SHORT PAPER

J. Chem. Research (S), 2003, 784–785

The synthesis and X-ray crystal structure of 9-carboxyhexahydro-7-methoxy-4a,7-ethano-benzopyran-5-en-1-one†

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9-Carboxyhexahydro-7-methoxy-4a,7-ethano-benzopyran-5-en-1-one (**1**) was prepared and examined by X-ray crystallography to probe its potential as a new peptide scaffold/template. The crystal structure of the anhydride precursor 7-(2-acetoxyethyl)-4-methoxy-3a,4,7,7a-tetrahydro-4,7-ethanoisobenzofuran-1,3-dione (**6**) is also reported.

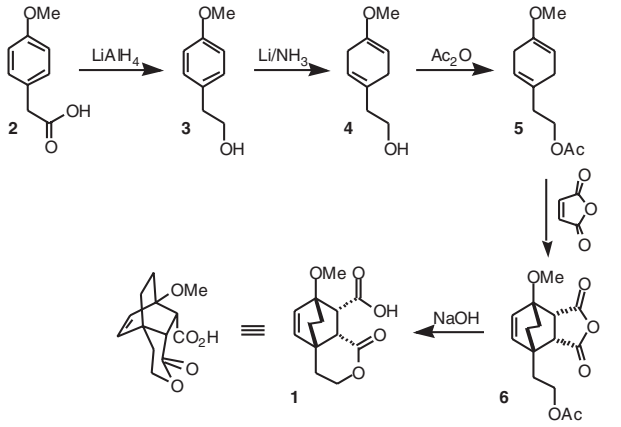
Keywords: peptide scaffold/template, 9-carboxyhexahydro-7-methoxy-4a,7-ethano-benzopyran-5-en-1-one, bicyclo[2.2.2]octane, δ-lactone, X-ray crystal structure

Templates, more commonly called scaffolds, play an important role in peptide and peptoid based drug design,[1] as they can probe defined conformational space, and hence appear numerous times in combinatorial library synthesis.[1] Scaffolds take many forms usually consisting of a rigid backbone with pendent carboxyl or amino functionality. Some well established examples include 1,3,5-triaxial substituted cyclohexanes (Kemp's acid[2]), all *cis* cyclopentane rings,[3] and the steroid nucleus.[4] However, caged bicyclo[*n.n.n*] compounds, especially bicyclo[2.2.2]octanes, have only seen limited use as scaffolds for drug design, although, recent reports suggest they are excellent substrates for this purpose.[5] In view of this, our group has investigated and optimised the synthesis of benzopyran **1** and obtained the X-ray crystal structure for the purpose of examining its potential as a highly rigid multifunctional scaffold.

Benzopyran **1** can be obtained in five steps in 54% overall yield from 4-methoxyphenylacetic acid **2**. Conversion of **2** to alcohol **3**[6] with lithium aluminium hydride followed by Birch reduction affords diene **4** in 83% overall yield.[7] Acetyl protection [AcCl/NEt_3 (>95%)] of diene **4** was essential for the subsequent Diels–Alder reaction with maleic anhydride to avoid low yields of **1**.[8] Reaction of **5** with maleic anhydride afforded the tricycle **6** (86%) which underwent lactonisation giving **1** (79%) when treated with aqueous sodium hydroxide (Fig. 1).

The crystal structure of **1** (Fig. 1) reveals the expected stereochemistry and connectivity. The methine protons attached to the chirotopic atoms C1 and C6 are *cis*. The lactone crystallised as a centrosymmetric H-bonded dimer with the acid functional groups forming the non-covalently bonded bridge (H4…O3' 1.92 Å; O4-H4…O3' 168°; O4…O3' 2.728(3) Å, symmetry operation -*x*+1, -*y*+1, -*z*+2). This is a common H-bonding motif for organic acids.

