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Stereochemistry of 11-Hydroxy-1,3,5,7,11-pentamethyl-2,4,6,8-tetraoxatricyclo[3.3.3.0$^{(3,7)}$]undecan-9-one and Related Diols

Asmita V. Patel,* Ioanna Alexandropoulou and Trevor A. Crabb

School of Pharmacy and Biomedical Science, University of Portsmouth, St. Michael's Building, White Swan Road, Portsmouth, Hampshire PO1 2DT, UK

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Abstract—11-Hydroxy-1,3,5,7,11-pentamethyl-2,4,6,8-tetraoxatricyclo[3.3.3.0$^{(3,7)}$]undecan-9-one adopts an equilibrium (in CD_2Cl_2 at −90°C) between ca. 68% of the conformer with a pseudo-axial C-11 methyl substituent and ca. 32% of the alternative pseudo-equatorially substituted conformer. The derived *cis*-9,11-diol, *cis*-9,11-dimethyldiol and *cis*-9-phenyl-11-methyldiol adopt conformational equilibria heavily biased towards the diaxial OH conformations which are stabilised by internal H-bonds involving the dioxolan ring oxygen atoms.
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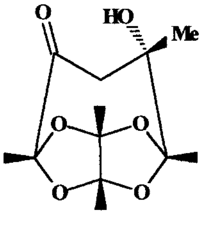
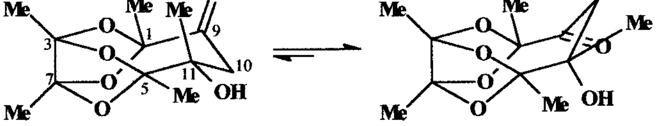
11-Hydroxy-1,3,5,7,11-pentamethyl-2,4,6,8-tetraoxatricyclo-[3.3.3.0$^{(3,7)}$]undecan-9-one (**1**), derived from the acid catalysed trimerisation of butan-2,3-dione[1–4] may exist in solution as an equilibrium between conformer **1a** (in which the OH group is pseudo-equatorial) and conformer **1b** (in which the OH group is pseudo-axial) interconvertible by partial pseudo-rotation of the 8-membered 1,3-dioxacyclo-octane ring. The most stable conformation of cyclo-octanone has been shown to be the chair-boat conformation[5,6] and conformers **1a** and **1b** contain both chair-boat and crown conformations of the 1,3-dioxacyclooctanone ring system (Scheme 1). For example, **1a** has a crown conformation containing C3 and a chair-boat conformation containing C7. Some deviation from classical chair-boat and crown conformations depicted in **1a** and **1b** are expected in order to minimise non-bonded interactions between C(11)–Me and C(5)–Me. In order to investigate the conformational equilibria in **1** and related 9,11-diols **2**,**3**,**4** and **5**, low temperature NMR spectroscopic studies were undertaken.

The ^1H NMR spectrum of **1** in CD_2Cl_2 at −90°C shows signals for the two conformers. In particular, two AB



1



1a **1b**

Scheme 1.

Keywords: stereochemistry; NMR; conformation; butan-2,3-dione tricyclic trimer.

* Corresponding author. Tel.: +23-92843575; fax: +23-92843565; e-mail: asmita.sautreau@port.ac.uk

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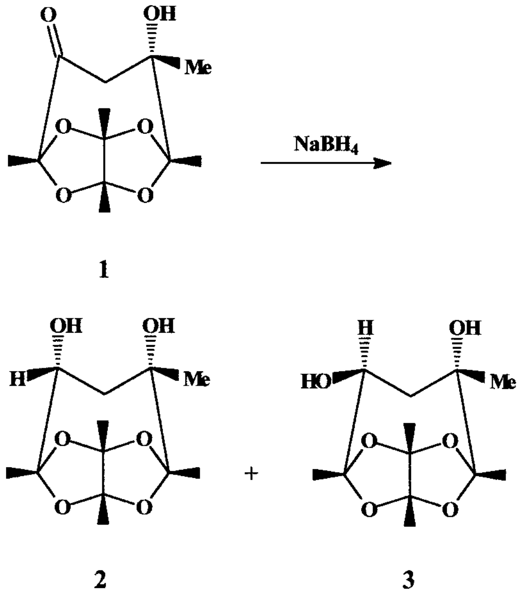


