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Rearrangement of α-Hydroxylamino Oximes to Cyclic Amidoximes by the Action of Sodium Borohydride.

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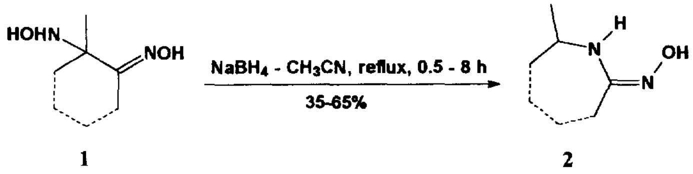
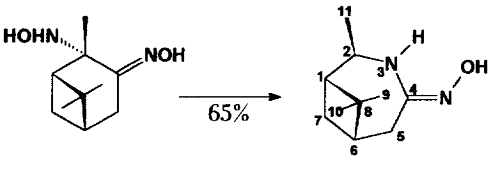
Abstract: Treatment of α-hydroxylamino and α-(O-acetyl)-hydroxylamino oximes, derived from nitrosochlorides of the monoterpenes α-pinene and (+)-3-carene, with sodium borohydride in acetonitrile medium results in rearrangement by ring-expansion and formation of chiral cyclic amidoximes in 35-65% yields. The reaction of α-hydroxylamino oximes with the less complex carbon frame (derivatives of cyclohexene, 1-methylcyclohexene, isobutylene, 2-butene, β,β-dimethylstyrene) does not lead to the ring expansion. Structure elucidation and conformational analysis of cyclic amidoximes of pinane and carane types are described. Possible reaction pathways are discussed.

Recently we reported the reductive Beckmann fragmentation of α-amino oximes under the action of sodium borohydride in acetonitrile medium.[1] α-Hydroxylamino oximes **1** were found to undergo unknown rearrangement to give cyclic amidoximes **2**. Synthesis of compounds **2** by other routes seems to be reasonably complicated, although molecules of this type were found among the products of the photoisomerization of N-nitrosodialkylamines.[2] The cyclic amidoximes formed appear to be interesting from the point of view of their biological activity, since the simplest compounds of this type possess antiamnestic and antihypoxive activity,[3] hypotensive activity,[4] some antireserpine activity which indicates thymoleptic and antidepressant potential,[5] trypanosomicidal and leishmanicidal activity.[6] Also various amidoximes form stable complexes with transition metal ions and are widely used for the extraction of metal ions from aqueous solutions.[7] On the basis of the natural terpene molecules, cyclic amidoximes can be prepared in optically active form, and these optically active amidoximes are rather useful as precursors of chiral catalysts and auxiliaries for asymmetric synthesis.[8] The reaction allows one to transform α-hydroxylamino oximes to the corresponding amidoximes:

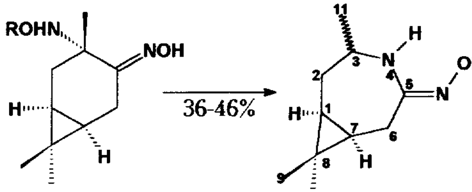


The transformation was carried out by refluxing a suspension of an α-hydroxylaminooxime and sodium borohydride in acetonitrile. α-Hydroxylamino oximes were prepared by the usual two-step procedure starting from unsaturated hydrocarbons.[9] At the first stage olefins were transformed to the corresponding nitrosochlorides which were subsequently treated with NH_2OH to give α-hydroxylamino oximes. The resulting cyclic amidoximes possessed usual basicity and were easily separated from by-products by extraction with aqueous acids followed by treatment of the extract with concentrated ammonia and extraction with ether.

We have tested, in this reaction, several α-hydroxylamino oximes derived from the following unsaturated hydrocarbons - cyclohexene, 1-methylcyclohexene, isobutylene (2-methylpropene), 2-butene, β,β-dimethylstyrene, α-pinene and (+)-3-carene. Surprisingly the satisfactory yields were achieved only in the case of pinane-type and carane-type derivatives **3** and **5**,**6** respectively:



3 **4**



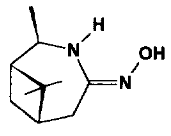
7:**8** = 1:1.3

5 R=H **6** R=Ac **7** αCH$_3$ **8** βCH$_3$

In the case of less complex α-hydroxylamino oximes derived from cyclohexene, 1-methylcyclohexene, isobutylene, β,β-dimethylstyrene, 2-butene, we failed to isolate cyclic amidoximes. Although in all the cases the initial product was completely exhausted, the reaction of β,β-dimethylstyrene derivative results in a complex mixture of products while after the reaction of α-hydroxylamino oximes derived from cyclohexene, 1-methylcyclohexene, isobutylene and 2-butene one can extract only a decreasingly small amount of an organic substance.

