Unusual acid-induced heterocyclisation of caryophyllene-type α-amino oximes: X-ray structure of (1*S*,2*S*,5*R*,8*S*)-1,4,4,8-tetramethyl-8-morpholin-4-yl-11-oxa-10-azatricyclo[7.2.2.0^{2,5}]tridec-9-ene

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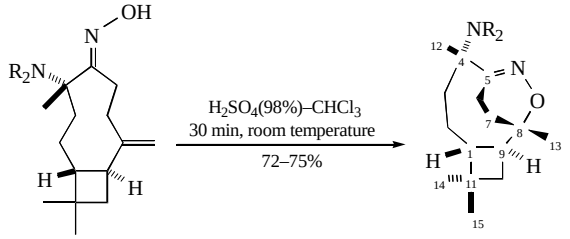
The acid-catalysed cyclisation of caryophyllene-type α-amino oximes results in the formation of new bridged heterocycles with the 5,6-dihydro-4*H*-[1,2]oxazine moiety.

Caryophyllene {(1*R*,4*E*,9*S*)-4,11,11-trimethyl-8-methylenebicyclo-[7.2.0]undec-4-ene} is a unique sesquiterpenoid because it can undergo various rearrangements of the carbon skeleton. Caryophyllene and its derivatives are extremely sensitive to acidic agents and undergo different cyclisations, isomerisations and rearrangements.[1,2] We report here on the new unusual acid-catalysed heterocyclisation of caryophyllene derivatives with the retention of the carbon frame.



a NR_2 = dimethylamino
b NR_2 = 4-morpholino

Scheme 1

Amino oximes **1a**,**b** (prepared from caryophyllene by the addition of NOCl followed by the treatment with an amine[3]) were found to react with concentrated H_2SO_4 at room temperature† without forming any tarry products to afford heterocyclisation products **2a**‡ and **2b**§ in very good yields. The NMR spectra of these compounds (signal assignments were carried out using 2D H–H COSY, 2D C–H COSY and 2D-NOESY) proved both compounds to belong to the same structural type with the same configuration of the 5,6-dihydro-4*H*-[1,2]oxazine moiety.¶ The stereochemistry of these compounds was determined by single-crystal X-ray diffraction analysis of morpholino derivative **2b**†† (Figure 1). The oxazine ring bonds C(8)–O(1) [1.453(3) Å] and O(1)–N(1) [1.441(2) Å] are elongated as compared to the average values 1.437(13) and 1.409(15) Å, respectively, for eight 5,6-dihydro-4*H*-[1,2]oxazine structures from the Cambridge Crystallography Database.[4] The oxazine ring adopts a distorted twist–boat shape. The conformation of the nine-membered heterocycle [C(1)–C(2)–C(3)–C(4)–C(5)=N(1)–O(1)–C(8)–C(9)] is almost the same as that of the nine-membered carbocycle in caryophyllene nitrosite and dinitrocaryophyllene,[5] as well as in caryophyllene nitrosochloride[6] (the differences in endocyclic torsion angles are less than 20°).

† Concentrated H_2SO_4 (1.5 ml) was added to a stirred solution of caryophyllene-type α-amino (*E*)-oxime **1a** or **1b** (1.08 mmol) in $CHCl_3$ (10 ml). The mixture was vigorously stirred at room temperature for 30 min, and then pH was adjusted to 10–11 by the addition of concentrated aqueous ammonia (ice-cold bath). The organic phase was separated, dried over $MgSO_4$ and concentrated at reduced pressure to leave a yellowish solid (0.290 g), which was percolated through SiO_2 (eluent Bu^{t}OMe) followed by crystallisation of the crude product from an appropriate solvent to afford cyclisation products **2a** or **2b** in good yields.

