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# First stereoselective cyclisation in the cembrane series: X-ray structure of (+)-(4*R*,8*R*,11*S*,12*E*,14*S*,16*R*)-11-isopropyl-4,8,14-trimethyl-14-morpholin-4-yl-3-oxa-2-azatricyclo[6.6.2.0$^{4,16}$]hexadeca-1,12-diene

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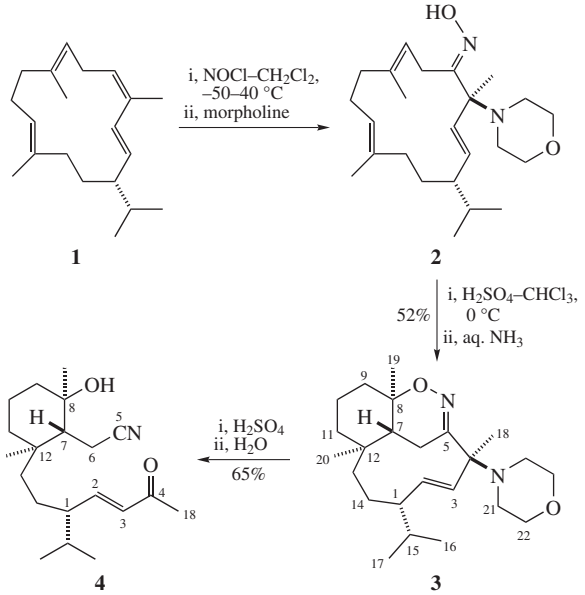
A simple synthetic derivative of natural diterpene cembrene [(1*S*,2*E*,4*S*,7*E*,11*E*)-4-morpholin-4-ylcembra-2,7,11-trien-5-one *E*-oxime] was found to be highly sensitive to acids (sulfuric and trifluoroacetic), and it is transformed under acidic conditions to a tricyclic bridged system with the 5,6-dihydro-4*H*-1,2-oxazine moiety.

Cembrene is a unique natural optically active diterpene hydrocarbon having a 14-membered carbocycle. Cembrene is a progenitor of the cembrane-type diterpenoids including a wide diversity of so-called cyclocembranoids.[1] There are several hundreds of natural cyclocembranoids discovered as yet in plants and animals. Most of cyclocembranoids show only hypothetic cognation with cembranoids because, in most of cases, cyclocembranoids cannot be prepared by the direct cyclisation of corresponding monocyclic cembranoids. Cembrene, as well as its simple derivative, possesses conformational flexibility. As a result, most of their addition reactions and cyclisation processes are regio- and stereo- unselective.[2,3] Here we report on the first regio- and stereoselective cyclisation of the simple cembrane-type compound to the 7,12-cyclocembrane derivative.

Cembrane-type α-amino oxime **2**, prepared from cembrene **1** *via* addition of NOCl,[4] is very sensitive to acids and can be easily transformed to the cyclisation product **3**, the cyclisation being stereo- and regioselective (Scheme 1).†

Both $^1$H and $^{13}$C NMR spectra of cyclisation product **3** at room temperature consist of a number of broad signals due to conformational exchange in the 10-membered carbocycle. At +95 °C in pyridine, the exchange becomes fast and allows one to record highly resolved NMR spectra (including 2D $^1$H–$^1$H and $^{13}$C–$^1$H correlations) showed cyclisation product **3** to belong to the 7,12-cyclocembrane series. The configuration of new compound **3** was proved by X-ray crystallography (Figure 1).‡ In spite of preparation under acidic conditions, cyclisation product **3** is very sensitive to acids. Thus, when starting compound **2** is treated in chloroform with sulfuric acid or trifluoroacetic acid for a longer period (10 h at 0 °C) or at room temperature (1 h at +25 °C), nitrile **4**§ becomes the only isolated product (Scheme 1).