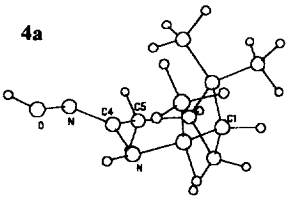
The resulting cyclic amidoximes have fixed configuration of the oxime moiety. Semi-empirical calculations show *Z*-isomers of these compounds to be by 0.5–2.0 kcal/mol more stable than *E*-isomers. These results are in agreement with the data for the simplest amidoximes.[10]

The only diastereomer **4** is formed in the case of rearrangement of pinane derivative **3**. *Z*-Configuration of the oxime group in the molecule of compound **4** was proved by the direct coupling constant $^1J_{C4\text{-}C5}$ (INADEQUATE-technique), whose value 51.5±0.5 Hz corresponds to *Z*-isomer rather than E-isomer (according to the literature[11]: ^1J=52 Hz for *Z*-isomer and 44 Hz for E-isomer). The configuration of C-2 atom in the cyclic amidoxime **4** was determined by comparing experimental and calculated NMR parameters. Molecular mechanics calculations are currently inapplicable for amidoximes.[12] Using the semi-empirical quantum chemical calculations (by PM3 and MNDO methods[13]) we specified the geometry of four possible structures **4a**-**4d** (two conformers for each C-2 epimer):

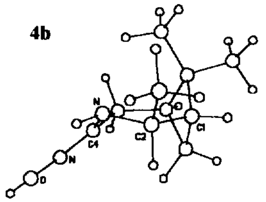


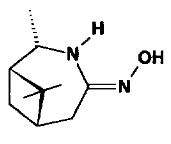
cis-isomer

4a

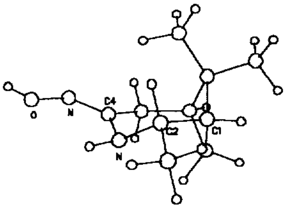


4b

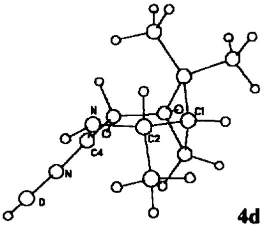




trans-isomer



4c



4d

Table 1. Calculated Heats of Formation and Experimental and Calculated Vicinal Couplings for Amidoxime **4**.

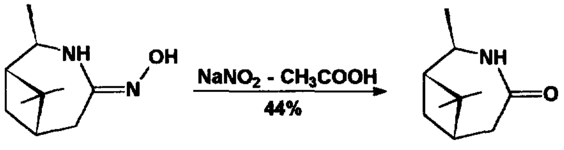
^3J	Hz				
	experimental	calculated[a]			
		4a	**4b**	**4c**	**4d**
H^1-H^2	2.4	3.8	2.4	1.9	2.8
αH^5-H^6	5.3	2.8	5.8	3.1	6.2
βH^5-H^6	2.5	4.4	2.0	3.9	1.9
C^8-H^2	8.5	8.8	8.1	3.6	1.3
$\Delta H°_f$, kcal/mol (MNDO)		3.3	1.5	0.7	1.3
$\Delta H°_f$, kcal/mol (PM3)		0.0	0.1	−0.5	−1.3

[a] Geometry optimization by MNDO and PM3 gave practically the same results (torsion angles: ± 2°; bond angles ± 1°; bond lengths ± 0.02Å)

Calculations of the vicinal coupling constants were carried out based on the specified geometry: $^3J_{H\text{-}H} = 5.8 - 1.2\times\cos\varphi + 3.9\times\cos2\varphi$[14] and $^3J_{H\text{-}C} = 4.3 - \cos\varphi + 3.6\times\cos2\varphi$.[11] Calculated and experimental values of the vicinal couplings as well as calculated heats of formation are collected in first.

