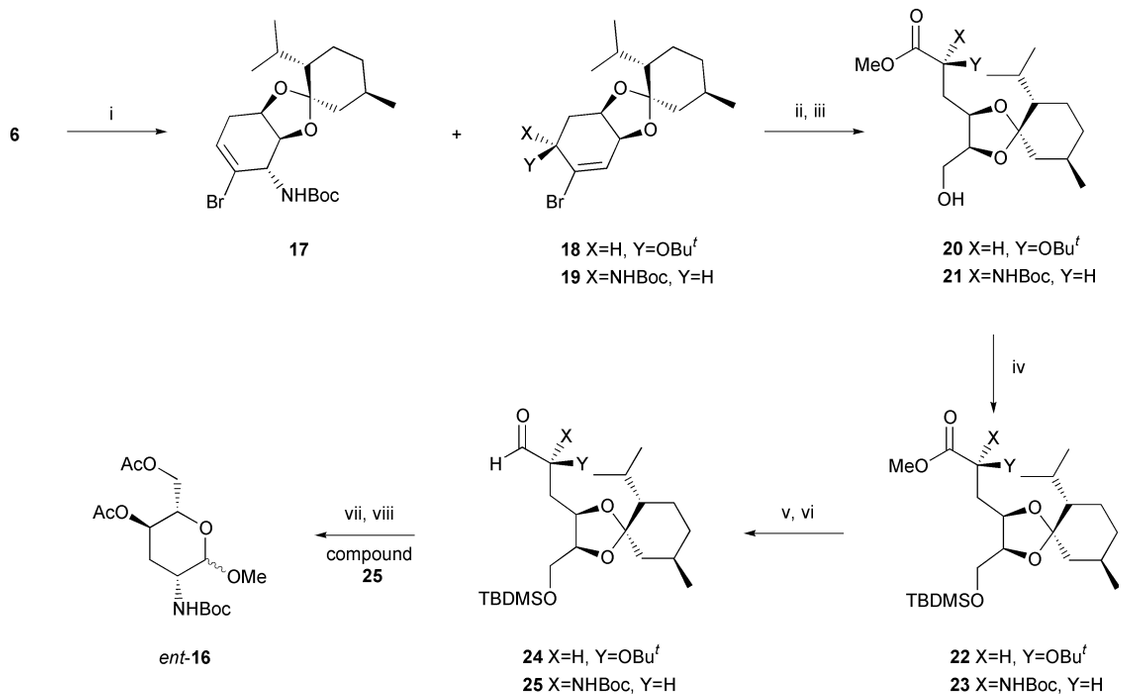
Fig. 1 ORTEP (with 50% probability ellipsoids) of compound **9** derived from X-ray crystallographic data.

X-ray crystallographic analyses and a chemical correlation study (*vide infra*).¶

The reaction sequences outlined in Scheme 2 serve to highlight the utility of compound **5** as a synthon for the preparation of various "D-series" deoxyaldohexoses. Thus, treatment of this ring-fused cyclopropane with silver isocyanate in the presence of *tert*-butyl alcohol afforded a mixture of bromocyclohexenes **7** {26%, $[a]_D = +76$ (*c* 1.1)}, **8** {17%, $[a]_D = -17$ (*c* 1.0)} and **9** {49%, mp = 55–56 °C, $[a]_D = +4$ (*c* 1.0)} that were readily separated from one another by flash chromatography on silica. The carbamates most likely arise *via* silver(I)-promoted electrocyclic ring-opening of the *gem*-dibromocyclopropyl moiety[10] and interception of the resulting π-allyl cation with isocyanate. The ensuing allylic isocyanates then react, at the *sp*-hybridised carbon, with *tert*-butyl alcohol to give compounds **7** and **9**. The structure of compound **9** was established by single crystal X-ray analysis (Fig. 1)‖ which also served to confirm the structures of compounds **3** and **5**. The all *cis*-relationship of the oxygen-containing groups associated with menthanediyl **8**, which was established by chemical correlation studies,** presumably arises *via* an S_N2 reaction between *tert*-butyl alcohol and the allylic isocyanate that also serves as a precursor to carbamate **9**.