**Scheme 1** The numbering scheme is given for NMR interpretation.

† The transformation was carried out as follows: concentrated $H_2SO_4$ (3 ml) was added dropwise to a stirred solution of amino oxime **2** (0.30 g, 0.77 mmol) in chloroform (10 ml) at 0 °C. After 3 h of vigorous stirring, the reaction mixture was carefully (0 °C) treated with an excess of concentrated aqueous ammonia to adjust pH 10–11. The organic layer was separated, and the aqueous phase was extracted with chloroform (3×15 ml). The combined organic extract was dried over anhydrous $Na_2SO_4$, filtered and concentrated under reduced pressure to leave the crude product, which was percolated through a silica gel column using mixtures of hexane and *tert*-butyl methyl ether as an eluent to remove impurities. The eluate was concentrated under reduced pressure to leave the reaction product, which was then crystallized from hexane–ethyl acetate to give pure cyclisation product **3**.

*(+)-(4*R*,8*R*,11*S*,12*E*,14*S*,16*R*)-11-isopropyl-4,8,14-trimethyl-14-morpholin-4-yl-3-oxa-2-azatricyclo[6.6.2.0$^{4,16}$]hexadeca-1,12-diene* **3**: yield 0.16 g (52%), white crystals with mp 113–115 °C (from hexane–ethyl acetate) and $[\alpha]_{578}^{24}$ +13 (*c* 4.9, $CHCl_3$). HRMS, *m*/*z*: 388.30898 ($[M]^+$, calc. for $C_{24}H_{40}N_2O_2$: 388.30898). MS, *m*/*z* (%): 388 (8), 371 (100), 286 (152), 284 (20), 258 (12), 208 (18), 166 (17), 81 (24). $^1$H NMR (500 MHz, [$^2H_5$]pyridine, +95 °C) $\delta$: 0.84 (s, 3H$^{20}$), 0.95 (d, 3H$^{16}$, *J* 6.6 Hz), 0.97 (d, 3H$^{17}$, *J* 6.6 Hz), 1.04 (ddd, H$_a^{11}$, *J* 14.0, 3.2 and 3.2 Hz), 1.11 (ddd, H$_a^{13}$, *J* 14.6, 10.9 and 5.8 Hz), 1.19 (ddd, H$_b^{11}$, *J* 14.0, 12.0 and 4.5 Hz), 1.30 (s, 3H$^{18}$), 1.35 (d, H$^7$, *J* 11.5 Hz), 1.37 (m, H$_a^{14}$), 1.45 (m, H$_b^{13}$), 1.46 (s, 3H$^{19}$), 1.50 (m, H$_a^{10}$), 1.50 (m, H$_a^9$), 1.55 (m, H$_b^{10}$), 1.57 (dd, H$_a^6$, *J* 14.0 and 11.5 Hz), 1.67 (dqq, H$^{15}$, *J* 9.6, 6.6 and 6.6 Hz), 1.80 (dddd, H$_b^{14}$, *J* 15.3, 10.8, 5.5 and 2.7 Hz), 2.01 (m, H$_b^9$), 2.04 (m, H$^1$), 2.27 (d, H$_b^6$, *J* 14.0 Hz), 2.60 (ddd, 2H$_a^{21}$, *J* 10.9, 6.2 and 3.0 Hz), 2.97 (ddd, 2H$_b^{21}$, *J* 10.9, 6.2 and 3.0 Hz), 3.79 (ddd, 2H$_a^{22}$, *J* 10.7, 6.2 and 3.0 Hz), 3.84 (ddd, 2H$_b^{22}$, *J* 10.7, 6.2 and 3.0 Hz), 5.50 (d, H$^3$, *J* 16.4 Hz), 5.79 (dd, H$^2$, *J* 16.4 and 7.8 Hz). $^{13}$C NMR (125 MHz, [$^2H_5$]pyridine, +95 °C) $\delta$: 164.75 (C$^5$), 137.10 (C$^2$), 136.77 (C$^3$), 82.91 (C$^8$), 70.62 (C$^4$), 68.05 (2C$^{22}$), 48.85 (2C$^{21}$), 48.20 (C$^1$), 45.00 (C$^7$), 41.66 (C$^9$), 37.52 (C$^{12}$), 34.74 (C$^{11}$), 33.94 (C$^{13}$), 30.63 (C$^{15}$), 28.78 (C$^{14}$), 23.29 (C$^{19}$), 22.46 (C$^{20}$), 21.99 (C$^{17}$), 21.83 (C$^{10}$), 20.93 (C$^{16}$), 20.76 (C$^6$), 10.09 (C$^{18}$).

