3,7-Diazabicyclo[3.3.0]octane-2,6-diones: synthesis, NMR spectra and structures

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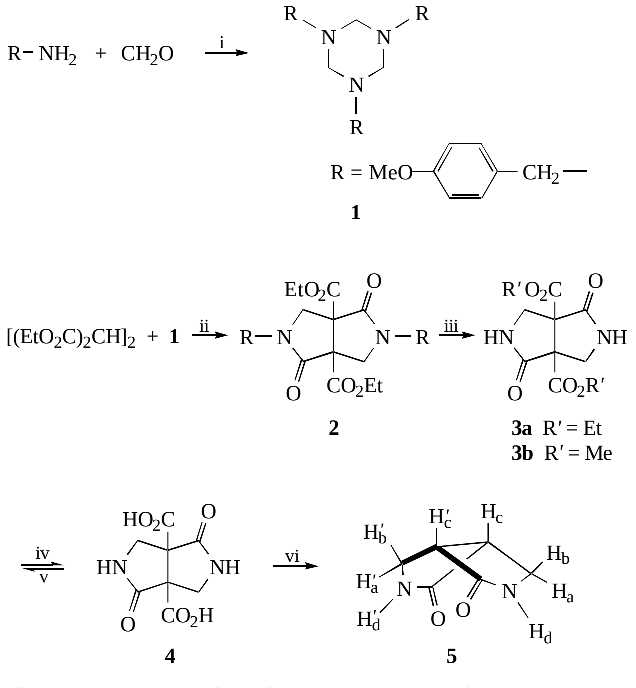
Parent 3,7-diazabicyclo[3.3.0]octane-2,6-dione **5**, the corresponding 1,5-dicarboxylic acid **4** and esters **3** have been synthesised for the first time; NMR spectra of the compounds were analysed, and the structures of **3b** and **5** were studied by X-ray crystallography; hydrogen bonding generates self-assembly in the form of heterochiral infinite diagonal zigzag tape in the crystal of **5**, while in the crystal structure of **3b** the H-bonded layers consist of homochiral spirals and heterochiral chains.

Bislactams of the 2,5-diazabicyclo[2.2.2]octane-3,6-dione series are capable of self-assembling only into heterochiral H-bonded suprastructures in the form of infinite linear zigzag tapes, which are packed in racemic crystals,[1–3] whereas an H-bonded self-assembly of bislactams of the bicyclo[3.3.*n*]alkane series ($n =$ = 0–3) leads principally either to a heterochiral diagonal zigzag tape or to a homochiral helical structure.[4] The latter occurs in the case of a chiral glycouril such as 2,6-diethyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione, which gives conglomerate crystals and readily undergoes spontaneous resolution by crystallisation.[4]

Therefore, we have studied a similar system of the 3,7-diazabicyclo[3.3.0]octane-2,6-dione series (Scheme 1).



Scheme 1 *Reagents and conditions*: i, in EtOH, 1 h at 20 °C; ii, cat. amount of CF_3CO_2H, 24 h at 100–120 °C; iii, $Ce(NH_4)_2(NO_3)_6$ (CAN) in MeCN–H_2O, stirring for 1 h and standing for 2.5 days at 20 °C, then $NaHCO_3$, separation of the precipitate, extraction with Et_2O, evaporation and crystallisation from CCl_4; iv, KOH in MeOH, 18 h at 20 °C and 1.5 h refluxing, evaporation and treatment with conc. HCl in Et_2O, evaporation, dissolution in MeCN, filtration and crystallisation from MeOH; v, in MeOH, treatment with ether solution of CH_2N_2; vi, 5 min at 220 °C.

Bicycle **2** was synthesised on the basis of tetraethyl ethane-1,1,2,2-tetracarboxylate using the method developed by Knowles *et al.*[5,6] However, in order to ensure subsequent N-deprotection, the aminomethylation was carried out using new reagent **1**. The cleavage of *p*-methoxybenzyl groups of **2** was achieved by oxidation with cerium ammonium nitrate (CAN) using the procedure described by Lehn *et al.*[1] Attempts of growing a crystal for the X-ray diffraction study of diethyl bislactamdicarboxylate **3a** were unsuccessful, and the latter compound was converted into diacid **4** and then into dimethyl ester **3b**. The latter forms suitable single crystals. Unsubstituted parent bislactam **5** was prepared for the first time by thermal decarboxylation of diacid **4**. All of the compounds were characterised by spectroscopic data.[†] The six-spin system of the ^{1}H NMR spectrum of **5** (*cf.* similar mono- and bislactones of the 2,7-dioxabicyclo[3.3.0]alkane series[8,9]) was analysed in detail (Figure 1). The structures of **3b** and **5** were confirmed by X-ray analysis.[‡] Torsion angles HCNH found in **3b** (H_aCNH_d 44°, H_bCNH_d 76°) and HCCH in **5** (H_aCCH_c 96°, H_bCCH_c 25°, $H_cCCH'_c$ 23°) correspond to the observed spin coupling constants $^3J_{HH}$ (*cf.* ref. 10).[†]