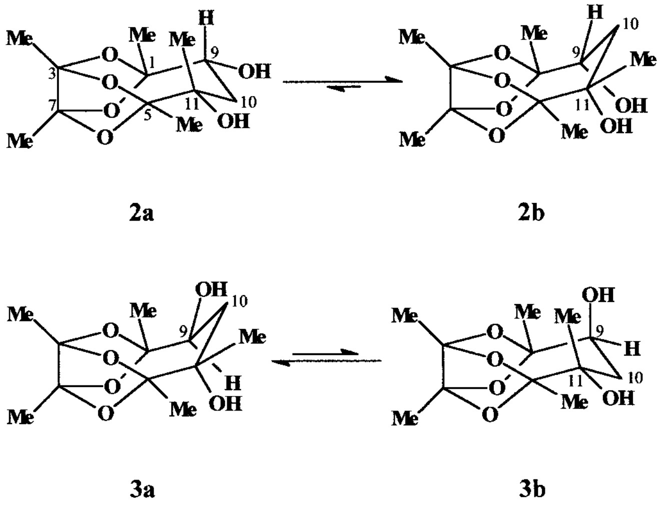
Scheme 2.

quartets for the C(10) methylene protons are clearly visible corresponding to a major conformer (ca. 68%) with δ 2.06 and 3.75 ($J_{\mathrm{gem}}=-11.2$ Hz) and a minor conformer (ca. 32%) with δ 2.21 and δ 3.69 ($J_{\mathrm{gem}}=-9.7$ Hz). The significant difference between the geminal coupling constants for the C-10 methylene protons provides a means of identifying the conformers. Thus in conformers of **1** the value of J_{gem} depends upon the dihedral angle between the C=O and adjacent C–H bonds[7] and on the dihedral angle between a C–H bond of the methylene group and the adjacent electronegative OH substituent.[8–10] In the latter case, when the C–C–OH plane bisects the H–H internuclear axis of the methylene group a small algebraic increase in J_{gem} (a smaller negative coupling constant) is expected, whereas in orientations such that the C–OH and the adjacent C–H bond lie in the same plane, an algebraic decrease in J_{gem} is expected (larger negative coupling constant).

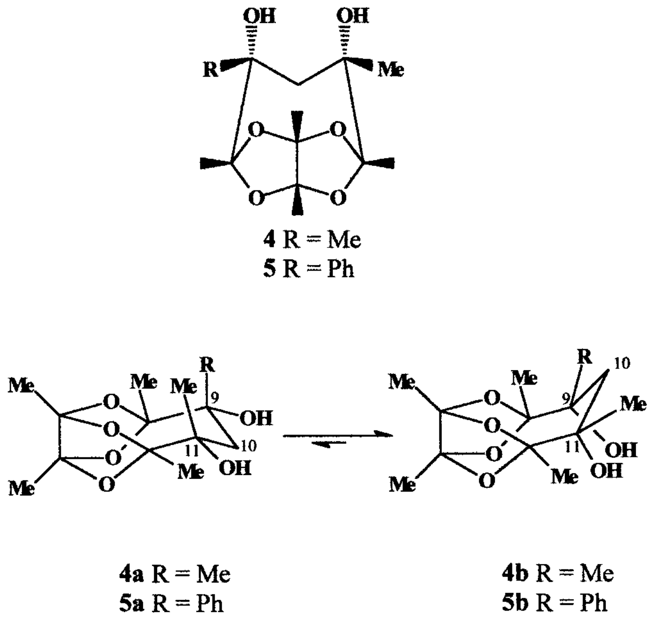
Models show that the C=O group in both conformers **1a** and **1b** makes similar projected angles with the adjacent CH$_2$ bonds and accordingly only a small differential effect on J_{gem} is expected, whereas different orientations of the OH group with the adjacent CH$_2$ bonds are indicated. In **1a** the HO–C–C plane approaches bisection of the H–H internuclear axis and a smaller negative coupling constant is expected. In **1b** the dihedral angle between C–OH and a C–H is ca. 180° and a larger negative coupling constant is expected. On this basis the pseudo-equatorial conformer **1a** is assigned to the minor conformer with $J_{\mathrm{gem}}=-9.7$ Hz and the pseudo-axial OH conformer **1b** with $J_{\mathrm{gem}}=-11.2$ Hz to the major conformer. The J_{gem} of -10.8 Hz in the room temperature NMR spectrum of **1** shows the predominance of conformer **1b**. The IR spectrum of **1** in a very dilute CCl$_4$ solution showed absorption indicative of intramolecular H-bonding at 3572 cm^{-1}.