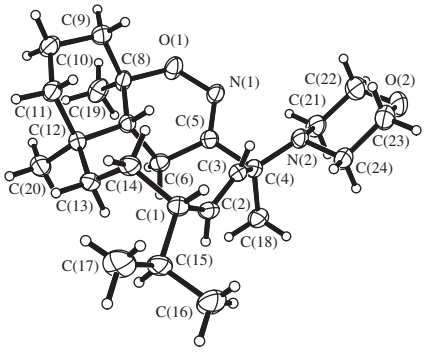
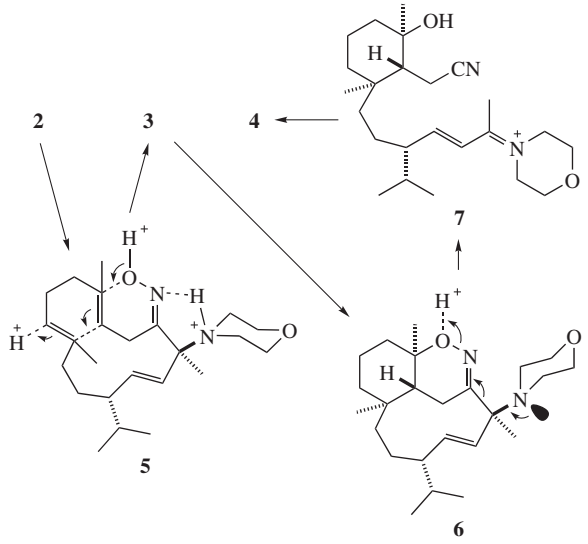



**Figure 1** Molecular structure of **3** in a crystal. The boat like conformation of dihydrooxazine ring can be characterized with the planar within ±0.011(1) Å C(7)–C(8)–O(1)–N(1) fragment and C(5), C(6) atom deviations from this plane by 0.603(6), 1.142(7) Å, respectively. The 10-member ring adopts almost the same conformation as was found for (*E*,2*R*,5*R*,6*R*,7*S*)-germacra-1(10),4(15)-diene-2,5,6-triol.[5]

The stereo- and regioselective acid-induced transformation **2** → **3** can be explained in terms of preprotonation of the substrate. Recently, we have mentioned that under acidic conditions primary protonation of α-amino oximes results in H-bonded ammonium salt, whose secondary protonation at a carbon–carbon double bond induces cyclisation.[6] In case of compound **2**, the primary protonation should lead to ammonium salt **5**, which forces the secondary protonation to take place at carbon 11, which is the most remote from the ammonium moiety (Scheme 2). Transformation **3** → **4** seems to be induced by protonation of the oxime ether oxygen (**6**) with the formation of immonium salt **7**, whose hydrolysis afforded nitrile **4**.




**Scheme 2**

Nitrile **4** is a product of the Beckmann fragmentation reaction, which is typical of substituted oximes having electron donors at the α-position to oxime. The Beckmann fragmentation of α-amino oximes normally does not proceed spontaneously, and even in case of quite labile terpenic α-amino oximes, the fragmentation requires the usage of TsCl, $SOCl_2$, $PCl_5$, *etc.*[7] Molecules of tricyclic compound **3** are characterized by the presence of strained 10-membered carbocycle and unfavourable *syn*-planar arrangement of nitrogen atoms of oxime and morpholine moieties. So, decrease of the molecular strain mentioned seems to be the driving force of easy fragmentation **3** → **4**.

