A Convenient *De Novo* Synthesis of Functionalised 2,4,6,8-Tetraoxaadamantanes

Werner Heilmayer,[a] Turkaram S. Dalvi,[a] C. Oliver Kappe,[a,c] Curt Wentrup,[c] Karl Gruber,[b] Heinz Sterk[a] and Gert Kollenz*[a]

[a] *Institute of Organic Chemistry, Karl-Franzens University Graz, A-8010 Graz, Austria*
[b] *Institute of Physical Chemistry, Karl-Franzens University Graz, A-8010 Graz, Austria*
[c] *Department of Chemistry, University of Queensland, Qld 4072, Australia*

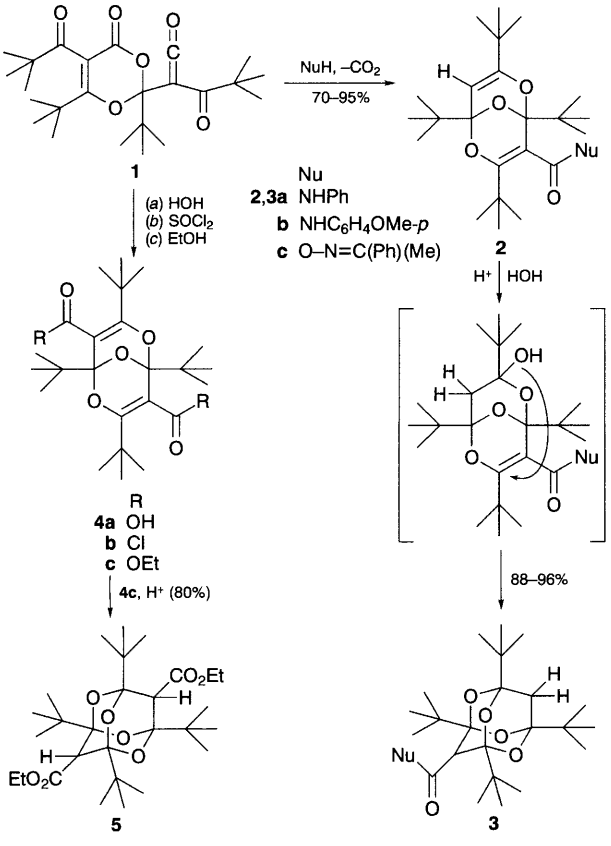
Trioxabicyclononadienes **2** and **4**, easily obtained by addition of nucleophiles to the stable α-oxoketene **1**, are transformed into the corresponding 2,4,6,8-tetraoxaadamantanes **3** and **5** in high yields by acid-catalysed hydrolysis.

Neat dipivaloylketene, generated in quantitative yield by preparative flash vacuum pyrolysis of 5-*tert*-butyl-4-pivaloylfuran-2,3-dione (400 °C, 10^{-2} mbar)[1] at room temperature slowly dimerizes in an unusual [2 + 4] cycloaddition reaction to the dioxinone **1**, which is a remarkably stable α-oxoketene. Compound **1** adds to aromatic amines (Scheme 1) to afford functionalized bridged trioxabicyclononadienes **2**.[2] In order to change the geometry of these molecules as well as to establish further reactive centres, addition reactions of various hydrogen halides to the C=C double bonds were carried out. Surprisingly, identical products were obtained in high yields, independently of the hydrogen halide used, namely the mono-functionalized tetraoxaadamantanes **3**, obviously stemming from hydrolysis of the double bonds and subsequent cyclisation to the stable 2,4,6,8-tetraoxaadamantane skeleton. This cyclisation could proceed either by addition of one mole of H_2O to the electron rich double bond *via* a subsequent Michael addition reaction as outlined in Scheme 1 or, alternatively, by addition of two moles of water to the two double bonds followed by a cyclocondensation reaction. Complete hydrolysis of the acetal moieties in **2** can be excluded since the so-formed dipivaloylacetic acid derivatives were found not to undergo ring closure to tetraoxaadamantanes under these reaction conditions.

Only a few compounds possessing the tetraoxaadamantane structure are currently known. They were obtained by acid-catalysed dimerisation of the corresponding 1,3-dicarbonyl compounds and lack any further functionalisation.[3–5]

Structure elucidation of compounds **3** was initially based on microanalytical and spectroscopic data.† In particular, the ^{1}H NMR spectra exhibited sharp singlets for CH_2 as well as CH protons (δ 1.7–1.8 and 3.0–3.1, respectively); the ^{13}C NMR spectrum of **3b** revealed long-range coupled (^3J = 2.5 Hz) signals for quarternary carbons at δ 99.8 and 101.9, respectively, indicating the presence of bis-oxygen bonded sp^3 carbon atoms.[6] However, the final confirmation of the tetraoxaadamantane structure was obtained by X-ray crystallographic analysis of **3b** (Fig. 1).‡ Compounds **3** exhibit C_s symmetry, the amide group occupies a position nearly perpendicular to the plane dividing the adamantane moiety (*e.g.* **3b**).