The bond lengths and angles in the crystal structures of **3b** and **5** (Figures 2 and 3) exhibit expected values and are very similar to the corresponding values in bislactams of the bicyclo[2.2.2]-octane series.[1,3] Both molecules are significantly twisted, the corresponding torsion angles C(7)–C(1)–C(4)–C(9) and H(1)–C(1)–C(4)–H(4) are equal to 25° and 23.5° for **3b** and **5**,

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[†] *Characteristics and spectroscopic data*. NMR spectra were recorded on Bruker WM 400 (400.13 MHz for ^{1}H and 100.62 MHz for ^{13}C) and Bruker AM 300 (300.13 MHz for ^{1}H) spectrometers with TMS as an internal standard. ^{1}H NMR spectrum of **5** was calculated by CALM.

1: yield 90%, mp 108–110 °C (EtOH–H_2O, 60:40). ^{1}H NMR ([$^2H_8$]-toluene, 90 °C) δ: 3.34 (s, 6H, 3CH_2N), 3.36 (s, 9H, 3MeO), 3.49 (s, 6H, 3NCH_2N), 6.68 and 7.14 (d, 12H, 3C_6H_4, ^3J 7.6 Hz).

2, yield 53.4%, mp 110 °C (toluene). ^{1}H NMR ($CDCl_3$) δ: 1.14 (t, 6H, 2*Me*CH_2, ^3J 7.3 Hz), 3.80 (s, 6H, 2MeO), 3.82 (dd, 4H, 4,8-CH_2, AB spectrum, $\Delta\nu$ 60.0, ^2J –10.4 Hz), 4.11 (q, 4H, 2CH_2O, ^3J 7.3 Hz), 4.46 (dd, 4H, 2NCH_2, AB spectrum, $\Delta\nu$ 236.0, ^2J –14.7 Hz), 6.85 and 7.12 (d, 8H, 2C_6H_4, ^3J 8.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 13.46 (qt, *Me*CH_2, ^1J 127.2 Hz, ^2J 2.9 Hz), 46.3 (ttt, CH_2N, ^1J 138.8 Hz, ^3J 3.6 Hz), 48.93 (tm, 4,7-CH_2, ^1J 148.2 Hz, ^3J 2.2 Hz), 54.83 (q, MeO, ^1J 143.1 Hz), 58.73 (m, 2,5-C, ^2J 3.6 Hz), 61.87 (tq, CH_2O, ^1J 149.0 Hz, ^2J 4.4 Hz), 113.77 (dd, 3′-C, ^1J 159.0 Hz, ^2J 4.4 Hz), 126.61 (m, 1′-C), 129.0 (ddt, 2′-C, ^1J 157.0 Hz, ^2J 4.4 Hz, ^3J 3.6 Hz), 158.9 (m, 4′-C), 165.9 (q, 2,6-CO, ^3J 3.6 Hz), 168.0 (m, CO_2).

3a: yield 63%, mp 160–161 °C (CCl_4). ^{1}H NMR (CD_3CN) δ: 1.19 (t, 6H, 2*Me*CH_2, ^3J 7.2 Hz), 3.76 (m, 4H, 4,8-CH_2, ABX spectrum, $\Delta\nu_{AB}$ 76.0, ^2J –10.4 Hz, $^3J_{H_aCNH}$ 1.2 Hz, $^3J_{H_bCNH}$ 0.0 Hz), 4.15 (m, 4H, CH_2O, ABX_3 spectrum), 6.66 (br. s, 2H, 2,7-NH). ^{13}C NMR ([$^2H_4$]methanol) δ: 14.25 (qt, *Me*CH_2, ^1J 127.2 Hz, ^2J 2.9 Hz), 46.13 (dd, 4,8-CH_2, ^1J 147.5 and 149.7 Hz), 62.0 (m, 1,5-C), 63.43 (tq, CH_2O, ^1J 149.0 Hz, ^2J 4.4 Hz), 167.82 (q, 2,6-CO, ^3J 3.6 Hz), 173.3 (qm, CO_2, ^3J 5.8 Hz).