‡ *X-ray crystallographic data for compound* **3**. $C_{24}H_{40}N_2O_2$, $M$ = 388.58, crystal class hexagonal, space group $P6_5$, $a = b$ = 10.5875(6) and $c$ = = 35.386(3) Å, $V$ = 3435.2(4) Å$^3$, $Z$ = 6, $d_{calc}$ = 1.127 g cm$^{-3}$, $\mu$ = 0.071 mm$^{-1}$, $\lambda$ = 0.71073 Å, crystal size 0.23×0.23×1.20 mm. The data were measured on a Bruker P4 diffractometer (MoKα radiation, $\theta$-2$\theta$ scans, $\theta < 25°$). Absorption corrections were applied by empirical method based on $\psi$-scans (transmission 0.9019–0.9250). The structure was solved by direct methods using SIR97 and refined by a full matrix least-squares anisotropic-isotropic (for atom H) procedure using SHELXL97 program. The hydrogen atom positions were calculated geometrically. The final indexes are $wR_2$ = 0.1229, $S$ = 1.034 for all 2058 $F^2$ and $R_1$ = 0.0477 for 1562 $F_0 > 4\sigma$.

CCDC 264880 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2009.

§ *2-{(1*R*,2*R*,6*R*)-2-hydroxy-6-[(*S*,*E*)-3-isopropyl-6-oxohept-4-enyl]-2,6-dimethylcyclohexyl}acetonitrile* **4**. Yield 65% after column chromatography, yellowish viscous oil. UV [in EtOH, $\lambda_{max}$/nm ($\varepsilon$)]: 228 (18400). IR ($c$ 1% in $CCl_4$, $\nu_{max}$/cm$^{-1}$): 3619 and 3598 (O–H), 2244 (C≡N), 1676 (C=O). HRMS, *m*/*z*: 319.25138 (calc. for $C_{20}H_{33}NO_2$ 319.25111). MS, *m*/*z* (%): 319 (31), 301 (13), 258 (11), 149 (12), 148 (36), 125 (31), 123 (13), 124 (12), 111 (13), 109 (19), 107 (16), 97 (29), 95 (30), 81 (23), 71 (31), 69 (17), 67 (17), 55 (23), 43 (100), 41 (24). $^1$H NMR (500 MHz, [$^2H_6$]acetone, +30 °C) $\delta$: 0.88 (s, 3H$^{20}$), 0.89 (d, H$^{17}$, $J$ 6.7 Hz), 0.94 (d, 3H$^{16}$, $J$ 6.7 Hz), 1.08 (s, 3H$^{19}$), 1.16 (ddd, H$^9_a$, $J$ 14.3, 13.4 and 4.6 Hz), 1.32 (m, H$^{11}_a$), 1.36–1.49 (m, H$^9_b$, H$^{11}_b$, 2H$^{13}$, H$^{14}_a$), 1.51–1.62 (m, 2H$^{10}$), 1.75 (m, H$^{14}_b$ and H$^{15}$), 1.79 (dd, H$^7$, $J$ 8.4 and 3.1 Hz), 1.89 (dddd, H$^1$, $J$ 9.9, 9.7, 5.3 and 4.6 Hz), 2.15 (dd, H$^6_b$, $J$ 17.3 and 8.4 Hz), 2.17 (s, 3H$^{18}$), 2.68 (dd, H$^6_a$, $J$ 17.3 and 3.1 Hz), 5.90 (d, H$^3$, $J$ 16.0 Hz), 6.60 (dd, H$^2$, $J$ 16.0 and 9.9 Hz). $^{13}$C NMR (125 MHz, [$^2H_6$]acetone, +30 °C) $\delta$: 196.55 (C$^4$), 149.60 (C$^2$), 132.87 (C$^3$), 121.09 (C$^5$), 71.86 (C$^8$), 51.02 (C$^7$), 50.06 (C$^1$), 42.68 (C$^{14}$), 42.10 (C$^9$), 37.84 (C$^{12}$), 37.24 (C$^{11}$), 32.08 (C$^{15}$), 26.71 (C$^{18}$), 25.42 (C$^{13}$), 23.24 (C$^{19}$), 21.10 (C$^{20}$), 20.90 (C$^{16}$), 20.18 (C$^{10}$), 19.34 (C$^{17}$), 12.36 (C$^6$).

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