The structure of the anhydride precursor **6** was also determined. This compound spontaneously resolves into its enantiomers upon crystallisation, with the structure containing two homochiral, but crystallographically independent, molecules in the asymmetric unit; only one of these is shown in Fig. 2. The two molecules have the same conformation and there are no significant differences between their bond lengths or angles. The stereochemistry at C1 and C6 is the same as that seen in the lactone relative **1**. In the absence of any



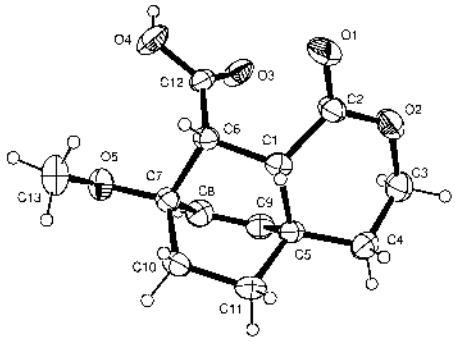


Fig. 1 ORTEP plot of compound **1** (30% probability ellipsoids).

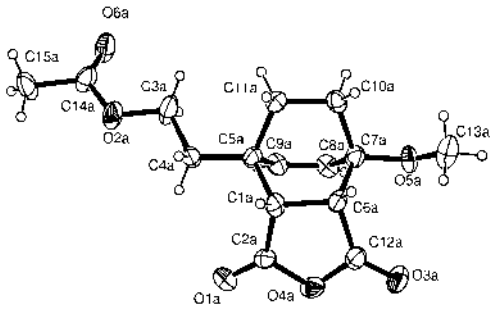


Fig. 2 ORTEP plot of compound **6** (30% probability ellipsoids). Only one of the two crystallographically independent molecules is shown.

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

classical H-bond donors, there are no strong inter- or intramolecular non-covalent interactions. The absolute configuration of **6** was not determined.

In conclusion compounds **1** and **6** are potential scaffolds for combinatorial libraries based on diversity-oriented synthesis aimed at maximum structural complexity and diversity from a minimum number of synthetic steps. In particular, libraries derived from the benzopyran scaffold **1** should give rise to rigid, stereochemically defined, and structurally diverse compounds, characteristics common to many natural products. The suitability of **1** as a scaffold for diversity-oriented combinatorial synthesis has been established, and the preparation of an encoded library[9] exploiting its unique molecular architecture will be reported elsewhere.

Experimental

Physical methods: ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ACF200 in deuteriochloroform ($CDCl_3$) and spectra referenced to chloroform (7.24 ppm). Accurate and low resolution mass spectral data were obtained on a KRATOS MS 25 RFA. Microanalyses were performed in-house by the University of Queensland Microanalytical Service. Melting points were determined on a Fischer Johns Melting Point apparatus and are uncorrected.

Syntheses: 7-(2-Acetoxyethyl)-4-methoxy-3a,4,7,7a-tetrahydro-4,7-ethanoisobenzofuran-1,3-dione ***6****:* Maleic anhydride (16.31 g, 0.166 mol) was added to the diene 5 (32.00 g, 0.163 mol) which contained a small portion of glass wool. The mixture was stirred at 150°C under a nitrogen atmosphere for 3h. On cooling a dark coloured solid formed. The solid residue was dissolved in a minimum amount of chloroform and added dropwise to a stirring mixture (7:1) of petroleum spirit and diethyl ether (250 ml). The light brown precipitate was collected by vacuum filtration (41.5 g, 86%). A small portion was purified by boiling with activated charcoal (dichloromethane) and cystallising from dichloromethane/light petroleum. M.p. 119–120°C ^{1}H NMR δ 1.37–1.92 (m, 4H), 2.03 (s, 3H), 2.14–2,43 (m, 2H), 3.14 (d, *J* 8.8, 1H), 3.36 (d, *J* 8.8, 1H), 3.45 (s, 3H), 4.13–4.36 (m, 2H), 5.99 (d, *J* 8.8, 1H), 6.28 (d, *J* 8.8, 1H). ^{13}C NMR ($CDCl_3$) δ 21.0, 27.7, 29.2, 33.0, 38.3, 46.5, 48.7, 51.0, 60.6, 77.6, 134.4, 134.8, 168.6, 170.6, 170.9. ^{13}C NMR (C_6D_6) δ 20.5, 27.7, 28.9, 33.3, 38.0, 46.0, 48.5, 50.5, 60.7, 77.5, 134.0, 135.1, 168.6, 170.3, 171.0. Mass spectrum *m/z* (EI) 206 (18%), 196 (20), 178 (30), 163 (2), 136 (100), 134 (26), 123 (11), 121 (13), 108 (5), 91 (6). Anal. Calcd for $C_{15}H_{18}NaO_6$: $M^{+\bullet}$ 317.1002 (ESI). Found: 317.0994. Anal. Calcd for $C_{13}H_{18}O_6$: C, 61.22; H, 6.16. Found: C, 60.92; H, 6.34.