3b: yield 74.2%, mp 222–223 °C (MeOH). ^{1}H NMR ($CDCl_3$) δ: 3.77 (s, 6H, 2MeO), 3.96 (m, 4H, 4,8-CH_2, ABX spectrum, $\Delta\nu_{AB}$ 52.0, ^2J –10.4 Hz, $^3J_{H_aCNH}$ 1.2 Hz, $^3J_{H_bCNH}$ 0.0 Hz), 6.72 (br. s, 2H, 3,7-NH).

4: yield 60%, mp 202–204 °C (MeOH). ^{1}H NMR ([$^2H_4$]methanol) δ: 3.81 (m, 4,8-CH_2, AB spectrum, $\Delta\nu$ 144.0, ^2J –10.5 Hz).

5: yield 72%, mp > 300 °C (decomp.) (H_2O). ^{1}H NMR ([$^2H_4$]methanol) δ: 3.22 (m, 2H, H_c, H'_c, $^3J_{CC'}$ 9.69 Hz), 3.54 (m, 2H, H_b, H'_b, $^2J_{ab} =$ $= {}^2J_{a'b'} = -10.47$ Hz, $^3J_{bc} = {}^3J_{b'c'} = 1.3$ Hz), 3.62 (m, 2H, H_a, $H_{a'}$, $^3J_{ac} =$ $= {}^3J_{a'c'} = 7.98$ Hz). ^{13}C NMR ([$^2H_4$]methanol) δ: 42.33 (d, 1,5-C, ^1J 145.0 Hz), 44.52 (t, 4,8-C, ^1J 146.8 Hz), 180.76 (s, 2,6-C).

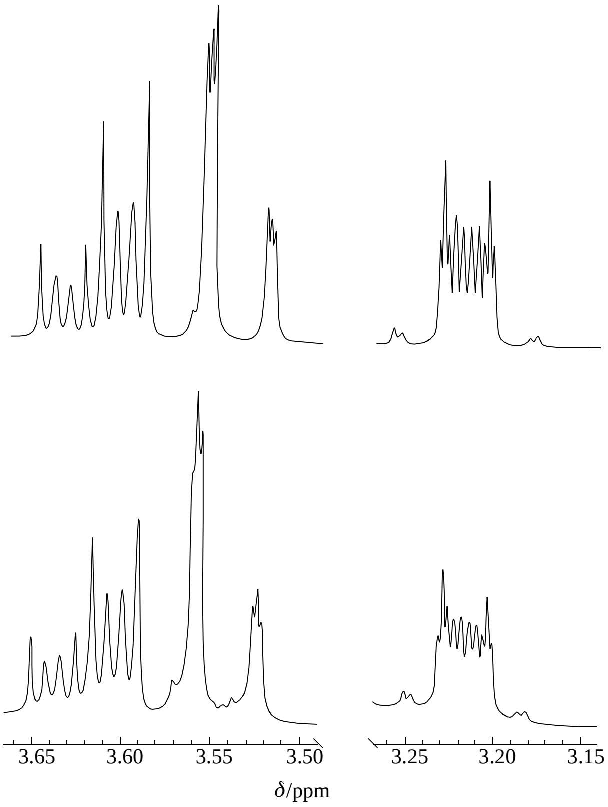

Figure 1 ^{1}H NMR spectrum of **5** in [$^2H_4$]methanol, experimental (above) and calculated (below).

respectively. The torsion angle C(2)–C(1)–C(4)–C(3) and the angle between two five-membered rings in both structures are similar and equal to 20.3° and 110.3°, respectively.

In the case of bislactam **5**, the expected self-assembly in the form of a heterochiral H-bonded [N(1)–H(1N)···O(2′) (× + *x*, 1 – *y*, × + *z*) N(1)O(1′) 2.860(4) Å; N(2)–H(2N)···O(1″) (–× + *x*, 1 – *y*, –× + *z*) N(2)O(2′) 2.856(3) Å] infinite diagonal zigzag tape parallel to the crystallographic plane *ab* is observed (Figure 4).

