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Synthesis of Nonracemic 2,3,6-Trisubstituted Piperidine Derivatives from Sugar Lactones via Tandem Wittig [2+3] Cycloaddition Reaction. A Novel Entry to Prosopis and Cassia Alkaloids

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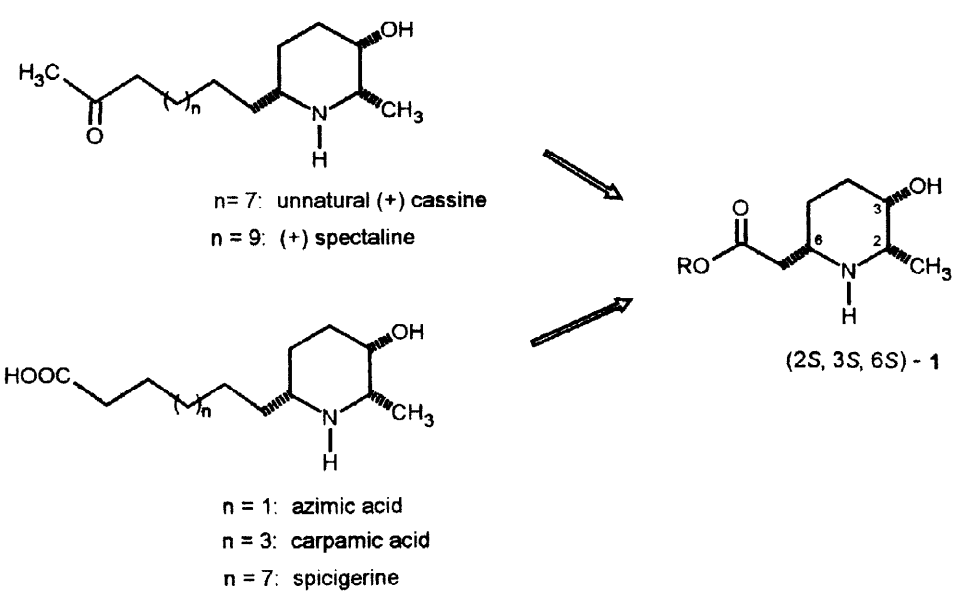
Abstract: Wittig reaction of the azido lactol **7** proceeds with concomitant 1,3-dipolar cycloaddition of the azido function to the α, ß-unsaturated ester function of **9a,b** which can not be isolated. The diastereomeric triazolines **10a,b** and the diazoamines **11a,b** were separated. The vinylogous urethane **13** can be hydrogenated diastereoselectively to the all-cis configurated piperidyl acetic ester derivative **14** which is deprotcted to **1**. Functional group transformations of the side chain is accomplished with the bicyclic urethane **15** which is converted to 3-hydroxydihydropinidine **20**.

2,3,6-Trisubstituted piperidine alkaloids are widely found in nature, e.g. in *Azima*, *Carica*, *Cassia* and *Prosopis* species.[1] Many of them display strong pharmacological activities, especially those from *Microcus philipinensis* and *Prosopis africana*. As a common structure these molecules possess a β-hydroxy piperidine ring with a side chain in position 6 and a methyl or hydroxymethyl group in position 2 of the heterocycle. Some of them like *carpamic acid*, *cassine* or *spectaline* have an **all-cis** configuration and are distinguished in the length and functionality of the side chain in position 6.

Scheme 1



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As we were interested in a general approach to this class of alkaloids we looked for a convergent synthesis of the piperidine ring with the substituents in all cis-configuration and a functionality in position 6 which allows a facile attachment of various side chains. Therefore we chose the chiral nonracemic piperidyl acetic ester *(2S, 3S, 6S)*-**1** as an intermediate, which already contains all stereogenic information for this class of piperidine alkaloids.

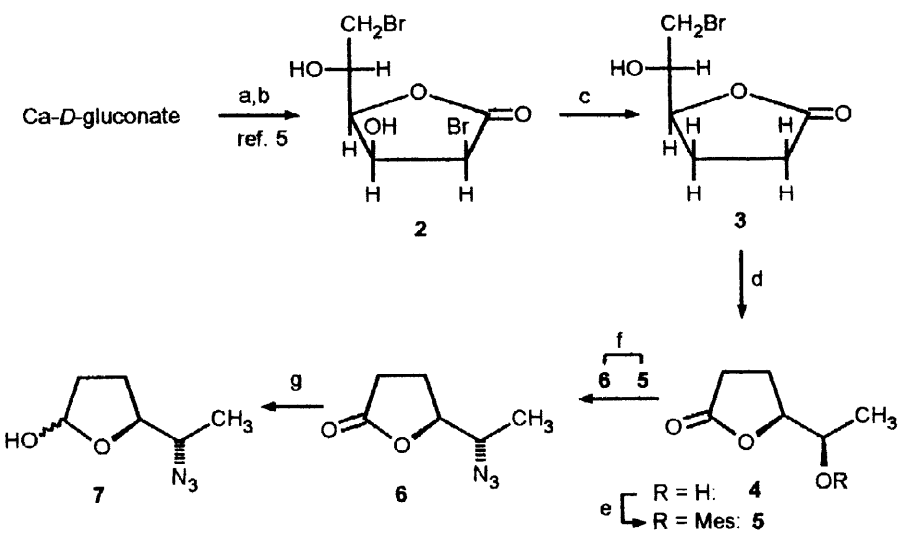
Stereoisomeric pure β-hydroxypiperidyl acetic esters have been described before in literature.[2] These syntheses use mostly biochemical or enzymatic transformations to get the stereogenic information.