9-Carboxyhexahydro-7-methoxy-4a,7-ethano-benzopyran-5-en-1-one **1:** Sodium hydroxide (1.43 g, 35.7 mmol) was dissolved in distilled water (50 ml) and the solution cooled in an ice-bath. Tricycle **6** (5 g, 17.0 mmol) was then added to the solution and the mixture allowed to warm to room temperature. After 40 min an additional equivalent of sodium hydroxide (0.80 g) was added and the mixture stirred for a further 1.5 h. The reaction flask was then placed in an ice-bath and the mixture acidified with conc. hydrochloric acid to pH 4. Extraction with chloroform afforded the crude product. A further portion of crude product was obtained after increasing the pH to 3 and evaporating the aqueous layer followed by extraction with chloroform. The combined crude extracts were crystallised (chloroform) and then recystallised (chloroform/petroleum spirit) affording the titled compound (3.39 g, 79%) as colourless needles, m.p. 180–181°C. ^{1}H NMR δ 1.30–1.73 (m, 3H), 1.74–2.05 (m, 3H), 2.75 (d, *J* 9.8, 1H), 3.39 (s, 3H), 3.54 (d, *J* 9.8, 1H), 4.34–4.61 (m, 2H), 6.03 (d, *J* 8.8, 1H), 6.27 (d, *J* 8.8, 1H), 7.10 (bs, OH). ^{13}C NMR δ 26.3, 31.4, 34.6, 35.9, 48.5, 50.7, 51.0, 66.6, 79.6, 131.1, 134.9, 170.3, 174.6. Mass spectrum *m/z* (EI) 252 ($M^{+\bullet}$, 4%), 234 (1), 224 (4), 208 (2), 206 (4), 196 (5), 193 (3), 179 (26), 166 (13), 161 (9), 154 (78), 136 (92), 123 (100), 121 (56), 108 (11), 105 (11), 91 (24). Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39; $M^{+\bullet}$ 252.0998. Found: C, 61.80; H, 6.39; 252.0993.

Crystallography: Cell constants were determined for both complexes by least-squares fits to the setting parameters of 25 independent reflections measured on an Enraf-Nonius CAD4 four-circle diffractometer employing graphite-monochromated Mo Kα radiation (0.71073 Å) and operating in the ω–2θ scan mode. Data reduction and empirical absorption correction (ψ-scans) were performed with the WinGX package.[10] The structure was solved by direct methods with SHELXS-86 and refined by full-matrix least-squares analysis with SHELXL-97.[11] All non-H atoms were refined with anisotropic thermal parameters and H-atoms were included at estimated positions and refined according to a riding model. Drawings of the molecules (Figs 1 and 2) were produced with ORTEP which show the atomic nomenclature.[12] Crystallographic data (in CIF format) have been deposited with the Cambridge Crystallographic Data Centre with deposition numbers 210346 (compound 1) and 210347 (compound 6).

Crystal data: Compound **1:** $C_{13}H_{16}O_5$, M = 252.26, monoclinic, a = 9.849(2), b = 11.791(1), c = 10.474(3) Å, β = 95.19(2)°, U = 1211.4(4) Å^3, D_c = 1.383 g cm^{-3}, T = 296 K, space group $P2_1/n$ (variant of $P2_1/c$, No. 14), Z = 4, μ(Mo-Kα) = 1.06 cm^{-1}, 2263 reflections measured, 2134 unique (R_{int} = 0.0265), R_1 = 0.0517 (obs. data), wR_2 = 0.1504 (all data).

Compound **6:** $C_{15}H_{18}O_6$, M = 294.29, monoclinic, a = 9.911(4), b = 13.490(1), c = 10.807(1) Å, β = 96.64(2)°, U = 1435.2(6) Å^3, D_c = 1.362 g cm^{-3}, T = 296 *K*, space group $P2_1$ (No. 4), Z = 4, μ(Mo-Kα) = 1.06 cm^{-1}, 2796 reflections measured, 2638 unique (R_{int} = 0.0340), R_1 = 0.0870 (obs. data), wR_2 = 0.3249 (all data).

Received 25 June 2003; accepted 8 September 2003
Paper 03/2000

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