The value of the vicinal constant $^3J_{C8\text{-}H2}$=8.5±0.5 Hz unequivocally indicates[15] the antiperiplanar orientation of atoms C8 and H2. Calculated values of the vicinal proton-proton couplings for conformer **4b** are in good agreement with the experimental ones.

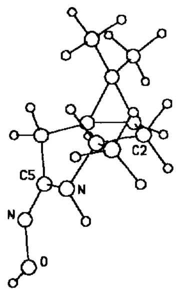
Treatment of amidoxime **4** with sodium nitrite in acetic acid results in deoximation[16] and formation of lactam **9**, which was earlier described as a product of Beckmann rearrangement of pinocamphone oxime.[17] Our ^1H NMR spectrum of compound **9** correlated well with the spectrum published, except for the value of the geminal coupling $^2J_{H5\alpha\text{-}H5\beta}$ (18.9±0.1 Hz in our experiments and −23 Hz in the reference[17]).



4 **9**

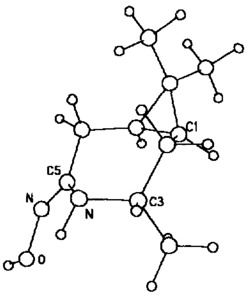
The reaction of the carane type hydroxylamino oxime **5** and its O-acylated derivative **6** results in a chromatographically homogeneous (TLC) mixture of C3 epimers **7** and **8**. The two isomers can be partially resolved by liquid chromatography. Chromatography of the mixture on a silica gel column (gradient of CH_3OH in $CHCl_3$) results in enriched fractions that allowed us to make precise assignments in the NMR and IR spectra of the epimers. Conformational analysis and PM3 calculations have shown that epimer **7** has five stable forms **7a** - **7e** while epimer **8** has only three - **8b**,**8c** and **8e**. Although the other two conformations **8a** and **8d** (with the same form of the seven-membered rings as in the conformations **7a** and **7d** correspondingly) can be constructed using molecular models, they are unstable and transformed to the stable conformations **8b** or **8c** during the geometry optimization.

Calculated spin-spin couplings $^3J_{H\text{-}H}$ for all the above stable conformations and experimental data are collected in second. Comparison of the calculated and experimental parameters proves that in the case of rearrangement of the carane-type derivatives the major product is 3βH-epimer **8** (conformation **8b**), and the minor product is 3αH-epimer 7 (conformation **7a**). This conclusion is also supported by IR data. The structure of the minor component (conformation **7a**) is unfavorable to the intramolecular hydrogen bond formation ($\nu_{N\text{-}H}$ = 3425 cm^{-1}), whereas the structure of the major epimer (conformation **8b**) favors the formation of the intramolecular hydrogen bond ($\nu_{N\text{-}H\cdots O}$ = 3380 cm^{-1}).

