# Novel terpene-based chiral bis-α-aminooximes and the corresponding macrocycles: X-ray structure of a ring-fused 5,7-dioxa-1,4,8,11-tetraazacyclotrideca-3,8-diene derivative

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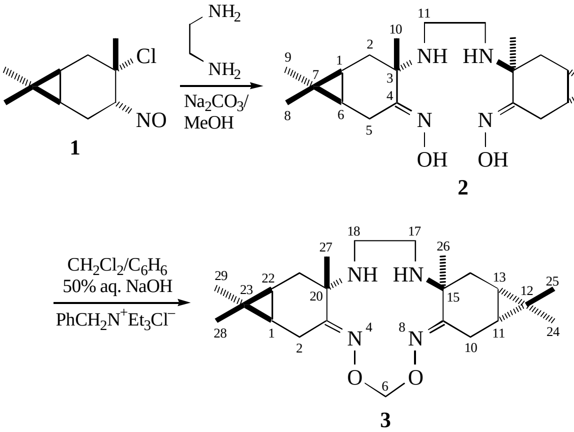
The treatment of (+)-3-carene nitrosochloride with 1,2-diaminoethane results in bis-α-aminoxime, which undergoes intramolecular cyclisation under phase-transfer conditions to yield an optically active macroheterocyclic compound with two carane moieties incorporated.

Optically active diamino dioximes and cyclic polyamines are of interest as ligands for asymmetric catalysis, whereas their achiral analogues are known as starting compounds for the preparation of complexes with $^{99}Tc_m$ for nuclear medicine.[1,2] The synthesis of bis-α-aminoximes can be carried out starting from the corresponding diamino diketones,[3] although we believe that the use of olefins nitrosochlorides as starting compounds is preferable.[4] The latter approach is simpler and allows one to design bis-α-aminoximes based on different unsaturated compounds. We report here on the synthesis of novel chiral bis-α-aminoximes from natural monoterpene (+)-3-carene and on the corresponding macroheterocycles resulted from the intramolecular junction of the two oxime groups.[5]

Bis-α-aminoxime **2** was synthesised from dimeric nitrosochloride **1** [prepared from natural (+)-3-carene[6]] by treatment with 1,2-diaminoethane.† Compound **2** is a crystalline solid soluble only in polar organic solvents like pyridine and methanol.‡

A molecule of bis-α-aminoxime **2** has the $C_2$ symmetry: the NMR spectra of the compound contain only one set of signals of the carane moiety (C-1 … C-10 atoms) and only one atom of the 1,2-diaminoethane bridge. According to the semi-empirical calculations (PM3), in the most stable conformation of the bis-α-aminoxime, both of the six-membered carbocycles have the same envelope-like conformation[7] shown in Figure 1. This conformation is absolutely ineligible for a macrocycle formation by the junction of oxime groups. We demonstrated earlier that carane-type α-aminoximes can change the six-membered carbocycle conformation in the formation of additional cycles.[8,9] We found that the treatment of compound **2** with $CH_2Cl_2$–NaOH under phase-transfer catalysis conditions resulted in the intramolecular binding of the two hydroxyls to form macrocycle **3**. The intermolecular binding results in oligomers, although compound **3** can be prepared in good yield.§ Macrocyclic compound **3**¶ is a polar substance (according to TLC on $SiO_2$ and $Al_2O_3$); however, it is readily soluble in non-polar solvents such as saturated hydrocarbons (*n*-hexane, light petroleum and *n*-octane).

The molecular structure of compound **3** is shown in Figure 2 according to X-ray diffraction data.†† The macrocycle in the molecule of compound **3** has approximately the $C_2$ symmetry



**Scheme 1**

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† A mixture of powdered $Na_2CO_3$ (0.88 g, 8.3 mmol), nitrosochloride **1** (3.35 g, 8.3 mmol), 1,2-diaminoethane (9.0 mmol) and methanol (15 ml) was stirred at 50 °C until the starting nitrosochloride completely dissolved. The solvent was removed in a vacuum, and the residue was treated with 3 M aq. HCl (20 ml) followed by extraction with *tert*-butyl methyl ether (3×10 ml). The organic extracts were thrown off, and the acidic aqueous solution was treated with concentrated aqueous ammonia (7 ml) to give a white precipitate, which was filtered off, washed with *tert*-butyl methyl ether (3×10 ml), and dried to give bis-α-aminoxime **2** in 30% yield.