The trioxygenated bromocyclohexenes **8** and **9** were independently subjected to ozonolytic cleavage in methanol–dichloromethane to give, after subsequent reduction of the ensuing hydroperoxide, the methyl esters **10** {94%, $[a]_D = -29$ (*c* 1.0)} and **11** {89%, $[a]_D = -42$ (*c* 1.0)}, respectively.[11] The C-6 hydroxy group within these latter compounds was protected as the corresponding TBDMS-ethers so as to form the fully protected hexanoic acid derivatives **12** {84%, $[a]_D = -31$ (*c* 1.0)} and **13** {99%, $[a]_D = -27$ (*c* 1.0)}, respectively. Reduction of the ester moiety within the latter pair of compounds was effected using DIBAL-H and the resulting 1°-alcohols then oxidised to the corresponding aldehydes, **14** {93%, $[a]_D = -35$ (*c* 1.3)} and **15** {80%, $[a]_D = -42$ (*c* 1.1)}, using the Dess–Martin periodinane. Sequential treatment of compound **15** with acidic methanol then acetic anhydride afforded an inseparable and *ca.* 6.3:1 mixture of the α- and β-forms of 2-amino-2,3-dideoxy-D-*arabino*-hexose derivative **16** {88% from **15**, $[a]_D = -8.6$ (*c* 1.1)} and thereby demonstrating that the menthanediyl protecting group is readily removed under rather mild conditions.

Access to the enantiomeric series of aldohexose derivatives involved, in the initial stages (Scheme 3), treatment of the *gem*-dibromocyclopropane **6** with silver isocyanate in the presence of *tert*-butyl alcohol so as to form the anticipated mixture of cyclohexenyl bromides **17** {23%, $[a]_D = -104$ (*c* 1.1)}, **18** {13%, $[a]_D = -5$ (*c* 1.2)} and **19** {55%, mp = 112–114 °C, $[a]_D = -73$ (*c* 1.1)} which could be separated from one another by flash chromatography. Independent subjection of the latter products to ozonolytic cleavage in methanol–dichloromethane followed by reductive work-up then afforded the hexanoic acid derivatives **20** {95%, $[a]_D = -25$ (*c* 1.0)} and **21** {95%, $[a]_D = -16$ (*c* 1.5)}, respectively. These were each converted, by standard means, into the corresponding TBDMS-ether derivatives, **22** {81%, $[a]_D = -8$ (*c* 1.0)} and **23** {90%, $[a]_D = -8$ (*c* 1.2)} respectively, which were, in turn, transformed into the aldehydes **24** {98%, $[a]_D = -13$ (*c* 1.0)} and **25** {88%, $[a]_D = -5$ (*c* 0.9)}. Sequential treatment of compound **25** with acidic methanol then acetic anhydride afforded an inseparable and



Scheme 3 *Reagents and conditions*: (i) AgOCN (7.0 mol equiv.), Bu^{t}OH, 80 °C, 72 h; (ii) O_3, CH_2Cl_2–MeOH, pyridine (4.0 mol equiv.), −90 °C, 0.2 h; (iii) KI (1.5 mol equiv.), $NaBH_4$ (6.0 mol equiv.), −90 to 0 °C, 1 h; (iv) TBDMSOTf (1.5 mol equiv.), 2,6-dimethylpyridine, CH_2Cl_2, 0–18 °C, 0.5 h (for **20**→**22**) or TBDMSCl (1.3 mol equiv.), Et_3N (1.8 mol equiv.), DMAP (trace), CH_2Cl_2, 18 °C, 7 h (for **21**→**23**); (v) DIBAL-H (2.0 mol equiv.), CH_2Cl_2, −78–18 °C, 8 h; (vi) Dess–Martin reagent (1.5 mol equiv.), pyridine, CH_2Cl_2, 0–18 °C, 4 h; (vii) 36% HCl (trace) in MeOH, 0–18 °C, 18 h; (viii) Ac_2O (mol equiv.), pyridine, 0–18 °C, 3 h.

ca. 2.2:1 mixture of the α- and β-forms of 2-amino-2,3-dideoxy-D-*arabino*-hexose derivative *ent*-**16** {83% from **25**, $[\alpha]_D = +4.5$ (*c* 1.2)}.

Compounds **14** and **24** represent differentially protected 3-deoxy-D-*ribo*-hexose and 3-deoxy-L-*ribo*-hexose derivatives, respectively, while congeners **15** and **25** are orthogonally protected forms of 2-amino-2,3-dideoxy-D-*arabino*-hexose and 2-amino-2,3-dideoxy-L-*arabino*-hexose, respectively. These rare monosaccharide derivatives, as well as related compounds that should be readily accessible by the rather simple methods described herein, are likely to prove useful as "building blocks" in the construction of a range of carbohydrates of biological interest.