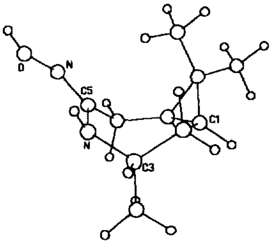


ϕ(H-N-C-N) = 38°
ϕ(O-N-C-N) = 6°
l(NH····O) = 2.53Å

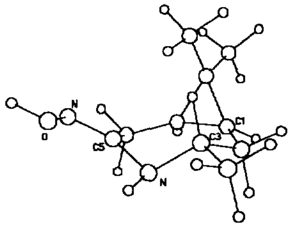
7a



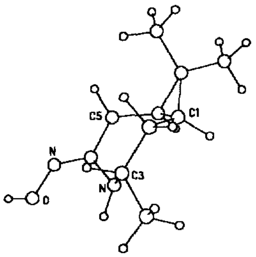
7b



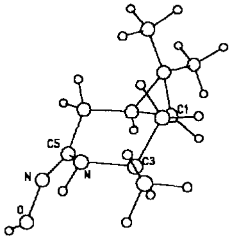
7c



7d

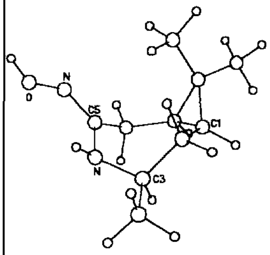


7e

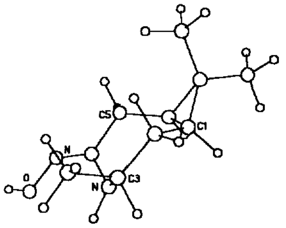


ϕ(H-N-C-N) = 6°
ϕ(O-N-C-N) = 6°
l(NH····O) = 2.43Å

8b



8c



8e

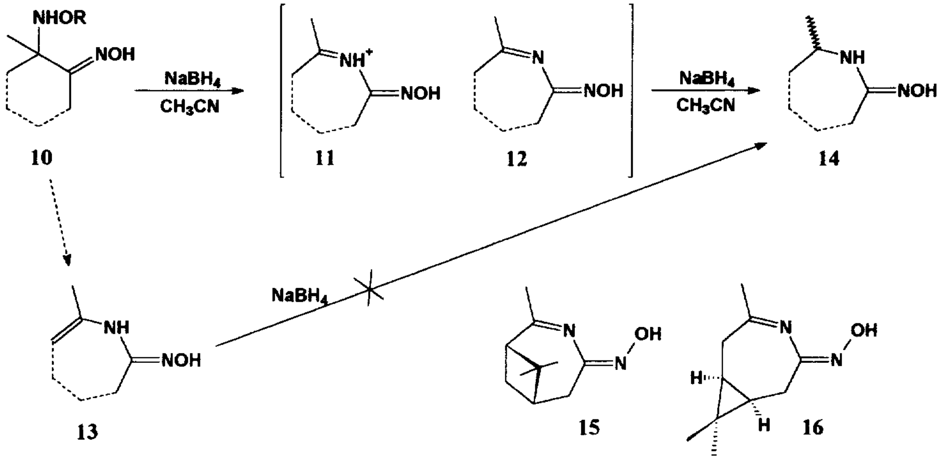
Table two Calculated Heats of Formation and Experimental and Calculated Vicinal Couplings for Amidoximes 7 and **8**.[a,b]

H^i-H^j	$^3J_{Hi\text{-}Hj}$, Hz									
	experimental	calculated					experimental	calculated		
	7	**7a**	**7b**	**7c**	**7d**	**7e**	**8**	**8b**	**8c**	**8e**
H^1-αH^2	**8.4**	**8.6**	6.5	7.5	5.6	5.7	**5.9**	**6.2**	9.1	6.1
H^1-βH^2	**2.5**	**2.4**	9.1	8.2	3.9	9.6	**10.4**	**9.5**	6.6	9.4
H^3-αH^2	**10.8**	**12.1**	5.3	2.5	12.2	2.0	**2.0**	**1.9**	1.9	5.9
H^3-βH^2	**3.6**	**2.7**	3.0	6.6	3.0	7.5	**11.4**	**11.0**	9.7	1.1
αH^6-H^7	**5.7**	**7.8**	6.5	10.0	6.4	6.3	**5.7**	**6.6**	6.4	6.4
βH^6-H^7	**10.1**	**8.2**	9.2	2.8	3.4	9.3	**10.4**	**9.2**	3.4	9.3
$\Delta H°_f$, kcal/mol (MNDO)		−2.0	−2.9	−2.0	0.1	−0.9		−3.6	−1.4	−1.2
$\Delta H°_f$, kcal/mol (PM3)		−0.9	0.7	5.9	7.2	3.2		0.5	2.6	1.8

[a] Geometry optimization by MNDO and PM3 gave practically the same results (torsion angles ± 2°; bond angles ± 1°; bond lengths ± 0.02Å).

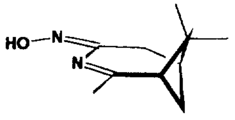
[b] Vicinal couplings H^1-$\alpha,\beta H^2$ and $\alpha,\beta H^6$-H^7 were calculated according to the formula $^3J_{H\text{-}H} = 6.3 + 3.9\times\cos2\varphi$, which had been obtained as a result of the analysis of the vicinal couplings of the cyclopropane protons in a number of known carane derivatives (least square method, s = 0.5, n = 14 in the range 15°<φ<150°).