‡ *(1S,2S,5R,8S)-1,4,4,8-Tetramethyl-8-dimethylamino-11-oxa-10-azatricyclo[7.2.2.0^{2,5}]tridec-9-ene* **2a**: yield 72%, white crystals, mp 122–123 °C (hexane), $[\alpha]_{578}^{22}$ –37 (*c* 11 mg cm^{-3}, $CHCl_3$). IR (KBr, ν_{max}/cm^{-1}): 1625 (C=N), 895 (N–O). MS, *m*/*z* (%): 278.23568 (10, M$^+$, calc. for $C_{17}H_{30}N_2O$ 278.23581), 263 (11), 235 (100), 218 (34), 203 (32), 192 (8), 179 (8), 177 (8), 166 (15), 148 (29), 147 (36), 138 (6), 124 (15), 123 (15), 109 (21), 98 (16), 97 (18), 85 (28), 70 (30), 56 (43), 44 (11), 41 (26).

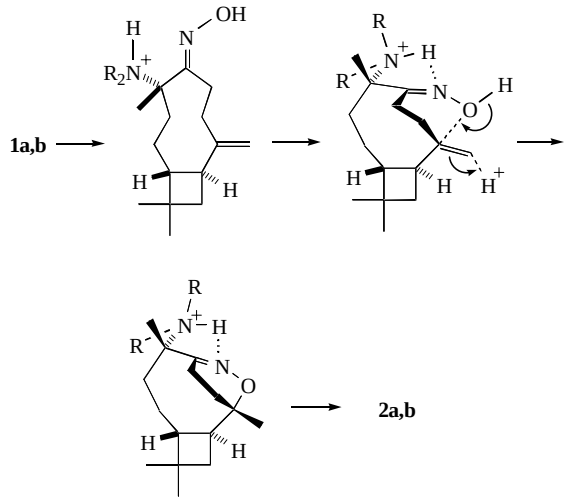
§ *(1S,2S,5R,8S)-1,4,4,8-Tetramethyl-8-morpholin-4-yl-11-oxa-10-azatricyclo[7.2.2.0^{2,5}]tridec-9-ene* **2b**: yield 75%, white crystals, mp 174–176 °C (MeCN), $[\alpha]_{578}^{22}$ –70 (*c* 3 mg cm^{-3}, $CHCl_3$). IR (KBr, ν_{max}/cm^{-1}): 1640 (C=N), 1130 (C–O), 895 (N–O). MS, *m*/*z* (%): 320.24639 (2, M$^+$, calc. for $C_{19}H_{32}N_2O_2$ 320.24636), 305 (3), 266 (1), 235 (100), 218 (37), 203 (38), 192 (7), 178 (7), 166 (8), 162 (12), 161 (13), 148 (35), 147 (37), 133 (10), 124 (14), 123 (13), 112 (8), 109 (11), 95 (16), 86 (12), 81 (13), 69 (17), 55 (23), 41 (26).

¶ NMR spectra were measured on a Bruker DRX-500 (500 MHz for ^{1}H, 125 MHz for ^{13}C) at 25–27 °C. Chemical shifts in square brackets were taken from the 2D carbon–proton shift correlation spectra.

For **2a** (60 mg cm^{-3} in $CDCl_3$–C_6D_6 1:1, v/v): ^{1}H NMR, δ: 2.20 (ddd, 9-H, *J* 10.9, 10.9 and 8.3 Hz), 2.16 (s, 6H, N*Me*$_2$), 1.99 (dd, 3-H$_\alpha$, *J* 15.0 and 7.4 Hz), [1.85, 1.84] (7-H), [1.76, 1.66] (6-H), 1.45 (dd, 10-H$_\alpha$, *J* 10.1 and 8.3 Hz), 1.42 (ddd, 2-H$_\alpha$, *J* 15.0, 11.5 and 9.0 Hz), 1.01 (13-H), 1.00 (dd, 1-H, 2-H$_\beta$, *J* 15.0, 10.9, 9.0 and 7.4 Hz), 0.99 (dd, 3-H$_\beta$, *J* 15.0 and 11.5 Hz), 0.88 (dd, 10-H$_\beta$, *J* 10.9 and 10.1 Hz), 0.86 (14-H), 0.83 (15-H), 0.78 (12-H). ^{13}C NMR, δ: 170.98 (C-5), 77.16 (C-8), 64.63 (C-4), 54.33 (C-1, *J* 128.6 Hz), 47.78 (C-9, *J* 133.9 Hz), 39.97 (C-3, *J* 128.1, 123.8 and 6×4.0 Hz), 38.83 (N*Me*$_2$), 36.03 (C-10, *J* 133.0, 128.5 and 7×4.9 Hz), 35.35 (C-11), 30.28 (C-7, *J* 133.7, 129.0, 6.7, 6.7 and 4.1 Hz), 29.44 (C-14, *J* 3×123.8 and 5×5.2 Hz), 23.19 (C-13, *J* 3×127.0 and 4.0 Hz), 22.19 (C-2, *J* 123.1 and 123.1 Hz), 20.66 (C-15, *J* 3×125.1 and 6×4.9 Hz), 19.88 (C-6, *J* 130, 130, 5.6 and 5.6 Hz), 12.96 (C-12, *J* 3×126.3 and 1.0 Hz).