Reduction of **1** with sodium borohydride in methanol gave a ca. 70:30 mixture of isomeric diols (Scheme 2). These were separated by centrifugal thin layer chromatography (cTLC) to give isomer **2** (major isomer) mp 95–98°C, and isomer **3** (minor isomer) mp 90–92°C. In order to assist in NMR assignments **1** was also reduced by lithium aluminium deuteride and a ca. 70:30 mixture of the 9-deuterio derivatives of **2** and **3** was obtained. The ^{1}H NMR spectrum of **2** and **3** at 25°C showed broadened signals characteristic of slow conformational interchange. The spectral signals coalesced on lowering the temperature until at -60°C the spectra of both isomers showed signals for two conformers corresponding to **2a** and **2b** and to **3a** and **3b** (Scheme 3). The low temperature ^{1}H NMR spectrum of the major isomer **2** showed a conformer ratio of ca. 93:7 in contrast to a ratio of ca. 43:57 in the spectrum of the minor isomer **3**.

The two conformers of the major isomer **2** were clearly differentiated on the basis of the J_{gem} for the C-10 methylene protons of -15.6 Hz in the spectrum of the major conformer and -13.7 Hz in that of the very minor conformer. The more negative J_{gem} of -15.6 Hz is characteristic of the stereochemistry in the diaxial OH conformer **2b** in which the electronegative OH substituents make a negative



Scheme 3.



4 R = Me
5 R = Ph

4a R = Me
5a R = Ph

4b R = Me
5b R = Ph

Scheme 4.

contribution to J_{gem}.[9,10] Vicinal couplings with the C-9 protons confirmed the **2b** assignment with $J_{10'ax',9'eq'}=0$ and $J_{10'eq',9'eq'}=7.3$ Hz consonant with dihedral angles estimated from Dreiding models. The J_{gem} of -13.7 Hz in the spectrum of the minor conformer **2a** is consonant with the expected effects of the two pseudo-equatorial OH groups on this parameter.[9] The near *trans*-diaxial orientation between H-9'ax' and H-10'ax' in **2a** was shown by the vicinal coupling constant of 10.6 Hz. In the spectrum of both **2a** and **2b** the low field proton signal of the C-10 methylene pair was assigned to the pseudoaxial H10 deshielded by the *cis*-oxygen atoms of the 1,3-dioxolan ring. Finally the ^{13}C NMR spectrum (−60°C in CD_2Cl_2) of **2a** and **2b** showed C-10 shifts of δ 45.3 and of 38.3 respectively consonant with differential β substituent effects on that carbon nucleus.

The ^1H NMR spectrum of the two conformers of **3** showed very similar J_{gem} values for the C-10 methylene protons of -14.5 and -14.8 Hz consonant with conformers **3a** and **3b**, both of which have one pseudo-axial and one pseudo-equatorial OH group. The major conformer (57% at −60°C) was assigned as conformer **3a** on the basis of $J_{10'ax',9'ax'}=10.7$ and $J_{10'eq',9'ax'}=0$ Hz. These vicinal coupling constants may be compared with those assigned in the spectrum of the minor (43% at −60°C) conformer **3b** of $J_{10'ax',\,9'eq'}=0$ and $J_{10'eq',\,9'eq'}=7.3$ Hz. In both spectra the low field C-10 proton was assigned on the basis of its proximity to the dioxolan ring oxygen atom. The vicinal couplings were very close to those in the similarly positioned conformers **2a** and **2b**. As in the case of the conformers of **2**, the stereochemistry depicted in **3a** and **3b** was confirmed by the C-10 ^{13}C NMR shifts of δ 45.1 in **3a** and δ 41.6 in **3b**.