Experimental

(±)-*cis*-Cyclopent-3-ene-1,2-diol [(±)-2]

Freshly cracked and twice-distilled cyclopentadiene (**1**) (62.0 g, 0.938 mol) was slowly added to a magnetically stirred and chilled (ice–water-bath) mixture of lead tetraacetate (284 g, 0.642 mol), acetic acid (580 ml, 10.2 mol) and water (24 ml, 1.32 mol) maintained under a nitrogen atmosphere. Shortly after completion of the addition of cyclopentadiene the reaction mixture became homogeneous and at this point the ice–water-bath was removed. Stirring was continued for 1 h then the reaction mixture was poured into diethyl ether (1200 ml) and the supernatant liquid decanted then filtered through a pad of TLC-grade silica gel. The filtrate was treated with Na_2CO_3 (300 g) and the resulting mixture stirred vigorously at 18 °C overnight. The resulting precipitate was removed by filtration and washed with diethyl ether (1 × 300 ml) then the combined filtrates were concentrated under reduced pressure to give a light-yellow oil. Distillation of this material afforded a *ca*. 1:1 mixture of regioisomeric mono-acetates (64.5 g, 48%) associated with diol (±)-**2** as a clear colourless oil, bp 101–104 °C, 15 mm Hg. A reaction mixture comprising these mono-acetates (79.0 g, 0.556 mol), K_2CO_3 (84.7 g, 0.614 mol) and MeOH (640 ml) was stirred vigorously at 18 °C while being protected from light. After 2 h diethyl ether (700 ml) was added and the ensuing mixture was filtered through a pad of TLC-grade silica gel. The pad was washed with diethyl ether (1 × 200 ml) and the combined filtrates concentrated under reduced pressure. The resulting light-yellow oil was subjected to distillation thereby affording diol (±)-**2**[9] (33.1 g, 60%) as a clear colourless oil, bp 96–98 °C (0.1 mm Hg). This material was identical, as judged by ^{1}H and ^{13}C NMR spectroscopic analysis, with authentic material.[9]

Compounds 3 and 4

A mixture of diol (±)-**2** (26.1 g, 261 mmol), (−)-menthone (48.3 g, 313 mmol) and *p*-TsOH (20 mg) in pentane (300 ml) was heated at reflux in an apparatus connected to a Dean–Stark trap. After 48 h the reaction mixture was cooled then treated with DBU (18 μL) and concentrated under reduced pressure to afford a light-yellow oil. Subjection of this material to flash chromatography (silica gel, 40:1 v/v hexane–ethyl acetate elution) afforded, after concentration of the appropriate fractions [$R_f = 0.4$ (15:1 hexane–diethyl ether elution)], a 1:1 mixture of the diastereoisomeric *menthanediyls* ***3*** *and* ***4*** (50.2 g, 81%) as a clear, colourless oil [Found: $M^{+\bullet}$, 236.1776. $C_{15}H_{24}O_2$ requires: $M^{+\bullet}$, 236.1776]; ν_{max} (KBr)/cm^{-1} 3057, 2869, 2844, 1615, 1455, 1365, 1304, 1161, 1117, 1091, 1082, 1042, 854, 720; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.71–0.93 (complex m, 22H), 1.20–1.39 (complex m, 4H), 1.56–1.69 (complex m, 6H), 1.82 (m, 1H), 1.87 (m, 1H), 2.05 (septet, $J = 7.2$ Hz, 2H), 2.44–2.52 (complex m, 4H), 4.65 (m, 1H), 4.73 (m, 1H), 5.01 (d, $J = 6.2$ Hz, 1H), 5.06 (d, $J = 5.9$ Hz, 1H), 5.72 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.8 (CH or CH_3), 19.3 (CH or CH_3), 22.6 (CH or CH_3), 22.7 (CH or CH_3), 23.8 (CH_2), 24.1(0) (CH or CH_3), 24.1(3) (CH_2), 24.6(1) (CH or CH_3), 24.6(4) (CH or CH_3), 30.8(9) (CH or CH_3), 30.9(3) (CH or CH_3), 35.1 (CH_2), 35.2 (CH_2), 38.8 (CH_2), 38.9 (CH_2), 44.4 (CH_2), 44.7 (CH_2), 48.3 (CH), 48.7 (CH), 77.0 (CH), 77.5 (CH), 85.0 (CH), 85.4 (CH), 113.2 (C), 130.6 (CH), 130.8 (CH), 132.3 (CH); *m*/*z* (EI, 70 eV) 236 [49%, $M^{+\bullet}$], 221 [44, $(M - CH_3^{\bullet})^+$], 179 (59), 151 (83), 69 (100).