Recently we communicated an entry to nonracemic 2-alkyl-5-hydroxy piperidines via a cycloaddition reaction.[3] In this report we use this method for the stereoselective synthesis of *(2S, 3S, 6S)*-**1** based on a ring enlargement reaction via tandem Wittig 1,3-dipolar cycloaddition[4] reaction for the construction of the piperidine ring, followed by a highly diastereoselective hydrogenation reaction.

Following the methodology of our published synthesis of epi-pseudoconhydrine[3] and its homologues in which we described this intramolecular cycloaddition reaction of a azido lactol with a primary azido function, we now communicate this type of reaction with the secondary azido lactol **7** (Scheme 2).

To this end, we started from Ca-*D*-gluconate, which was converted to the stereoisomeric pure lactone **4** in a three step reaction sequence.[5] The hydrogenation has to take place in two steps to get the β-hydroxy function eliminated by hydrobromic acid in a base free medium.

Scheme 2

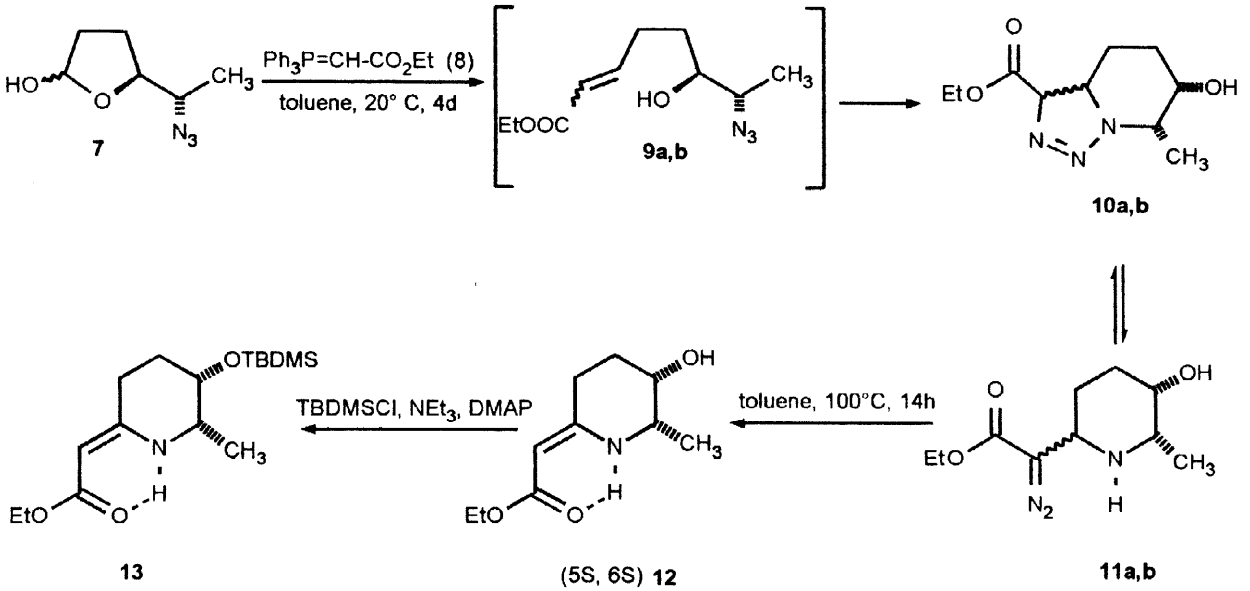


a: HBr, HOAc; **b**: MeOH; **c**: H_2, Pd/C, EtOH; **d**: H_2, Pd/C, NEt_3, EtOAc; **e**: MesCl, NEt_3, CH_2Cl_2, -30 → +20°C; **f**: LiN_3, DMF, 70°C, 18 h; **g**: DiBAl-H, -60°C, THF.