The reaction between **1** and methyl lithium has been shown previously[3] to give rise to only the *cis*-9,11-dimethyl diol **4**. The broadened signals in the ^1H NMR spectrum of **4** at room temperature coalesced on lowering the temperature until at −60°C signals for both conformers were observed in the ratio ca. 85:15 (Scheme 4). The spectrum of the major conformer showed an AB quartet for the C(10) methylene protons at δ 1.73 and 2.49 ($J_{gem}=-15.6$ Hz) whereas that of the minor conformer showed the AB quartet at δ 1.85 and 2.73 ($J_{gem}=-13.7$ Hz). Conformer **4b** has the two hydroxyl groups in axial orientations with respect to a methylene C–H on C(10) and these make a negative contribution to the geminal coupling constants compared to conformer **4a**, in which both of the OH groups are equatorial and a small positive contribution to the coupling constant is expected. On this basis the major conformer was assigned as **4b** and the minor as **4a**.

Reaction between **1** and phenyllithium gave only one isomer assigned the *cis*-configuration **5** by analogy with the stereochemistry of the dimethyldiol **4**. The ^1H and ^{13}C NMR spectra of the *cis*-diol **5** at −90°C showed the presence of only one conformer assigned conformation **5b** from the value of J_{gem} for the C-10 methylene protons of -15.6 Hz.

All three *cis*-9,11-diols **2**, **4** and **5** adopt conformational equilibria heavily biased towards the diaxial 9,11-OH conformers **2b**, **4b** and **5b**. In the IR spectra in dilute solutions of all three compounds strong intramolecular H-bonding is indicated by absorption at 3547 cm^{-1} consistent with H-bonding between the axial OH and the acetal oxygen atoms in **2b**, **4b** and **5b**. The observed conformational preferences are therefore not unexpected since it is well known that the energy of the H-bond can have a considerable effect on conformational equilibria. This has been clearly shown for the related 5-hydroxy-1,3-dioxan system.[11] In **2b**, **4b** and **5b** this H-bonding stabilisation outweighs the unfavourable near-*gauche* interactions between the C1 and C9 and between the C5 and C11 substituents. In addition, the alternative conformers **4a** and **5a** are destabilised by severe 1,3-*syn*-axial Me/Me and Me/Ph non-bonded interactions respectively.

Experimental

General

^{1}H and ^{13}C NMR spectra were recorded at room temperature in $CDCl_3$ or CD_2Cl_2 and at low temperature in CD_2Cl_2 solutions on a JEOL GSX FT spectrometer at 270.16 (^{1}H) and 67.97 (^{13}C) MHz with tetramethylsilane as internal standard. Coupling constants (*J*) are quoted in Hertz. Mass spectra were obtained on a JEOL JMS DX 303 mass spectrometer, operating in either an alternating chemical ionisation (CI)-electron impact (EI) low resolution mode or in a high resolution EI mode. Mps were determined on a hot-stage microscope and are uncorrected. IR spectra were recorded on a Perkin–Elmer 683 spectrophotometer as 0.0005 M solutions in CCl_4 using a 10 mm pathlength cell. Thin layer chromatography (TLC) was carried out on glass silica gel (60 G) plates (0.5 mm) with chloroform and 1% of methanol as solvent, unless otherwise specified. Centrifugal TLC was run on a centrifugal TLC, Chromatotron model 7924T with circular silica gel (60 G) plates (4 mm) made with 70 G silica and 150 ml water.

11-Hydroxy-1,3,5,7,11-pentamethyl-2,4,6,8-tetraoxatricyclo[3.3.3.0$^{(3,7)}$]undecan-9-one (1)