However, in the crystal structure of **3b**, either the homochiral spirals or heterochiral zigzag tapes were not observed. The difference in the crystal packing of the centrosymmetric **5** and **3b** structures is probably caused by the CO_2Me 1,5-substituents. As the result of shielding due to the CO_2Me groups, molecules in the crystal structure of **3b** are assembled into H-bonded heterochiral layers (Figure 5) with a hydrophobic surface (CO_2Me groups) (Figure 5). It is noteworthy that nitrogen hydrogens [H(1N) and H(2N)] play different roles in the formation of the above layers. The H(2N) atoms [H-bond N(2)–H(2N)···O(1′) (1 – *x*, × + *y*, 3/2 – *z*), N(2)···O(1′) 3.039(3) Å] take part in the formation of the homochiral spirals [Figure 6(*a*)] directed along the crystallographic axes *b*, while the H(1N) atoms [H-bond N(1)–H(1N)···O(2′) (*x*, 3/2 – *y*, –× + *z*) N(1)···(O2′) 2.895(3) Å] interlink these spirals into layers by perpendicular heterochiral chains directed along the crystallographic axes *c* [Figure 6(*b*)].

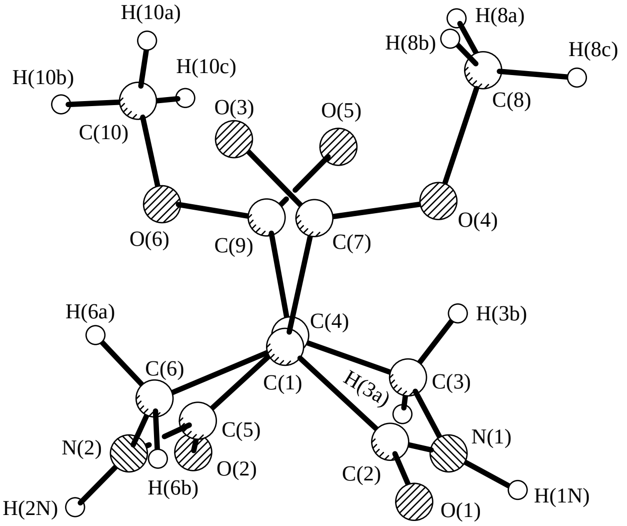

Figure 2 The general view of **3b**.

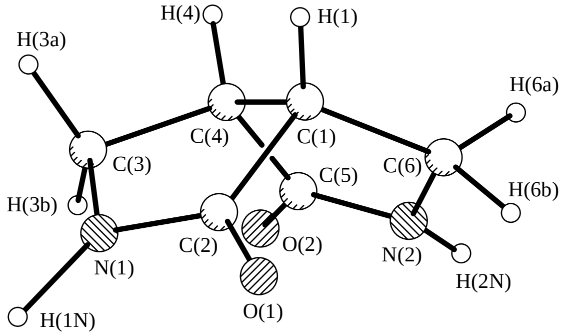

Figure 3 The general view of **5**.

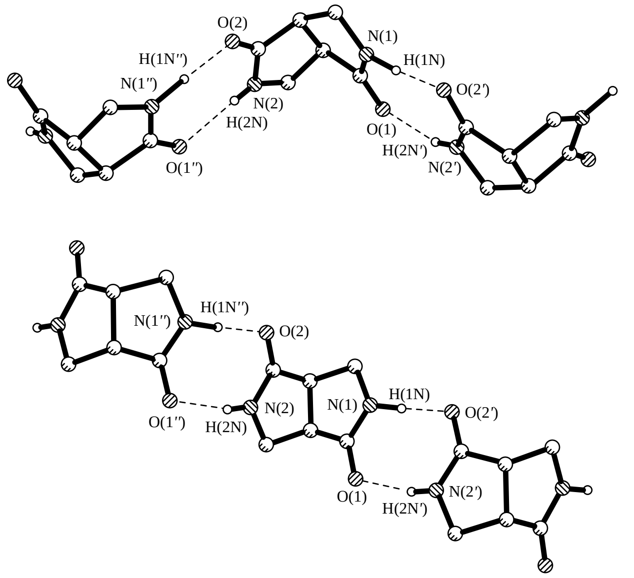

Figure 4 The zigzag heterochiral tape in two projections in the crystal structure of **5**. The hydrogens that do not take part in the formation of H-bonds are omitted for clarity.