After converting the hydroxy function of **4** to the mesylate **5**, the following nucleophilic substitution with lithium azide provided the azido lactone **6** with excellent diastereoselectivity (> 95 % d.e.).[6] Treatment of **6** with diisobutylaluminum hydride (DiBAl-H) at -50°C produced a diastereomeric mixture of the acetals **7** (Scheme 2).

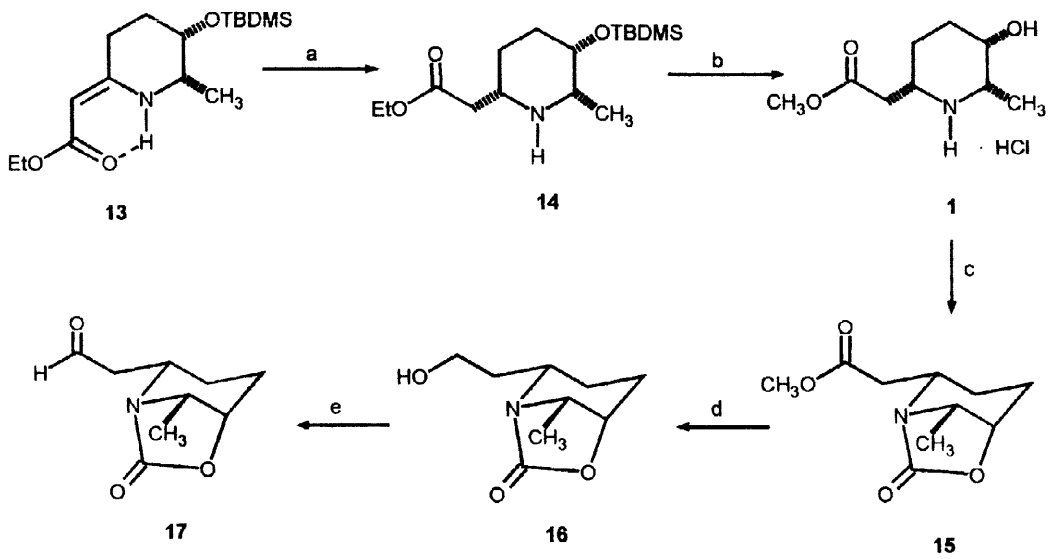
When **7** was treated with ethoxycarbonyl methylene(triphenyl)phosphorane **8** at room temperature a smooth Wittig reaction took place. The obvious intermediate **9** could not be isolated, because an intramolecular 1,3-dipolar cycloaddition followed immediately. This tandem reaction provided the diastereomeric triazolines **10** and the diazoamines **11** in a ratio of about 2 : 1.[7] Triphenylphosphine oxide as the byproduct was separated by column chromatography on silica gel with dichloromethane / methanol 9 : 1. When traces of a base like triethylamine were added, equilibration between **10** and **11** was catalyzed (Scheme 3).

Scheme 3



Contrary to our work on azasugars[7] we found only a low stereoselectivity for position 6 namely *(6'R)*-**11**/*(6'S)*-**11** ≈ 2 : 1. Therefore we used a three step reaction sequence to elaborate the *(6'S)*-stereochemistry selectively. A mixture of the compounds **10** and **11** gave a stereochemically homogeneous product **12**, when they were heated in toluene at 90 - 100 °C. Thereby elimination of nitrogen took place[8] and concomitant 1,2-H shift provided Z configurated olefin[9] as the only product. We anticipated that catalytic hydrogenation of the double bond would occur mainly from the less shielded ß-side of the molecule when a bulky protecting group at the OH-function is present. Treatment with Bu^tMe_2SiCl, imidazole and a catalytic amount of DMAP provided the silyl ether **13** with *syn*-configuration of the two substituents. Hydrogenation of the double bond of the vinylogous urethane **13** with Pd /C occurred exclusively from the less shielded ß-face. A cis configurated compound **14** was isolated as the only product with better than 98% d.e. (Scheme 4).

Scheme 4



a: Pd/C, H_2, EtOH; **b**: MeOH, HCl, 50°C, 2h, **c**: Boc_2O, DABCO, THF; **d**: DiBAl-H, THF; **e**: $(CF_3CO)_2O$, DMSO, CH_2Cl_2,-50°C.