This compound was prepared by the method of Diels and Jost[1] as white crystals mp 108–110°C, lit.[1] mp 109–111°C; $\nu_{max}(CCl_4)$ 3572 cm^{-1}; δ_H (270 MHz, CD_2Cl_2 at 20°C): 1.24 (Me), 1.37 (Me), 1.39 (Me), 1.54 (Me), 1.56 (Me), 2.44 and 3.26, (2H, AB, $J_{10'ax',10'eq'}=-10.8$ Hz, 2H-10); δ_H (270 MHz, CD_2Cl_2 at −90°C): 2.06 and 3.75 (2H, AB, $J_{10'ax',10'eq'}=-11.2$ Hz, 2H-10 in **1a**), 2.21 and 3.69 (2H, AB, $J_{10'ax',10'eq'}=-9.7$ Hz, 2H-10 in **1b**); δ_C (68 MHz, CD_2Cl_2 at 20°C): 20.2 (Me), 20.9 (Me), 21.5 (Me), 22.1 (Me), 24.0 (Me), 47.0 (C-10), 81.4 (C-11), 106.1 (C), 111.9 (C), 112.2 (C), 112.8 (C) and 212.3 (C=O); δ_C (67 MHz, CD_2Cl_2 at −90°C): conformer **1a**, 46.4 (C-10), 82.4 (C-11), 105.9 (C), 111.5 (C), 111.7 (C), 112.4 (C) and 214.7 (C=O); conformer **1b**, 53.9 (C-10), 79.8 (C-11), 106.0 (C), 112.1 (C), 113.4 (C) and 210.6 (C=O).

9,11-Dihydroxy-1,3,5,7,11-pentamethyl-2,4,6,8-tetraoxatricyclo[3.3.3.0$^{(3,7)}$]undecane (2 and 3)