Compounds 5 and 6

Bromoform (121 g, 478 mmol) was added to a vigorously stirred mixture of menthanediyls **3** and **4** (7.38 g of a 1:1

mixture, 31.2 mmol), benzene (40 ml), TEBAC (300 mg, mmol) and NaOH (56 ml of 50% w/v aqueous solution) maintained at *ca*. 0 °C (ice-bath). After 1 h the cooling bath was removed and stirring continued at *ca*. 18 °C for 48 h. The ensuing thick, brown reaction mixture was diluted with petroleum spirit (40–60 fraction, 300 ml) and the separated organic phase washed with brine (1 × 100 ml) then dried ($MgSO_4$), filtered and concentrated under reduced pressure (*ca*. 10 mm Hg). The resulting yellow oil was subjected to heating at 45–55 °C and 12 mm Hg in order to remove excess bromoform. The ensuing brown residue was subjected to flash chromatography (silica gel, 35:1 v/v 40–60 petroleum spirit–diethyl ether elution) and concentration of the appropriate fractions afforded a *ca*. 1:1.2 mixture of the diastereomeric *gem*-dibromocyclopropanes **5** and **6** (12.5 g, 98%) as a pale-yellow oil. A 1.2 g sample of this material was subjected to gravity column chromatography [330 g of TLC-grade silica gel contained in a 7 cm id chromatography column, gradient elution from neat 40–60 petroleum spirit to 80:1 v/v 40–60 petroleum spirit–diethyl ether] and in this manner two fractions, A and B, were obtained.

Concentration of fraction A ($R_f = 0.2$) afforded compound **5** as a clear, colourless oil, $[\alpha]_D = -9.45$ (*c* 1.00) [Found: $M^{+\bullet}$, 406.0145. $C_{16}H_{24}{}^{79}Br_2O_2$ requires: $M^{+\bullet}$, 406.0143]; ν_{max} (KBr)/cm^{-1} 2950, 2930, 2868, 1455, 1305, 1158, 1117, 1082, 1053, 996; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79–0.93 (complex m, 10H), 1.32–1.76 (complex m, 6H), 1.83 (d, $J = 15.5$ Hz, 1H), 2.19–2.24 (complex m, 3H), 2.43 (m, 1H), 2.51 (d, $J = 7.1$ Hz, 1H), 4.51 (d, $J = 5.6$ Hz, 1H), 4.61 (td, $J = 5.6$ and 2.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2 (CH or CH_3), 22.6 (CH or CH_3), 23.9 (CH_2), 24.2 (CH or CH_3), 25.1 (CH or CH_3), 30.9 (CH or CH_3), 35.1 (CH_2), 35.5 (C), 36.9 (CH_2), 38.5 (CH), 41.4 (CH), 43.6 (CH_2), 48.4 (CH), 84.2 (CH), 84.8 (CH), 115.9 (C); *m*/*z* (EI, 70 eV) 410 (31%) 408 (58) 406 (32) ($M^{+\bullet}$), 395 (32) 393 (54) 391 (31) [$(M - CH_3^{\bullet})^+$], 239 (73) 237 (100) 235 (73), 69 (99).