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‡ *Crystallographic data for* **3b** *and* **5** at 25 °C: crystals of $C_{12}H_{12}N_2O_6$ **3b** are monoclinic, space group $P2_1/c$, $a = 14.467(5)$ Å, $b = 6.597(2)$ Å, $c = 11.892(6)$ Å, $\beta = 108.91(3)°$, $V = 1073.7(7)$ Å^3, $Z = 4$, $M = 280.24$, $d_{calc} = 1.734$ g cm^{-3}, μ(MoKα) = 1.41 cm^{-1}, $F(000) = 584$; crystals of $C_6H_8N_2O_2$ **5** are monoclinic, space group Pn, $a = 7.2740(10)$ Å, $b = 4.5630(10)$ Å, $c = 9.308(2)$ Å, $\beta = 90.03°$, $V = 308.94(10)$ Å^3, $Z = 2$, $M = 140.14$, $d_{calc} = 1.507$ g cm^{-3}, μ(MoKα) = 1.15 cm^{-1}, $F(000) = 148$. Intensities of 2491 reflections for **3b** and of 1563 reflections for **5** were measured on a Siemens P3 diffractometer at 25 °C (λ MoKα radiation, $\theta/2\theta$ scan technique, $2\theta_{max}$ 52° and 56° for **3b** and **5**, respectively); 2369 independent reflections for **3b** and 1374 for **5** were used in further calculations and refinement. The structures were solved by the direct method and refined by a full-matrix least-squares technique against F^2 in the anisotropic–isotropic approximation. Hydrogen atoms were located from the difference Fourier synthesis and refined in the isotropic approximation. The refinement converged to $wR_2 = 0.1522$ and COF = 1.058 for all independent reflections [$R_1 = 0.0409$ is calculated against F for the 1907 observed reflections with $I > 2\sigma(I)$] for structure **3b** and to $wR_2 = 0.0883$ and COF = 1.006 for all independent reflections [$R_1 = 0.0883$ is calculated against F for the 1291 observed reflections with $I > 2\sigma(I)$] for structure **5**. All calculations were performed using SHELXTL PLUS 5.0 on an IBM PC/AT. Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details, see ‘Notice to Authors’, *Mendeleev Commun.*, Issue 1, 1999. Any request to the CCDC for data should quote the full literature citation and the reference number 1135/40.

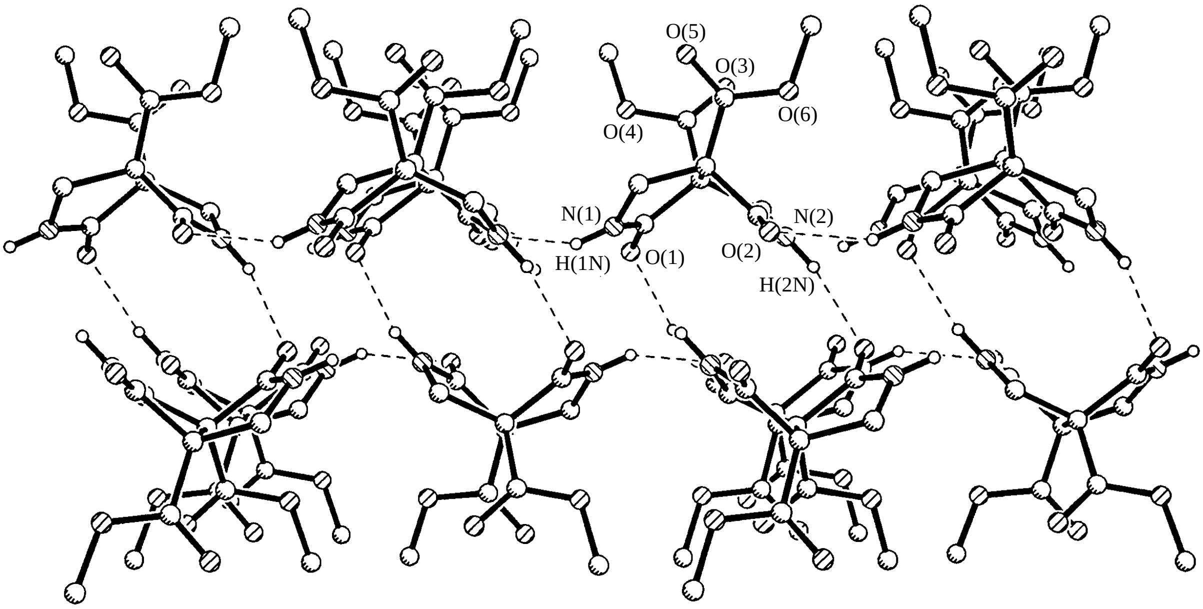

Figure 5 The H-bonded layers in the crystal structure of **3b**. The hydrogens that do not take part in the formation of H-bonds are omitted for clarity.