Sodium borohydride (3.65 g, 0.096 mol) was added to **1** (5.56 g, 0.021 mol) in dry methanol (100 ml) and the mixture was stirred for 4 h. Inorganic material was filtered off and the solvent evaporated in vacuo. The residue was dissolved in chloroform (150 ml) and extracted with water (3×100 ml). The organic phase was dried over anhydrous sodium sulphate and the solvent evaporated in vacuo to give an oily mixture of the two isomers of 9,11-dihydroxy-1,3,5,7,11-pentamethyl-2,4,6,8-tetraoxatricyclo[3.3.3.0$^{(3,7)}$]-undecane (4.77 g, 82%). Part of the isomeric mixture (1.84 g) was separated by centrifugal TLC (cTLC) over silica with chloroform (800 ml) as the eluting solvent. A total of 42 fractions were collected and examined by TLC. Those which were similar were combined to give pure *cis*-9,11-dihydroxy-1,3,5,7,11-pentamethyl-2,4,6,8-tetraoxatricyclo[3.3.3.0$^{(3,7)}$]-undecane (**2**) as white amorphous powder mp 95–98°C (0.82 g, 14.7%); $\nu_{max}(CCl_4)$ 3547 cm^{-1}; δ_H (270 MHz, CD_2Cl_2 at −60°C): conformer **2a**, 1.68 (1H, d, $J_{10'eq',10'ax'}=-13.7$ and $J_{10'eq',9'ax'}=0$ Hz, H-10'eq'), 2.38 (1H, dd, $J_{10'ax',10'eq'}=-13.7$ and $J_{10'ax',9'ax'}=10.6$ Hz, H-10'ax') and 3.68 (1H, d, $J_{9'ax',10'ax'}=10.6$ and $J_{9'ax',10'eq'}=0$ Hz, H-9'ax'); conformer **2b**, 1.81 (1H, dd, $J_{10'eq',10'ax'}=-15.6$ and $J_{10'eq',9'eq'}=7.3$ Hz, H-10'eq'), 2.14 (1H, d, $J_{10'ax',10'eq'}=-15.6$ and $J_{10'ax',9'eq'}=0$ Hz, H-10'ax') and 3.14 (1H, d, $J_{OH,9'eq'}=7.7$ Hz, C(9)–O*H*), 3.93 (1H, dd, $J_{9'eq',OH}=7.7$, $J_{9'eq',10'eq'}=7.3$ and $J_{9'eq',10'ax'}=0$ Hz, H-9'eq') and 4.06 (1H, s, C(11)–O*H*); δ_C (67 MHz, CD_2Cl_2 at −60°C): conformer **2a**, 22.9 (Me), 23.7 (Me), 25.0 (Me), 45.3 (C-10), 72.9 (C-9), 75.6 (C-11), 110.4 (C), 112.2 (C) and 113.5 (C),; conformer **2b**, 21.9 (Me), 22.5 (Me), 23.6 (Me), 26.8 (Me), 27.1 (Me), 38.3 (C-10), 74.8 (C-9), 75.6 (C-11), 107.7 (C), 111.1 (C), 112.3 (C) and 112.4 (C); HRMS (EI): M$^+$, found 260.1253. $C_{12}H_{20}O_6$ requires 260.1260 and pure *trans*-9,11-dihydroxy-1,3,5,7,11-pentamethyl-2,4,6,8-tetraoxatricyclo[3.3.3.0$^{(3,7)}$]- undecane (**3**) as white crystals mp 90–92°C (0.28 g, 4.85%); $\nu_{max}(CCl_4)$ 3547 cm^{-1}; δ_H (270 MHz, CD_2Cl_2 at −60°C): conformer **3a**, 1.62 (1H, d, $J_{10'eq',10'ax'}=-14.5$ and $J_{10'eq',9'ax'}=0$ Hz, H-10'eq'), 2.54 (1H, dd, $J_{10'ax',10'eq'}= -14.5$ and $J_{10'ax',9'ax'}=10.7$ Hz, H-10'ax'), 3.81 (1H, d, $J_{9'ax',10'ax'}=10.7$ and $J_{9'ax',10'eq'}=0$ Hz, H-9ax), 3.82 (1H, brs, C(9)–O*H*), and 4.42 (1H, brs, C(11)–O*H*); conformer **3b**, Me proton absorptions for **3a** and **3b** occur as overlapping singlets between δ1.48 and 1.11, 1.93 (1H,dd, $J_{10'eq',10'ax'}=-14.8$ and $J_{10'eq',9'eq'}=7.3$ Hz, H-10'eq'), 2.22 (1H, d, $J_{10'ax',10'eq'}=-14.8$ and $J_{10'ax',9'eq'}=0$ Hz, H-10'ax'), 2.57 (1H, brs, C(9)–O*H*), 3.26 (1H, brs, C(11)–O*H*), and 4.10 (1H, m, H-9'eq'); δ_C (67 MHz, CD_2Cl_2 at −60°C): conformer **3a**, 22.1 (Me), 22.7 (Me), 23.7 (Me), 25.1 (Me), 26.4 (Me), 45.1 (C-10), 72.2 (C-9), 75.3 (C-11), 111.1 (C), 111.6 (C), 112.5 (C) and 112.7 (C); conformer **3b**, 22.0 (Me), 22.7 (Me), 23.0 (Me), 24.2 (Me), 26.9 (Me), 41.6 (C-10), 73.6 (C-9), 75.0 (C-11), 108.4 (C), 111.4 (C), 112.0 (C) and 113.3 (C); HRMS (EI): M$^+$, found 260.1262. $C_{12}H_{20}O_6$ requires 260.1260.

9,11-Dihydroxy-1,3,5,7,9,11-hexamethyl-2,4,6,8-tetraoxatricyclo[3.3.3.0$^{(3,7)}$]undecane (4)