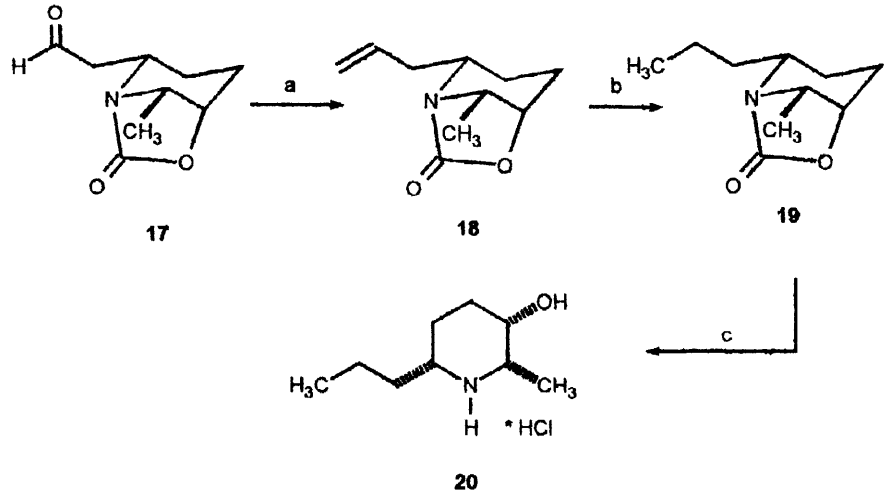
Desilylation of **14** with methanolic hydrochloric acid gave the methyl tert.-butyldimethylsilyl ether as an easily removable byproduct. When the reaction mixture was heated to 50°C complete transesterification took place, so that the desired precursor *(2S, 3S, 6S)*-**1** was isolated in form of its methyl ester hydrochloride.

Wittig reactions are widely used to build up the aliphatic side chain of piperidine alkaloids. Starting from a 6-piperidyl ethanal, the amino and the hydroxy function had to be protected before. To avoid different protecting groups for the O- and N functionality we envisaged a cyclic urethane as the simpliest solution for this problem.

Indeed treatment of **1** with Boc_2O and diazabicyclooctane as a preferred base provided compound **15**, in which both functional groups were protected by a bridged urethane. In a first step either the amino or the hydroxy function of **1** was protected by the butoxycarbonyl group, followed by an intramolecular substitution reaction. With carbonyldiimidazole instead of Boc_2O the same results were obtained.

The ester function of **15** was converted to the desired aldehyde **17** selectively in a modified two step sequence, which we already have used for our pseudoconhydrine synthesis. Reduction of the ester with diisobutylaluminum hydride gave the alcohol **16**, which was oxidised by a Moffat reaction to produce the aldehyde **17**, which is an excellent precursor for *cassia* and *prosopis* alkaloids. For example, elongation of the side chain with methylene(triphenyl)phosphorane led to bicyclic olefin **18**, which was, after hydrogenation, deprotected to 3-hydroxydihydropinidine **20** (Scheme 5).

Scheme 5



a: $Me^{+}PPh_3Br^{-}$, $NaN(SiMe_3)_2$, Et_2O; **b**: Pd/C, H_2, EtOH; **c**: MeOH, HCl.

In summary we described a facile entry to all cis configurated ß-hydroxypiperidine derivatives via tandem Wittig-[2+3] cycloaddition reaction. This approach with its excellent diastereomeric control is currently applied to the synthesis of prosophylline and derivatives thereof.

Experimental

General: Solvents were dried according to common methods and distilled before use. TLC: Merck precoated silica gel 60 F-254 plates; detection with iodine vapour or UV light. Column chromatography: silica gel Merck 60 (0.063 - 0.2 mm). M.p. are uncorrected. Optical rotations: Perkin Elmer 241 spectrometer. IR spectra (KBr): Perkin Elmer 681. Mass spectra: Finnigan 8200 spectrometer. ^1H, ^{13}C NMR spectra: Bruker AC 200 and AC 600 spectrometer; chemical shifts in ppm relative to solvent as internal standard, coupling constants in Hz.

(3*S*, 4*S*, 5*R*, 1′*S*)-3-Bromo-5-(2′-bromo-1′-hydroxy)ethyl-4,5-dihydro-4-hydroxy-2-(3H)-furanone (2)

1 was prepared from Ca-*D*-gluconate according to procedure of ref.[5]. Yield: 11.4 g (42 %), colourless crystals, m.p.: 131°C; (ref.[5]: 38-44 %, 130-132°C).- ^1H NMR (CD_3OD, 200 MHz): δ (ppm) = 5.31 (d, $J_{3,4}$ = 4.4 Hz, 1 H, 3-H), 4.92 (br, 2 H, OH), 4.73 (dd, $J_{3,4}$ = 4.4 Hz, $J_{4,5}$ = 2.9 Hz, 1 H, 4-H), 4.61 (dd, $J_{5,1'}$ = 8.9 Hz, $J_{4,5}$ = 2.9 Hz, 1 H, 5-H), 4.39 - 4.28 (m , 1 H, 1′-H), 3.92 (dd, $J_{2'a,2'b}$ = 11.0 Hz, $J_{1',2'a}$ = 2.7 Hz, 1 H, 2′-H_a), 3.77 (dd, $J_{2'a,2'b}$ = 11.0 Hz, $J_{1',2'b}$ = 5.4 Hz, 1 H, 2′-H_b), (ref.[5]: 5.22 (d, $J_{3,4}$ = 4.4 Hz, 1 H, 3-H), 4.67 (dd, $J_{3,4}$ = 4.4 Hz, $J_{4,5}$ = 3.2