For **2b** (65 mg cm^{-3} in $CDCl_3$): ^{1}H NMR, δ: 3.72 and 3.63 (2ddd, NCH_2CH_2O, *J* 11.0, 6.5 and 2.8 Hz), 2.63 and 2.42 (2ddd, NCH_2CH_2O, *J* 10.8, 6.5 and 2.8 Hz), 2.19 (dd, 3-H$_\alpha$, *J* 15.6 and 7.3 Hz), [2.13] (9-H), [2.10, 2.08] (7-H), [2.14, 1.99] (6-H), 1.53 (dd, 10-H$_\alpha$, *J* 10.3 and 8.3 Hz), 1.43 (ddd, 2-H$_\alpha$, *J* 14.9, 11.2 and 8.9 Hz), 1.22 (dd, 3-H$_\beta$, *J* 15.6 and 11.2 Hz), 1.165 (dd, 1-H, *J* 10.6 and 8.9 Hz), 1.160 (dd, 2-H$_\beta$, *J* 14.9 and 7.3 Hz), 1.06 (13-H), 1.04 (12-H), 1.00 (dd, 10-H$_\beta$, *J* 11.2 and 10.3 Hz), 0.88 (15-H), 0.86 (14-H). ^{13}C NMR, δ: 171.15 (C-5), 77.21 (C-8), 67.32 (NCH_2CH_2O), 64.91 (C-4), 54.51 (C-1), 48.01 (C-9), 46.82 (NCH_2CH_2O), 39.29 (C-3), 36.26 (C-10), 35.70 (C-11), 30.45 (C-7), 29.72 (C-14), 23.29 (C-13), 22.17 (C-2), 20.87 (C-15), 20.50 (C-6), 15.69 (C-12).

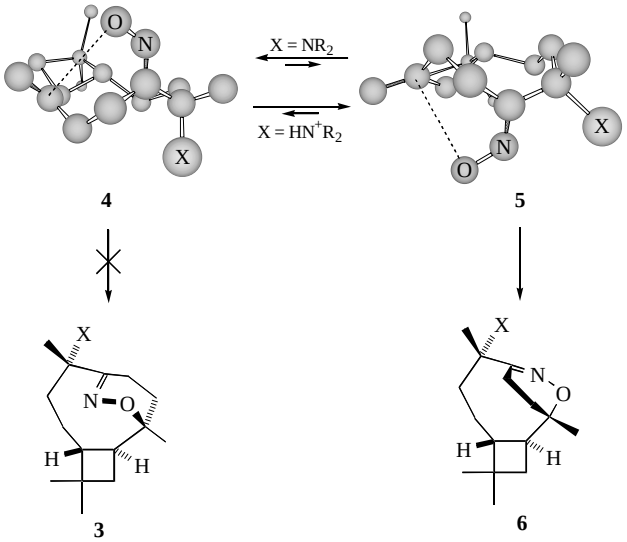
†† 1801 independent reflections were measured on a Bruker P4 diffractometer with graphite-monochromated MoKα radiation using $\theta/2\theta$ scans with $\theta < 25°$. The crystal system of compound **2b** is monoclinic, space group $P2_1$, a = 11.429(1), b = 6.3262(7), c = 13.868(1) Å, β = 111.814(5)°, V = 930.89(2) Å^3, $C_{19}H_{32}N_2O_2$, M = 320.47, Z = 2, d_{calc} = 1.143 g cm^{-3}, μ = 0.074 mm^{-1}, $F(000)$ = 352, crystal size 0.22×0.35×1.20 mm. The structure was solved by the direct methods (SHELXS-97) and refined in the anisotropic–isotropic approximation using SHELXL-97 to wR_2 = = 0.1074, S = 1.065 for all reflections (R = 0.0377 for 1699 $F > 4\sigma$). The absorption correction was applied using an integration method. The positions of hydrogen atoms were calculated using a riding model. 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, 2000. Any request to the CCDC for data should quote the full literature citation and the reference number 1135/74.