The reaction takes place only in the presence of aliphatic nitrile. Treatment of the α-hydroxylamino oximes with $NaBH_4$ in the absence of a nitrile resulted in the recovered starting compound or gave a complex mixture of products. The mechanism of the transformation **10→11,12** is not clear yet. O-Acylated derivatives of α-hydroxylamino oximes are known to undergo rearrangement under the action of bases,[18] enamine **13** being the primary rearrangement product in the case of the 3-carene derivative. This enamine is not the intermediate species in the reaction of cyclic amidoxime formation because compound **13** is stable towards $NaBH_4$ and is not reduced to **14** in boiling acetonitrile.

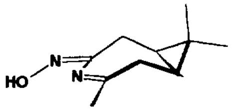


10 **11** **12** **14** **13** **15** **16**

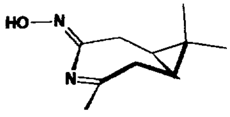
Immonium salt **11** (or the corresponding imine **12**) seems to be the intermediate compound in this reaction. The reduction of **11** (or **12**) with an excess of $NaBH_4$ (the usual reaction of imines and immonium salts) leads to the final product **14**. Just the formation of the single isomer in the reaction of pinane derivative **3** and two C-3 epimers in the case of 3-carene derivatives **5** and **6** lend support to this scheme. We have analyzed the molecular models of pinane-type (**15**) and carane-type (**16**) imines.[19] Pinane-type derivative **15** is conformationally rigid and has a slightly deformed Y-like conformation (**17**)[20] of the heterocycle. Analysis of the van der Waals model shows that the β-side of the double bond is completely blocked by one of the methyls of *gem*-dimethyl fragment and only the α-side of the double bond is accessible for the attack of a reducing agent. Therefore the only isomer **4** is formed in the reaction and appears due to the α-attack of the reducing agent. Carane-type imine **16** is a rather flexible molecule having at least two stable forms **18** and **19**. Both α- and β-sides of the double bond in both forms are accessible for the reagent. Therefore two epimers **7** and **8** are formed in the reaction.



17



18



19

Nevertheless, the above explanation does not preclude the possibility of a single electron transfer process that is discussed in the reaction of O-substituted hydroxylamines with $LiAlH_4$ also leading to the ring expansion.[21]

EXPERIMENTAL

All the solvents used were reagent quality. Diethyl ether was freshly distilled. Removal of all solvents was carried out under reduced pressure and all commercial reagents were used without additional purification. Analytical TLC plates were **Silufol®** (Silpearl on aluminum foil, Czechoslovakia). Preparative column chromatography was performed on SiO_2 ("KSK", Russia, 100-200 mesh, air dried and activated at 140°C for 5h). IR spectra were obtained using a **Specord M-80** infrared spectrophotometer. A **Polamat A** polarimeter was used to measure optical rotation at 578 nm. Melting points were obtained using a **Kofler** melting point apparatus. Mass spectra were obtained on a **Finnigan MAT 8200** instrument using the Electron Impact Ionization technique (100-220°C, 70eV). ^1H and ^{13}C NMR spectra were recorded at room temperature using a **Bruker AM-400** instrument (**^1H** 400.13 MHz, ^{13}C 100.61 MHz) locked to the deuterium resonance of the solvent using standard Bruker NMR Software System. The chemical shifts were calculated relative to the solvent signal ($CDCl_3$) using as the internal standard: δ_H 7.24 ppm and δ_C 76.90 ppm. Carbon-carbon coupling constants $^1J_{C\text{-}C}$ were measured by a standard version of INADEQUATE with adjustment at 40 Hz.

Starting oximes **3, 5** and **6** were synthesized from the corresponding hydrocarbons (α-pinene and (+)-3-carene) *via* crystalline nitrosochlorides and were identical with that published earlier: (±)-(1*S**,2*S**,5*S**)-2-hydroxylaminopinocamphone *E*-oxime (**3**) : m.p.: two points at 111-113°C and 119-121°C (from CH_3CN) (lit.: 149-150°C from EtOAc for the sample with unknown optical purity[9]); (1*S*,3*S*,6*R*)-3-hydroxyamino-4-caranone *E*-oxime (**3**)[20,22.] , (1*S*,3*S*,6*R*)-3-N-acetoxyamino-4-caranone (E)-oxime (**4**)[22]. Samples of the well-known α-hydroxylamino oximes derived from the unsaturated hydrocarbons such as cyclohexene, 1-methylcyclohexene, (2-methylpropene), 2-butene, and β,β-dimethylstyrene were given by Prof. Alexey Ya. Tikhonov (Novosibirsk Institute of Organic Chemistry).