Hz, 1 H, 4-H), 4.64 (dd, $J_{5,1'}$ = 8.5 Hz, $J_{4,5}$ = 3.2 Hz, 1 H, 5-H), 4.26 (m, 1 H, 1′-H), 3.80 (dd, $J_{2'a,2'b}$ = 11.6 Hz, $J_{1',2'a}$ = 2.6 Hz, 1 H, 2′-H_a), 3.60 (dd, $J_{2'a,2'b}$ = 11.6 Hz, $J_{1',2'b}$ = 5.0 Hz, 1 H, 2′-H_b)).- ^{13}C NMR (CD_3OD, 50.3 MHz): δ (ppm) = 173.7 (s, C-2), 83.6 (d, C-5), 71.3 (d, C-4), 68.9 (d, C-1′), 49.2 (d, C-3), 38.4 (t, C-2′).- IR (KBr): ν (cm^{-1}) = 3550 - 3240 (O-H), 2940 (C-H), 1780 (C=O), 1170 (C-O).- $[\alpha]_D^{20}$ = +51.8 (c = 0.7, EtOAc), (ref.[5]: +52.2, (c = 0.7, EtOAc)).- $C_6H_8O_4Br_2$, (303.93): calcd. C 23.71, H 2.65, found C 23.79, H 2.42.

(5*S*, 1′*S*)-5-(2′-Bromo-1′-hydroxy)ethyl-4,5-dihydro-2-(3H)-furanone (3)

Prepared from **2** according to procedure of ref.[5]. Yield: 7.42 g (71 %), colourless crystals, m.p.: 73°C, (ref.[5]: 71 %, 76-77°C).- ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) = 4.57 (q, $J_{5,1'}$ = $J_{1',2'}$ = 6.9 Hz, 1 H, 1′-H), 4.01 - 3.92 (m, 1 H, 5-H), 3.63 - 3.58 (m, 3 H, 2-$H_{a,b}$, OH), 2.59 - 2.46 (m, 2 H, 3-$H_{a,b}$), 2.31 - 2.17 (m, 2 H, 4-$H_{a,b}$).- ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ (ppm) = 177.6 (s, C-2), 80.2 (d, C-5), 71.5 (d, C-1′), 34.2 (t, C-2′), 28.2 (t, C-3), 22.4 (t, C-4), (ref.[5]: 177.4 (C-2), 80.1 (C-5), 71, 4 (C-1′), 34.2 (C-2′), 28.0, 22.3 (C-3,4)). - IR (KBr): ν (cm^{-1}) = 3550 - 3240 (O-H), 2960 (C-H), 1760 (C=O), 1185 (C-O).- $[\alpha]_D^{20}$ = +19.6 (c = 4.3, $CHCl_3$), (ref.[5]: +20.3, (c = 5, $CHCl_3$)).- $C_6H_9O_3Br$, (209.03): calcd. C 34.48, H 4.34, found C 34.27, H 4.20.

(5*S*, 1′*R*)-4,5-Dihydro-5-(1′-hydroxy)ethyl-2-(3H)-furanone (4)

Prepared from **3** according to procedure of ref.[5]. Distillation over 10 cm Vigreux gave pure **4**. Yield: 3.59 g (78 %), colourless oil, R_f = 0.20 (Et_2O), b.p.: 132-135°C / 5 mbar, (ref.[5]: 77 %, 110-115°C / 0.3 Torr).- ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) = 4.33 - 4.25 (m, 1 H, 1′-H), 4.02 - 3.85 (m, 1 H, 5-H), 3.03 - 2.62 (br, 1 H, OH), 2.49 - 2.29 (m, 2 H, 3-$H_{a,b}$), 2.17 - 2.02 (m, 2 H, 4-$H_{a,b}$), 1.09 (d, $J_{1',2'}$ = 6.5 Hz, 3 H, 2′-H).- ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ (ppm) = 177.9 (s, C-2), 83.7 (d, C-5), 67.1 (d, C-1′), 28.4 (t, C-3), 20.9 (t, C-4), 17.7 (q, C-2′), (ref.[5]: 178.1 (C-2), 87.3 (C-5), 67.3 (C-1′), 28.3, 20.9 (C-3,4), 17.7 (C-2′)).- IR (neat): ν (cm^{-1}) = 3550 - 3240 (O-H), 2980, 2930 (C-H), 1765 (C=O), 1190 (C-O).- $[\alpha]_D^{20}$ = +9.3 (c = 3.7, $CHCl_3$), (ref.[5]: +9.1, (c = 4, $CHCl_3$)).- $C_6H_{10}O_3$, (130.14): calcd. C 55.37, H 7.74, found C 55.23, H 7.49.