Scheme 2

The formation of compounds **2a** and **2b** requires cyclisation (Scheme 2), which is unusual in the caryophyllene series. First, the formation of a carbocation at the C-8 carbon by the protonation of the $\Delta^{8,13}$ double bond in caryophyllene-type compounds usually results in rearrangement due to migration of the neighbouring carbon–carbon bond and the cyclobutane ring expansion. The formation of cyclisation products **2a** and **2b** is not accompanied by a rearrangement of the carbon skeleton even under severe conditions (concentrated H_2SO_4 at room temperature).

Second, due to the presence of a nine-membered carbon ring most of caryophyllene-type compounds are conformationally inhomogeneous. This is the reason for low stereoselectivity of transformations due to a significant barrier of the interconversion of conformers providing conformational control for most reactions and the formation of pairs of diastereomers. Thus, contrary to usual reactions in the caryophyllenes series, the acid-catalysed cyclisation of compounds **1a**,**b** resulted in the sole stereoisomer, whose formation is shown in Scheme 3. Semi-empirical quantum-chemical calculations (AM1 and PM3 methods) showed the relative stability of ammonium forms of the starting compounds (structures **4** and **5**, $X = HN^+R_2$) to be opposite as compared to the stability of free amines (structures **4** and **5**, $X = NR_2$), the cyclisation **5** → **6** being thermodynamically preferable to the cyclisation **4** → **3**.



	Calculation method	Heat of formation, $\Delta\Delta H_f^0$/kcal mol^{-1}			
		3	**4**	**5**	**6**
$X = NR_2$	AM1		0.0	0.4	
	PM3		0.0	2.5	
$X = HN^+R_2$	AM1	7.8	6.6	2.1	0.0
	PM3	7.2	4.6	3.9	0.0

Scheme 3

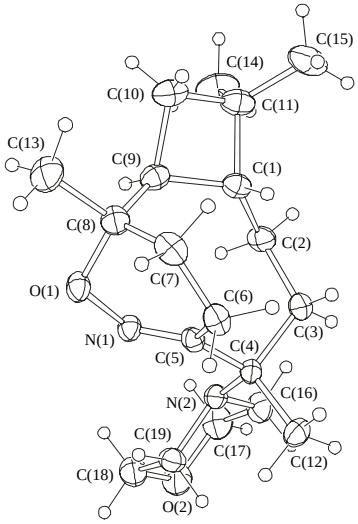


Figure 1 Molecular structure of compound **2b**. Selected bond lengths (Å): C(8)–O(1) 1.453(3), O(1)–N(1) 1.441(2); selected bond angles (°): C(8)–C(9)–C(1)–C(2) 92.0(3), C(9)–C(1)–C(2)–C(3) –104.1(3), C(1)–C(2)–C(3)–C(4) 85.2(3), C(2)–C(3)–C(4)–C(5) –49.5(2), C(3)–C(4)–C(5)=N(1) 105.2(2), C(4)–C(5)=N(1)–O(1) –171.7(1), C(5)=N(1)–O(1)–C(8) 46.0(2), N(1)–O(1)–C(8)–C(9) 51.3(2), O(1)–C(8)–C(9)–C(1) –95.8(3).

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