‡ *N,N′-Bis{(1*S*,3*S*,6*R*)-4-[(*E*)-hydroxyimino]-3,7,7-trimethylbicyclo[4.1.0]-hept-3-yl}-1,2-diaminoethane* **2**. White crystals, mp 163.0–165.5 °C (from 10% aq. MeOH), $[\alpha]^{22}$ +169 (*c* 0.463, MeOH). IR ($CHCl_3$, $\nu$/cm$^{-1}$): 3640 (O–H), 945 (=N–OH).

§ An aqueous NaOH solution (50%, 30 ml) and $PhCH_2N^+Et_3Cl^-$ (0.2 g) were added to a suspension of powdered bis-α-aminoxime **2** (2 mmol) in a mixture of $C_6H_6$ (40 ml) and $CH_2Cl_2$ (80 ml) with stirring. The resulting mixture was stirred at 50 °C for 2 h (until the disappearance of the starting compound, TLC monitoring). The organic layer was separated and dried over $Na_2SO_4$ followed by removal of the solvent in a vacuum and by chromatography of the crude product ($SiO_2$, hexane–EtOAc) to afford macrocycle **3** in 60% yield.

¶ *(1*R*,11*R*,13*S*,15*S*,20*S*,22*S*)-5,7-dioxa-4,8,16,19-tetraaza-12,12,15,20,23,23-hexamethylpentacyclo[20.1.0.0$^{3,20}$.0$^{9,15}$.0$^{11,13}$]tricosa-3,8-diene* **3**. White crystals, mp 217.0–220.0 °C (EtOAc), $[\alpha]^{22}$ +151 (*c* 2.65, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$: 0.68 (ddd, 2H, H-22 and H-13, *J* 9.2, 9.2 and 5.8 Hz), 0.74 (s, 6H, H-28 and H-24), 0.78 (m, 2H, H-1 and H-11), 0.98 (s, 6H, H-27 and H-26), 1.07 (s, 6H, H-29 and H-25), 1.23 (dd, 2H, $H_\beta$-21 and $H_\alpha$-14, *J* 14.9 and 5.8 Hz), 1.88 (dd, 2H, $H_\alpha$-21 and $H_\beta$-14, *J* 14.9 and 9.2 Hz), 2.37 (m, 4H, H-18 and H-17), 2.48 (m, 4H, $H_\alpha$-2 and $H_\beta$-2, $H_\alpha$-10 and $H_\beta$-10), 5.38 (s, 2H, H-6). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$: 14.57 (C-28 and C-24), 15.96 (C-22 and C-13), 17.22 (C-1 and C-11), 18.74 (C-23 and C-12), 19.24 (C-2 and C-10), 22.13 (C-27 and C-26), 27.59 (C-29 and C-25), 33.84 (C-21 and C-14), 43.26 (C-18 and C-17), 54.25 (C-20 and C-15), 94.28 (C-6), 161.99 (C-3 and C-9). IR ($CHCl_3$, $\nu$/cm$^{-1}$): 980. MS, *m/z* (%): 402.29873 (3, calc. for $C_{23}H_{38}N_4O_2$ 402.29946), 373 (3), 355 (3), 344 (3), 251 (7), 208 (6), 206 (7), 191 (100), 179 (34), 177 (31), 166 (45), 165 (35), 150 (44), 138 (25), 136 (21), 109 (17), 108 (24), 107 (29), 96 (47), 95 (33), 82 (40), 71 (27), 55 (19), 44 (20), 43 (18), 42 (21), 41 (20).