(5*S*, 1′*R*)-4,5-Dihydro-5-(1′-mesyloxy)ethyl-2-(3H)-furanone (5)

To a solution of **4** (3.34 g, 25.6 mmol) in dichloromethane (120 ml) dry triethylamine (4.0 ml, 28.0 mmol) was added at -40°C. After 5 min freshly distilled methanesulfonyl chloride (2.1 ml, 26.8 mmol) was added dropwise at this temperature. Stirring was continued for 15 min below -30°C. Then the reaction mixture was allowed to reach room temperature and was stirred for another 2 h. A saturated solution of ammonium chloride (50 ml) and 0.5 M hydrochloric acid (100ml) were added. The organic layer was separated, the aqueous was extracted with dichloromethane (100ml) twice. The combined organic layers were washed with a saturated solution of sodium chloride (100 ml), dried with sodium sulfate and evaporated. The residue was recrystallised from dichloromethane / petroleum ether (30-50°C). Yield: 5.24 g (98 %), colourless crystals, m.p.: 72°C.- ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) = 4.73 (qd, $J_{1',2'}$ = 6.6 Hz, $J_{5,1'}$ = 3.0 Hz, 1 H, 1′-H), 4.39 (td, $J_{4a,5}$ = $J_{4b,5}$ = 7.0 Hz,

$J_{5,1'}$ = 3.0 Hz, 1 H, 5-H), 2.83 (s, 3 H, C*H*$_3$-SO_2-), 2.40 - 1.93 (m, 4 H, 3-$H_{a,b}$, 4-$H_{a,b}$), 1.21 (d, $J_{1',2'}$ = 6.6 Hz, 3 H, 2'-H).- ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ (ppm) = 175.9 (s, C-2), 79.6 (d, C-5), 78.0 (d, C-1'), 37.7 (q, CH_3-SO_2-), 27.3 (t, C-3), 20.9 (t, C-4), 15.8 (q, C-2').- IR (KBr): ν (cm^{-1}) = 3020, 2980, 2930 (C-H), 1775 (C=O), 1350 (S=O), 1170.- $[\alpha]_D^{20}$ = -5.6 (c = 1.5, $CHCl_3$). - $C_7H_{12}O_5S$, (208.22): calcd. C 40.38, H 5.80, S 15.40, found C 40.37, H 5.49, S 15.55.

(5*S*,1'*S*)-5-(1'-Azido)ethyl-4,5-dihydro-2-(3H)-furanone (6)

To a solution of **5** (4.16 g, 20.0 mmol) in DMF (80 ml) lithium azide (985 mg, 20.1 mmol) was added. The mixture was heated with stirring to 60°C for 18 h. After evaporation of the solvent in vacuo the residue was dissolved in water 150 ml and extracted with diethyl ether (3 x 150 ml). The combined organic layers were dried with sodium sulfate. The solvent was evaporated, and the residue was purified by column chromatography on silica gel with ethyl acetate. Yield: 2.39 g (77 %), pale yellow oil, R_f = 0.64 (EtOAc).- ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) = 4.29 (td, $J_{4a,5}$ = $J_{4b,5}$ = 7.2 Hz, $J_{5,1'}$ = 4.9 Hz, 1 H, 5-H), 3.46 (qd, $J_{1',2'}$ = 6.7 Hz, $J_{5,1'}$ = 4.9 Hz, 1 H, 1'-H), 2.48 - 1.84 (m, 4 H, 3-$H_{a,b}$, 4-$H_{a,b}$), 1.19 (d, $J_{1',2'}$ = 6.7 Hz, 3 H, 2'-H).- ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ (ppm) = 176.1 (s, C-2), 81.6 (d, C-5), 59.4 (d, C-1'), 27.7 (t, C-3), 24.0 (t, C-4), 14.7 (q, C-2').- IR (KBr): ν (cm^{-1}) = 2985, 2940 (C-H), 2110 (-N_3), 1780 (C=O), 1455, 1180.- $[\alpha]_D^{20}$ = +97.0 (c = 5.6, $CHCl_3$).- $C_7H_9O_2N_3$, (155.16): calcd. C 46.45, H 5.84, N 27.08, found C 46.82, H 6.33, N 24.75.