A 21 round bottom flask was set up and equipped with mechanical stirrer, pressure equilibrium funnel, reflux condenser and drying tube. Diethyl ether, (1000 ml) was placed in the flask and then the tricyclic trimer **1** (34.42 g, 0.133 mol) was added and dissolved. Methyllithium (1.4 M, 200 ml, 0.28 mol) was added dropwise under an atmosphere of dry nitrogen, with some evolution of methane and a slight exothem. The resulting solution was refluxed gently for 4 h and the reaction quenched by the addition of water (50 ml). The mixture was allowed to stand overnight, the ether phase separated off, dried over anhydrous sodium sulphate, and evaporated. The resulting white residue was recrystallised from petroleum ether (bp 40–60°C) to give 9,11-dihydroxy-1,3,5,7,9,11-hexamethyl-2,4,6,8-tetraoxatricyclo[3.3.3.0$^{(3,7)}$]-undecane as white crystals mp 108–110°C, lit.[3] 109–111°C (29.75 g, 81.54%); $\nu_{max}(CCl_4)$ 3547 cm^{-1}; δ_H (270 MHz, $CDCl_3$ at 20°C): 1.23 (2Me), 1.40 (2Me), 1.56 (Me), 1.58 (Me), 1.79 (1H, brs, H-10), 2.40 (1H, brs, H-10) and 3.74 (2H, s, C(9)– and (11)–O*H*); δ_H (270 MHz, CD_2Cl_2 at −50°C): conformer **4a**, 1.38 (2Me), 1.49 (2Me), 1.59 (2Me), 1.85 (1H, d, $J_{10'ax',10'eq'}=-13.7$ Hz, H-10'eq'), 2.73 (1H, d, $J_{10ax,10eq}=-13.7$ Hz, H-10'ax') and 3.52 (2H, s, C(9)- and C(11)–O*H*); δ_C (68 MHz, $CDCl_3$ at 20°C): 22.3 (Me), 22.8 (Me), 24.4 (2Me), 28.8 (2Me), 47.4 (C-10), 76.4 (C-11), 111.1 (C), 112.1 (2C) and 112.6 (C); conformer **4b**, 1.23 (2Me), 1.41 (2Me), 1.59 (Me), 1.61 (Me), 1.73 (1H, d, $J_{10'eq',10'ax'}=-15.6$ Hz, H-10'eq'), 2.49 (1H, d, $J_{10'ax',10'eq'}=-15.6$ Hz, H-10'ax') and 4.12 (2H, s, C(9)- and C(11)–O*H*); δ_C (68 MHz, CD_2Cl_2 at −50°C): conformer **4a**, 23.0 (2Me), 23.4 (2Me), 23.6 (2Me), 51.4 (C-10), 75.9 (C-9 and C-11), 111.9 (C) and 113.6 (C); conformer **4b**, 22.2 (Me), 22.7 (Me), 24.5 (2Me), 29.1 (Me), 29.5 (Me), 46.2 (C-10), 76.3 (C-9 and C-11), 110.7 (C), 111.6 (C) and 112.6 (C); HRMS (EI): M^+, found 274.1406. $C_{13}H_{22}O_6$ requires 274.1416.

9,11-Dihydroxy-9-phenyl-1,3,5,7,11-pentamethyl-2,4,6,8-tetraoxatricyclo[3.3.3.0$^{(3,7)}$]undecane (5)

Phenyllithium (25.63 ml, 0.05 mol) was added to **1** (5 g, 0.02 mol) in dry diethyl ether (40 ml) under an atmosphere of dry nitrogen. Initially the solution was a clear yellow and on addition of half of the quantity of phenyllithium it became gradually more viscous and milky. The solution was refluxed for 24 h, cooled and water added. The mixture was extracted with diethyl ether. The organic layer was dried over anhydrous sodium sulphate and the solvent removed in vacuo. Recrystallisation of the crystalline product from petroleum ether (bp 40–60°C) gave 9,11-dihydroxy-9-phenyl-1,3,5,7,11-pentamethyl-2,4,6,8-tetraoxatricyclo[3.3.3.0$^{(3,7)}$]undecane as crystals, mp 118–120°C (4.8 g, 73.7 %); $\nu_{max}(CCl_4)$ 3547 cm^{-1}; δ_H (270 MHz, CD_2Cl_2 at −90°C): 0.90 (Me), 1.16 (Me), 1.41 (Me), 1.60 (Me), 1.63 (Me), 1.76 (1H, d, $J_{10'eq',10'ax'}=-15.6$ Hz, H-10'eq'), 2.89 (1H, d, $J_{10'ax',10'eq'}=-15.6$ Hz, H-10'ax'), 3.85 (O*H*), 4.39 (O*H*) and 7.20–7.33 (5H, m, Ph); δ_C (67 MHz, CD_2Cl_2 at −90°C):, 22.5 (Me), 23.1 (Me), 24.8 (Me), 26.6 (Me), 29.7 (Me), 48.2 (C-10), 76.9 (C-11), 80.2 (C-9), 111.3 (C), 112.2 (C), 112.5 (C), 113.7 (C) and 147.5, 128.2–124.7 (Ph). HRMS (EI): M^+, found 336.1569. $C_{18}H_{24}O_6$ requires 336.1572.

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