Acid-catalysed hydrolysis (*p*-TsOH, 20 °C) of the α-oxoketene **1** affords the dicarboxylic acid **4a**, which can easily be converted into the bis(acid chloride) **4b** and the bis(ester) **4c** by standard procedures.[2b] The adamantane diester **5** comes from hydrolysis of **4c** (Scheme 1). Compound **5** exhibits axial chirality (C_2 symmetry) as established by ^{1}H NMR studies (200 MHz, $CDCl_3$). Using Eu(hfc)$_3$ as chiral shift reagent a splitting (ratio 1 : 1) of signals was observed (*e.g.* the tertiary C–H (C-9, 10) δ 2.9 and 3.0; with Eu(hfc)$_3$ δ 2.95, 2.97 and 3.23, 3.25 respectively). The multiple splitting of most of the signals of **5** in the ^{1}H as well as the ^{13}C NMR spectrum† stems from the dissymmetry of the molecule (two types of *tert*-butyl groups and two types of quarternary ring carbons exhibiting two signals each in the ^{13}C NMR under all conditions) as well as hindered



Scheme 1

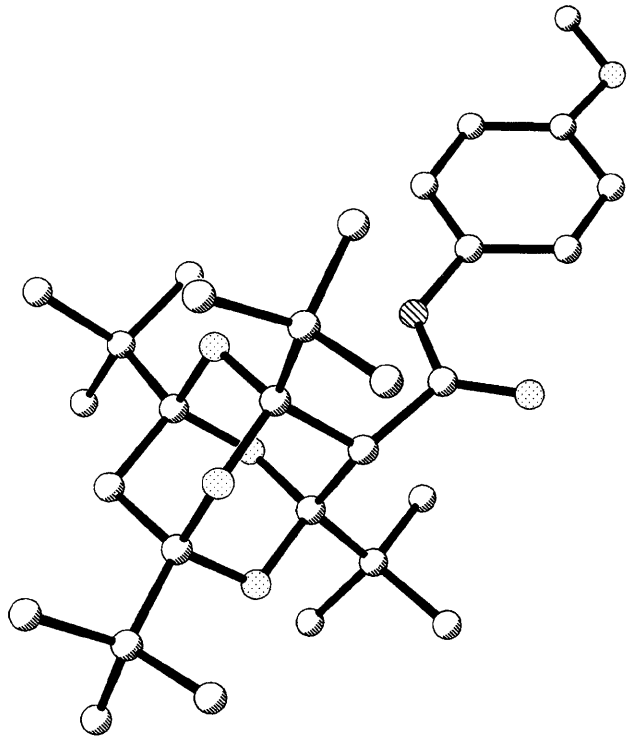


Fig. 1 The molecular structure of **3b**

rotations of the ester and the *tert*-butyl groups, since all remaining split signals collapse to one signal each by warming (60, 90 and 110 °C) in bromoform [external reference $(CD_3)_2SO$].

In conclusion, the *de novo* synthesis of the tetraoxaadamantane skeleton reported here provides a facile and efficient route to highly functionalized 2,4,6,8-tetraoxaadamantanes; their ability to serve as spacer molecules or host systems when incorporated into macrocyclic ring systems is under active investigation.

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Footnotes

† All new compounds gave spectroscopic and analytical data in accordance with the assigned structures. *Selected spectroscopic data* for **3b**: IR(KBr) ν/cm^{-1} 3410 (NH), 3000–2850 (CH), 1670 (C=O), 1600 (C=C). ^{1}H NMR ($CDCl_3$) δ 0.95, 1.05, 1.15 (3s, 36H, 4 Bu^t), 1.75 (s, 2H, CH_2), 3.05 (s, 1H, CH), 3.80 (s, 3H, OMe), 6.85, 7.40 (dd, 4H, arom.), 8.2 (s, 1H, NH). ^{13}C NMR ($CDCl_3$), selected carbons only: δ 26.3 (t, C-9, CH_2), 51.2 (d, C-10, CH), 56.0 (q, OCH_3), 99.45, 101.72, 101.76 (m, C-1, C-3, C-5, C-7), 167.8, 168.0 (2s, C=O, rotamers). *Selected spectroscopic data* for **5**: IR(KBr) ν/cm^{-1} 1760 (C=O). ^{1}H NMR ($CDCl_3$) δ 4.1 (dq, CH_2), 3.0, 2.9 (2s, CH), 1.3 (dt, CH_3), 1.10, 1.05 (dd, 18H), 0.95 (d, 18H). ^{13}C NMR ($CDCl_3$, 293 K; $CHBr_3$, 403 K) δ 171.6, 171.55, 168.45, 168.40 (C=O) collapse at 403 K to 170.0 (1s, br), 101.12, 100.95, 100.07, 99.97 (quaternary ring carbons) collapse to 101.4, 100.3 (2s); 60.88, 60.86, 60.16, 60.157 (OCH_2) collapse to 60.24 (1s), 47.66, 47.60, 43.95, 43.87 (CH) collapse to 45.83 (1s, br); 40.67, 40.61, 40.45, 40.41 (CMe_3) collapse to 40.86, 40.66 (2s); 24.17, 24.53, 24.80, 24.90, 25.17, 25.28 (CMe_3) collapse to 25.54, 24.89 (2s), 13.86, 13.60 (CH_3) collapse to 14.1 (1s).