(5*S*,1'*S*)-5-(1'-Azido)ethyl-2,4-tetrahydro-2-hydroxyfuran (7a, b)

To a solution of **6** (2.23 g, 14.36 mmol) in THF (10 ml) diisobutylaluminum hydride (14.3 ml, 1 M solution in hexane) was added slowly at -78°C. The mixture was stirred for 45 min. An additional portion of the DiBAl-H solution (5.7 ml) was added and the mixture was stirred for at least 6 h at -60°C. Then it was cooled to -78°C and quenched by the addition of water (20 ml) with vigorous stirring. The mixture was allowed to reach room temperature and 1 M hydrochloric acid (100 ml) and dichloromethane (600 ml) were added. The organic layer was separated, dried with sodium sulfate, filtered and evaporated. The residue was purified by column chromatography on silica gel with ethyl acetate. Yield: 1.83 g (81 %), pale oil, R_f = 0.55 (EtOAc) for both epimers.- ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) = 5.55 / 5.46 (m, 1 H, 2-H), 4.33 - 3.20 (m, 3 H, OH, 5-H, 1'-H), 2.17 - 1.40 (m, 4 H, 3-H, 4-H), 1.17 / 1.14 (d, $J_{1',2'}$ = 6.7 Hz, 3 H, 2'-H).- ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ (ppm) = 98.3 / 98.7* (d, C-2), 83.5 / 80.9 (d, C-5), 60.1 / 62.1 (d, C-1'), 33.5 / 32.6 (t, C-3), 26.5 / 26.2 (t, C-4), 15.9 / 15.7 (q, C-2').- MS (70 eV, EI): *m/z* (%): 157.1 (0.1) [M^+], 87.1 (100) [M^+-$C_2H_4N_3$], 69.1 (50.0), 57.1 (15.8), 43.0 (31.5), 41.0 (49.0).- IR (KBr): ν (cm^{-1}) = 3550 - 3240 (O-H), 2980, 2920, 2870 (C-H), 2100 (-N_3), 1455, 1250, 1060.- $C_7H_{11}O_2N_3$, (157.16): calcd. C 45.85, H 7.05, N 26.74, found C 44.72, H 7.02, N 22.91.

* ratio of epimers: 1.2 : 1

Ethyl (2*S*, 3*S*)-3-Hydroxy-2-methyl-1,8,9-triazabicyclo[3.4.0]non-8-ene-7-Carboxylate (10a,b) and Ethyl (2′*S*, 3′*S*)-2-Diazo-6′(3′-hydroxy-2′-methyl)piperidyl Acetate (11a,b)

To a solution of **7a,b** (1.27 g, 8.08 mmol) in toluene (10 ml) triphenylcarbethoxymethylene phosphorane **8** (2.81 g, 8.08 mmol) was added. The mixture was stirred for 5 d at room temperature. The solvent was evaporated below + 30°C and the residue was purified from Ph_3PO by column chromatography on silica gel with dichloromethane / methanol 9 : 1. Two fractions were isolated. Total yield: 1.59 g (89 %), which contained 973 mg of the triazolines **10a,b** (53 %), colourless oil, R_f = 0.43 - 0.32 (CH_2Cl_2 / MeOH 9 : 1) and 624 mg of the diazoamines **11a,b** (34 %), yellow oil, R_f = 0.18 - 0.12 (CH_2Cl_2 / MeOH 9 : 1).- spectroscopic data of **10a,b**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) = 4.54 - 4.40 (m 1 H, 7-H), 4.15 (q, J_{vic} = 7.1 Hz, 2 H, CH_3-CH_2-), 3.70 (br, 1 H , OH), 3.58 - 3.23 (m, 3 H, 2,3,6-H), 1.98 - 1.55 (m, 4 H, 4,5-H), 1.53 (d, $J_{Me,2}$ = 6.7 Hz, 3 H, CH_3-), 1.24 (t, J_{vic} = 7.1 Hz, 3 H, CH_3-CH_2-).- ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ (ppm) = 168.4 / 168.1 (s, C=O), 81.4 / 81.1 (d, C-7), 68.1 / 68.6 (d, C-3), 61.6 / 61.2 (t, CH_3-CH_2-), 59.2 / 55.3 (d, C-6), 57.9 / 52.7 (d, C-2), 30.7 / 27.7 (t, C-4), 22.7 / 26.2 (t, C-5), 15.0 (q, CH_3-), 13.9 (q, CH_3-CH_2-).- spectroscopic data of **11a,b**: ^{1}H-NMR ($CDCl_3$, 200 MHz): δ (ppm) = 4.50 - 3.35 (m, 2 H, 3′,6′-H), 4.14 / 3.97 (q, J_{vic} = 7.1 Hz, 2 H, CH_3-CH_2-), 2.94 - 2.50 (m, 3 H, 2′-H, NH, OH), 2.25 - 1.30 (m, 4 H, 4′,5′-H), 1.19 / 1.21 (t, J_{vic} = 7.1 Hz, 3 H, CH_3-CH_2-), 1.03 / 1.01 (d, $J_{Me,2'}$ = 6.5 Hz, 3 H, CH_3-).- ^{13}C-NMR ($CDCl_3$, 50.3 MHz): δ (ppm) = 166.3 (s, C-1), 66.8 / 66.3 (d, C-3′), 60.7 / 61.6 (t, CH_3-CH_2-), 55.6 / 58.1 (d, C-6′), 51.0 / 50.7 (d, C-2′), 31.5 / 30.8 (t, C-5′), 23.1 / 22.7 (t, C-4′), 18.2 / 17.4 (q, CH_3-), 14.3 / 14.0 (q, CH_3-CH_2-).- IR (neat): ν (cm^{-1}) = 3520 - 3240 (O-H), 2980, 2930 (C-H), 2090 (C=N_2), 1735 (C=O).- $C_{10}H_{17}N_3O_3$, (227.25).