†† Syntex $P2_1$ diffractometer (CuKα radiation with a graphite monochromator, $\theta/2\theta$-scan mode, 2497 independent reflections with $2\theta < 140°$). Crystals of **3** are orthorhombic: $a = 9.311(1)$, $b = 10.588(1)$, $c = 23.663(3)$ Å, $V = 2332.8(4)$ Å$^3$, space group $P2_12_12_1$, $C_{23}H_{38}N_4O_2$, $M = 402.57$, $Z = 4$, $D_c = 1.146$ g cm$^{-3}$, $\mu = 0.582$ mm$^{-1}$, crystal size 0.5×0.4×0.3 mm. Absorption corrections (transmission 0.786–0.896) by the integration method for real crystal faces were applied. The structure was solved by direct methods (SHELX-86) and refined by anisotropic full-matrix least-squares (SHELXL-93) to $wR_2 = 0.1394$, $S = 1.043$ for all reflections [$R = 0.0503$ for 1821 $F > 4\sigma(F)$]. Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at Cambridge Crystallographic Data Centre (CCDC). For details, see ‘Notice to Authors’, *Mendeleev Commun.*, Issue 1, 2000. Any request to the CCDC for data should quote the full literature citation and the reference number 1135/71.

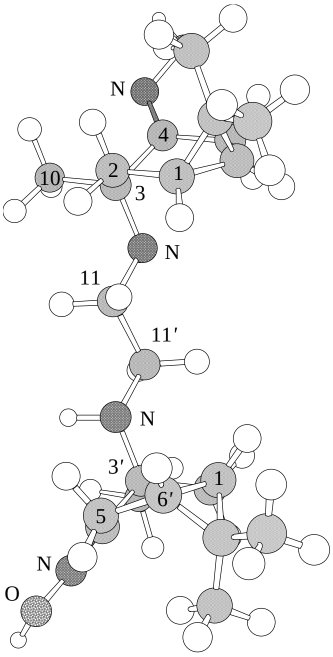

**Figure 1** The most stable molecular conformation of **2** according to PM3 calculations: ∠N=C(4)–C(3)–N 127°, ∠C(3)–N–C(11)–C(11′) 179°, ∠N–C(11)–C(11′)–N 178°.

with the $C_2$-axis crossing the atom C(12) and the middle of the C(11)–C(11A) bond.

The mean deviation between the formally equivalent torsion angles is equal to 3.0°, but the maximum difference reaches 9.4°. There are only two compounds containing a *trans,trans*-cyclotrideca-1,6-diene fragment in the Cambridge Structural Database.[10] In both of these compounds,[11] the macrocycle conformation is asymmetrical and substantially different from that of compound **3**. The conformation of the six-membered rings in **3** is closer to the distorted envelope conformation observed for (1*S*,3*S*,6*R*)-3-chlorocaran-4-one *E*-oxime[12] than to the envelope form found in (1*S*,3*S*,6*R*)-3-dimethylaminocaran-4-one *E*-oxime.[7]

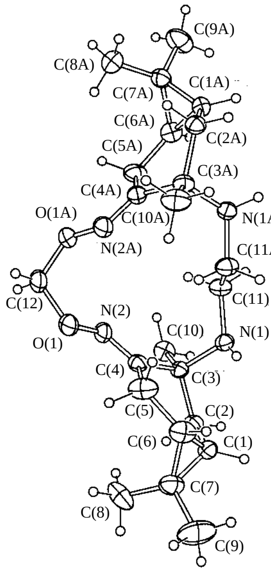

**Figure 2** Molecular structure of compound **3** according to X-ray diffraction data. Selected bond lengths (Å): N(1)–C(3) 1.474(4), 1.478(5); N(1)–C(11) 1.467(5), 1.455(5); C(11)–C(11A) 1.489(5); C(3)–C(4) 1.528(4), 1.513(5); C(4)=N(2) 1.273(5), 1.275(5); N(2)–O(1) 1.430(4), 1.432(5); O(1)–C(12) 1.407(6), 1.416(5); selected bond angles (°): C(11)–N(1)–C(3) 117.8(3), 117.6(3); C(4)=N(2)–O(1) 109.0(3), 109.9(4); N(2)–O(1)–C(12) 108.8(3), 109.4(4); N(1)–C(11)–C(11A) 115.8(3), 113.2(3); O(1)–C(12)–O(1A) 112.9(3).

Thus, the reactions of the nitrosochlorides of natural optically active terpenes with ω-diamines opens a way to chiral bis-α-aminoximes and novel chiral macrocycles.

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