General procedure of the fragmentation. A stirring suspension of an α-hydroxylamino oxime (1 mmol) and sodium borohydride (0.2 g, 6 mmol) in CH_3CN (5 mL) was heated to boiling point and allowed to reflux for a certain period of time (8h for **3**, 9h for **5** and 20 min for **6**). The solvent was removed at reduced pressure and the residue was treated with water (5 mL) followed by addition (dropwise) of 9N aq HCl (4 mL). The resultant mixture was extracted with Et_2O (2×8 mL). The aqueous phase was treated with concentrated aq NH_3 (6 mL, pH 11) and extracted with Et_2O (2×10 mL). The combined ethereal extracts were washed with water (5 mL), brine (5 mL), dried ($MgSO_4$) and concentrated at reduced pressure to give the corresponding amidooxime as viscous yellowish oil (R_f = 0.25, CH_3OH:$CHCl_3$ = 2:8 v/v).

(±)-(1S,6R*)-2,7,7-Trimethyl-3-azabicylco[4.1.1]octan-4-one Z-oxime* (**4**). Yield 65%. M.p. 98.5-100.5° (CH_3CN); IR (*c* 1% in $CHCl_3$): ν_{max} = 3600, 3380, 3200, 1620, 1300, 910 cm^{-1}; MS, *m/z* (%):182.1421 (**M^+**, 100%, calc. for $C_{10}H_{18}H_2O$ 182.1419), 167 (62), 165 (28), 149 (9), 127 (29), 122 (20), 111 (16), 95 (15), 83 (40), 69 (34), 55 (44), 44 (35), 41 (47); ^1H NMR ($CDCl_3$) 1.08 *s* 3H (H^8), 1.21 *d* 3H (H^{10}), 1.24 *s* 3H (H^9), 1.32 *d* ***J*** = 11.8 Hz, 1H (αH^7), 1.93 *dddd* ***J*** = 7.6, 5.3, 4.2 and 2.5 Hz, 1H (H^5), 2.02 *ddd* ***J*** = 8.4, 4.2 and 2.4 Hz, 1H (H^1), 2.41 *ddd* ***J*** = 11.8, 8.4 and 7.6 Hz, 1H (βH^7), 2.57 *dd* ***J*** = 17.1 and 5.3 Hz, 1H (αH^4), 2.70 *dd* ***J*** = 17.1 and 2.5 Hz, 1H (βH^4), 3.63 *qd* ***J*** = 6.9 and 2.4 Hz, 1H (H^2); ^{13}C NMR ($CDCl_3$): 21.59 (C^8), 22.40 (C^{10}), 27.10 (C^7), 30.53 (C^9), 31.29 (C^4), 38.46 (C^5), 38.83 (C^6), 47.40 (C^1), 54.41 (C^2), 155.67 (C^3).

(1S,7R)-3,8,8-Trimethyl-4-azabicylco[5.1.0]octan-5-one Z-oxime (ca. 1:1.3 mixture of C-3 epimers **7** and **8**). The crude amidoxime was chromatographed on a silica gel column (0–10% CH_3OH in $CHCl_3$) to give an

analytical sample. Yield 36% from **3** and 46% from **4**. $[\alpha]_{578}^{22}$ −22.3 (*c* 3.3 in $CHCl_3$); IR (*c* 1% in CCl_4): ν_{max} = 3625, 3220, 1635, 1325, 900 cm^{-1}; IR (*c* 0.01% in CCl_4): ν_{max} = 3620 3425 3380 3220 cm^{-1}; MS, *m/z* (%):182.1417 (M^+, 40%, calc. for $C_{10}H_{18}H_2O$ 182.1419), 167 (11), 165 (56), 149 (8), 125 (7), 122 (12), 112 (19), 108 (12), 100 (51), 95 (18), 83 (100), 81 (44), 79 (21), 69 (32), 67 (38), 55 (44), 53 (33), 44 (100), 41 (93).