‡ *X-Ray crystallographic analysis* of **3b**: A colourless prismatic crystal was grown by the slow vapour diffusion of acetonitrile into a chloroform solution of **3b**. The crystal was orthorhombic, space group $Pca2_1$, with cell dimensions a = 17.35(2), b = 9.105(9), c = 18.36(2) Å and V = 2901(6) Å^3. Z = 4 molecules ($C_{30}H_{47}NO_6$, M_W = 517.7) in the unit cell (D_c = 1.19 g cm^{-3}). Intensity data were measured for 2989 reflections (2813 unique, R_{int} = 0.0288, $2\theta_{max}$ = 50°) at 93(2) K on a modified STOE 4-circle diffractometer using a crystal with dimensions 0.6 × 0.5 × 0.2 mm [F(000) = 1128, λ(Mo-Kα) = 0.7107 Å, μ = 0.081 mm^{-1}]. The structure was solved by direct methods and refined by full-matrix least-squares analysis with SHELXL-93[7] minimizing the residuals for F^2. All hydrogen atoms were visible in difference Fourier maps, but were calculated at their theoretical positions. For the methyl groups a cyclic Fourier synthesis was performed, the symmetry averaged maximum of which gave the proton locations. All hydrogen atoms were treated as 'riding' on the respective heavy atom with isotropic displacement parameters 1.2 times larger than that of the heavy atom. For methyl groups the factor was 1.5 and an additional torsion angle was refined. Anisotropic displacement parameters were assigned to all non-hydrogen atoms; rigid-bond restraints were applied. Convergence was reached at $R1$ = 0.0421 [2285 reflections with $I > 2\sigma(I)$] and $\omega R2$ = 0.1093 {all unique data, $\omega = 1/[\sigma^2(F_o^2) + (0.0483P)^2 + 0.1115P]$ where $P = (F_o^2 + 2F_c^2)/3$} for 347 parameters and 112 restraints. The Goodness-of-fit on F^2 was 1.086. The largest difference peak and hole in the last map were 0.241 and −0.198 e Å^{-3}, respectively. The absolute structure could not be determined unambiguously. No absorption or extinction correction was applied to the data. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

References

1 C. O. Kappe, R. A. Evans, C. H. L. Kennard and C. Wentrup, *J. Am. Chem. Soc.*, 1991, **113**, 4234; C. O. Kappe, G. Färber, C. Wentrup and G. Kollenz, *J. Org. Chem.*, 1992, **57**, 7078.

2 (*a*) C. O. Kappe, G. Färber, C. Wentrup and G. Kollenz, *Tetrahedron Lett.*, 1992, **33**, 4553; (*b*) C. O. Kappe, G. Kollenz, W. M. F. Fabian, C. Wentrup and G. Färber, *J. Org. Chem.*, 1993, **58**, 3361.

3 For H,Me-substituted 2,4,6,8-tetraoxaadamantanes, see: (*a*) Y. A. Shabab, *Org. Magn. Res.*, 1977, **9**, 580; (*b*) S. Tsuboi, T. Ono and A. Takeda, *Heterocycles*, 1986, **24**, 2007; (*c*) S. Kashino, M. Haisa, S. Tsuboi, T. Ono and A. Takeda, *Acta Crystallogr., Sect. C*, 1983, **9**, 103; (*d*) M. G. B. Drew, G. W. A. Fowles, D. A. Rice and K. J. Shanton, *J. Chem. Soc., Chem. Commun.*, 1974, 614; (*e*) K. A. Chelatov, A. I. Prokofev and M. I. Kabachnik, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 1990, 1686; *Chem. Abstr.*, 1990, **113**, 211950z.

4 Me,Ph-substituted derivatives: L. Dolejs and Z. Arnold, *Coll. Czech. Chem. Commun.*, 1966, **31**, 4187; S. O. Almquist, *Acta Chem. Scand.*, 1968, **22**, 1367; S. R. Kuhlmey, H. Adolph, K. H. Rieth and G. Opitz, *Liebigs Ann. Chem.*, 1979, 617; see also ref. 3(*b*).

5 F,Me-tetraoxaadamantanes, see: R. Dersch and C. Reichardt, *Liebigs Ann. Chem.*, 1979, 1330; 1348–1358.

6 G. Kollenz, W. Ott, E. Ziegler, E. M. Peters, K. Peters, H. G. von Schnering, V. Formacek and H. Quast, *Liebigs Ann. Chem.*, 1984, 1137, and references cited therein.

7 G. M. Sheldrick, SHELXL-93, Program for crystal structure refinement, University of Göttingen, 1993.