Concentration of fraction B ($R_f = 0.25$) afforded compound **6** as a light-yellow oil, $[\alpha]_D = -30.4$ (*c* 1.06) [Found: $M^{+\bullet}$, 406.0147. $C_{16}H_{24}{}^{79}Br_2O_2$ requires: $M^{+\bullet}$, 406.0143]; ν_{max} (KBr)/cm^{-1} 2950, 2869, 1455, 1305, 1161, 1112, 1082, 1051, 1006, 743; ^{1}H NMR (300 MHz, $CDCl_3$) 0.83–0.93 (complex m, 10H), 1.24–1.75 (complex m, 6H), 1.82 (dm, $J = 15.4$ Hz, 1H), 2.10 (dd, $J = 15.4$ and 5.5 Hz, 1H), 2.20–2.31 (complex m, 2H), 2.42 (t, $J = 7.2$ Hz, 1H), 2.52 (d, $J = 7.2$ Hz, 1H), 4.52 (d, $J = 5.3$ Hz, 1H), 4.55 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2 (CH or CH_3), 22.6 (CH or CH_3), 24.0 (CH_2), 24.2 (CH or CH_3), 25.1 (CH or CH_3), 30.9 (CH or CH_3), 35.0 (CH_2), 36.0 (C), 36.5 (CH_2), 38.5 (CH), 41.9 (CH), 43.6 (CH_2), 48.4 (CH), 84.5 (CH), 85.3 (CH), 115.9 (C); *m*/*z* (EI, 70 eV) 410 (40%) 408 (58) 406 (41) ($M^{+\bullet}$), 395 (34) 393 (53) 391 (31) [$(M - CH_3^{\bullet})^+$], 239 (67) 237 (100) 235 (67), 69 (100).

Each "cycle" of above-mentioned gravity column chromatographic procedure provides 350–400 mg samples of the diastereomerically pure cyclopropanes **5** and **6** and those fractions containing mixtures of these compounds are readily recycled.

Acknowledgements

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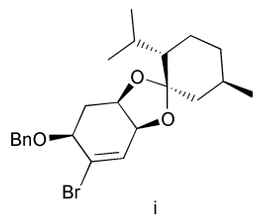
Notes and references

† All new and stable compounds had spectroscopic data [IR, NMR, mass spectrum] consistent with the assigned structure. Satisfactory combustion and/or high resolution mass spectral analytical data were obtained for new compounds and/or suitable derivatives.

‡ The use of higher boiling solvents in this acetalisation reaction leads to the formation of samples of compounds **3** and **4** which appear to be contaminated with the epimeric (at the spiro-carbon) menthanediyls.

§ All optical rotations were determined in chloroform solution at 20 °C.

¶ The illustrated *anti*-relationship between the cyclopropyl and menthanediyl moieties within compounds **5** and **6** has not been rigorously proven but follows by analogy with stereochemical outcomes of reactions leading to closely related compounds.[9] Further support for the structure of compound **6** follows from single crystal X-ray analysis of benzyl ether i which is obtained, as the major reaction product, upon treatment of the former compound with silver isocyanate in neat benzyl alcohol.



i

‖ *Crystal data for* **9**: $C_{23}H_{31}BrO_3$, $M_r = 435.407$, $T = 200.0(1)$ K, monoclinic, space group $P2_1$, $Z = 2$, $a = 8.2977(13)$, $b = 8.1755(12)$, $c = 16.318(2)$ Å, $\beta = 94.645(11)°$, $U = 1103.3(3)$ Å^3, $\rho_{calc} = 1.31$ g cm^{-3}, $F(000) = 456$, $\mu(MoK\alpha) = 1.88$ mm^{-1}, 4562 unique data ($2\theta_{max} = 55°$), 2418 with $I > 3\sigma(I)$; $R = 0.051$, $R_w = 0.060$, $S = 1.03$.

Data were measured on a Nonius Kappa CCD diffractometer (graphite crystal monochromator, $\lambda = 1.54180$ Å). Refinement was by full-matrix least squares analysis on *F* using the CRYSTALS[12] structure analysis suite. Structure solution was by direct methods (SIR92).[13] CCDC reference number 207/500. See http://www.rsc.org/suppdata/p1/b0/b008146i/ for crystallographic files in .cif format.

** Compound **8** was subject to treatment with trifluoroacetic acid then aqueous trifluoroacetic acid which resulted in cleavage of both the menthanediyl and *tert*-butyl ether moieties. The ensuing triol was converted into the corresponding acetonide under standard conditions and the latter compound {mp 68–70 °C, $[\alpha]_D$ +143.4 (*c* 0.64, $CHCl_3$)} proved spectroscopically identical with its optical antipode {mp 69–70 °C, $[\alpha]_D$ −141 (*c* 1.03, $CHCl_3$)} that has been prepared from (−)-quinic acid (1,3,4,5-tetrahydroxycyclohexanecarboxylic acid) by Paquette and co-workers (*J. Am. Chem. Soc*., 1997, **119**, 3038).

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