(1S,3R,7R)-3,8,8-Trimethyl-4-azabicylco[5.1.0]octan-5-one Z-oxime [major component] (**8**). IR (*c* 0.01% in CCl_4): ν_{max} = 3625, 3380 cm^{-1}; ^1H NMR ($CDCl_3$): 0.71 *ddd* ***J*** = 10.4, 9.2 and 5.9 Hz, 1H (H^1), 0.79 *ddd* ***J*** = 10.1, 9.2 and 5.7 Hz, 1H (H^7), 0.99 *s* 3H (H^9), 1.04 *s* 3H (H^{10}), 1.13 *d* ***J*** = 6.5 Hz, 3H (H^{11}), 1.42 *ddd* ***J*** = 14.9, 5.9 and 2.0 Hz, 1H (βH^2), 1.84 *ddd* ***J*** = 14.9, 11.4, and 10.4 Hz, 1H (αH^2), 2.19 *dd* ***J*** = 15.4 and 10.1 Hz, 1H (βH^6), 2.44 *dd* ***J*** = 15.4 and 5.7 Hz, 1H (αH^6), 3.58 *dqd* (***J*** = 11.4, 6.5 and 2.0 Hz, 1H (H^3); ^{13}C NMR ($CDCl_3$): 14.80 (C^9), 19.31 (C^8), 22.72 (C^7), 24.37 (C^1), 24.78 (C^{11}), 26.85 (C^6), 28.38 (C^{10}), 31.37 (C^2), 50.95 (C^3), 154.83 (C^5).

(1S,3S,7R)-3,8,8-Trimethyl-4-azabicylco[5.1.0]octan-5-one Z-oxime [minor component] (7). IR (*c* 0.01% in CCl_4): ν_{max} = 3625, 3425 cm^{-1}; ^1H NMR ($CDCl_3$): 0.55 *ddd* ***J*** = 9.2, 8.4 and 5.9 Hz, 1H (H^1), 0.87 *ddd* ***J*** = 10.1, 9.2 and 5.7 Hz, 1H (H^7), 0.99 *s* 3H (H^9), 1.00 *s* 3H (H^{10}), 1.15 *d* ***J*** = 6.5 Hz, 3H (H^{11}), 1.69 *ddd* ***J*** = 15.0, 10.8 and 8.4 Hz, 1H (αH^2), 1.78 *ddd* ***J*** = 15.0, 3.6 and 2.5 Hz, 1H (βH^2), 2.08 *dd* ***J*** = 15.4 and 10.1 Hz, 1H (βH^6), 2.44 *dd* ***J*** = 15.4 and 5.7 Hz, 1H (αH^6), 3.21 *dqd* (***J*** = 10.8, 6.5 and 3.6 Hz, 1H (H^3); ^{13}C NMR ($CDCl_3$): 14.89 (C^9), 18.07 (C^8), 20.38 (C^7), 22.09 (C^{11}), 23.10 (C^1), 24.88 (C^6), 28.71 (C^{10}), 32.61 (C^2), 46.29 (C^3), 154.83 (C^5).

(±)-(1S,6R*)-2,7,7-Trimethyl-3-azabicylco[4.1.1]octan-4-one* (**9**). Yield 44%. M.p. 94-96° (from CH_3CN) (lit.[17]: 90-92° from undefined solvent, sample with unknown optical purity). IR (*c* 1% in CCl_4): ν_{max} = 3270, 3200, 1640 cm^{-1}; ^1H NMR ($CDCl_3$:CCl_4 = 1:1) 1.04 ($3H^8$), 1.22 ($3H^{10}$), 1.23 ($3H^9$), 1.34 (H^{7b}), 1.82 (H^5), 2.07 (H^1), 2.44 (H^{7a}), 2.57 (H^{4b}), 2.65 (H^{4a}), 3.65 (H^2), coupling constants: J_{H1-H2} = 2.4 Hz, J_{H1-H5} = 4.2 Hz, J_{H1-H7a} = 8.3 Hz, J_{H2-H10} = 6.9 Hz, $J_{H4a-H4b}$ = 18.9 Hz, J_{H4a-H5} = 2.7 Hz, J_{H4b-H5} = 3.9 Hz, J_{H5-H7a} = 7.8 Hz, $J_{H7a-H7b}$ = 11.7 Hz; ^{13}C NMR ($CDCl_3$) 21.52 (C^8), 21.75 (C^{10}), 27.55 (C^7), 30.46 (C^9), 37.59 (C^5), 37.86 (C^4), 38.70 (C^6), 47.20 (C^1), 53.89 (C^2), 174.91 (C^3).

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