Apparently, a strong twist of the molecular skeleton in **5** hinders the self-assembly in a homochiral helical suprastructure because of a too small pitch of the helix.

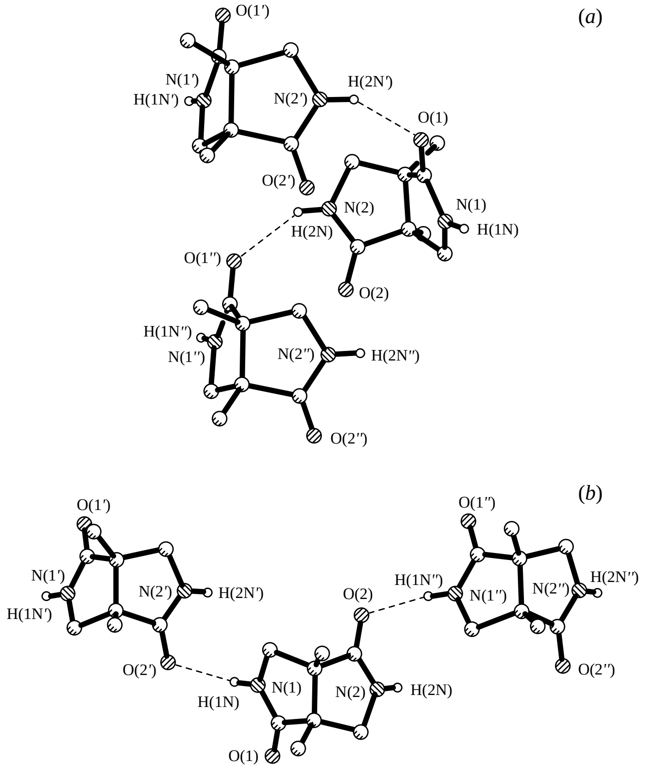

Figure 6 The H-bonded (*a*) homochiral spirals and (*b*) heterochiral chains in the crystal structure of **5**. The hydrogens of CH_2 groups are omitted for clarity.

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References

1 M.-J. Brienne, J. Gabard, M. Leclercq, J.-M. Lehn, M. Cesario, C. Pascard, M. Cheve and G. Dutruc-Rosset, *Tetrahedron Lett.*, 1994, **35**, 8157.
2 M.-J. Brienne, J. Gabard, M. Leclercq, J.-M. Lehn and M. Cheve, *Helv. Chim. Acta*, 1997, **80**, 856.
3 R. G. Kostyanovsky, Yu. I. El'natanov, O. N. Krutius, I. I. Chervin and K. A. Lyssenko, *Mendeleev Commun.*, 1998, 228.
4 R. G. Kostyanovsky, K. A. Lyssenko, G. K. Kadorkina, O. V. Lebedev, A. N. Kravchenko, I. I. Chervin and V. R. Kostyanovsky, *Mendeleev Commun.*, 1998, 231.
5 P. Knowles and N. V. Harris, *J. Chem. Soc., Perkin Trans. 1*, 1983, 1475.
6 G. Darnbrough, P. Knowles, S. P. O'Connor and F. J. Tiernet, *Tetrahedron*, 1986, **42**, 2339.
7 Ch. J. Welch, *J. Chem. Educ.*, 1997, **74**, 247.
8 A. S. R. Anjaneyulu, A. Madhusudhana Rao, V. Kameswara Rao, L. Ramachandra Row, A. Pelter and R. S. Ward, *Tetrahedron*, 1977, **33**, 133.
9 R. Cooper, E. C. Levy and D. Lavie, *J. Chem. Soc., Chem. Commun.*, 1977, 794.
10 H. Quast, C. Becker, E. Geissler, K. Knoll, E. M. Peters, K. Peters and H. G. von Schnering, *Liebigs Ann. Chem.*, 1994, 109.

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