Ethyl (2*S*, 3*S*)-6-(3-Hydroxy-2-methyl)piperidylidene Carboxylate (12)

A mixture (1.45 g (6.38 mmol) of the triazolines **10a,b** and the diazoamines **11a,b** in toluene (20 ml) was heated for 14 h to 90-100°C. The solvent was evaporated, the brown residue was purified by column chromatography on silica gel with ethyl acetate. Yield: 863 mg (68 %), yellow oil, R_f = 0.57 (EtOAc).- ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) = 8.34 (br, 1 H, 1-H), 4.34 (s, 1 H, C*H*-CO_2Et), 3.98 (q, J_{vic} = 7.1 Hz, 2 H, CH_3-CH_2-), 3.85 - 3.83 (m, 1 H, 3-H), 3.39 - 3.32 (m, 1 H, 2-H), 2.74 (br, 1 H, OH), 2.61 - 2.44 (m, 1 H, 5-H_a), 2.17 (dt, $J_{5a,5b}$ = 16.8 Hz, $J_{4a,5b}$ = $J_{4b,5b}$ = 5.7 Hz, 1 H, 5-H_b), 1.83 - 1.73 (m, 2 H, 4-$H_{a,b}$), 1.19 (d, $J_{2,Me}$ = 6.9 Hz, 3 H, -CH_3), 1.15 (t, J_{vic} = 7.1 Hz, 3 H, CH_3-CH_2-).- ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ (ppm) = 170.5 (s, C=O), 161.8 (s, C-6), 80.5 (d, CH-CO_2Et), 66.5 (d, C-3), 58.2 (t, CH_3-CH_2-), 50.7 (d, C-2), 27.2 (t, C-5), 23.9 (t, C-4), 17.3 (q, CH_3-), 14.4 (q, CH_3-CH_2-).- IR (neat): ν (cm^{-1}) = 3550 - 3220 (O-H, N-H), 2980, 2930, 2895 (C-H), 1635 (C=O), 1595 (C=C), 1505, 1245.- $[\alpha]_D^{20}$ = -31.1 (c = 1.0, $CHCl_3$). - $C_{10}H_{17}NO_3$, (199.24): calcd. C 60.28, H 8.59, N 7.03, found C 59.93, H 8.68, N 6.79.

Ethyl (2*S*, 3*S*)-6-(3-*tert.*-Butyldimethylsilyloxy-2-methyl)piperidylidene Carboxylate (13)

To a solution of **12** (1.63 g, 8.19 mmol) in DMF (20 ml) imidazole (1.61 g, 23.65 mmol), 4-dimethylaminopyridine (1.12 g, 9.17 mmol) and *tert.*-butyldimethylsilyl chloride (1.38 g, 9.17 mmol) were added. The mixture was stirred at room temperature for at least 4 d. The reaction was monitored by thin layer chromatography. The solvent was evaporated, the residue was dissolved in water (100 ml) and extracted with ether (3 x 100 ml). The combined organic layers were dried with sodium sulfate and the solvent was evaporated. The residue was purified by column chromatography on silica gel with ether. About 10 % starting material was recovered. Yield: 1.95 g (76 %), pale yellow crystals, R_f = 0.80 (Et_2O), m.p.: 42°C.- ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) = 8.52 (br, 1 H, 1-H), 4.35 (s, 1 H, C*H*-CO_2Et), 4.05 (q, J_{vic} = 7.1 Hz, 2 H, CH_3-C*H*$_2$-), 3.89 - 3.83 (m, 1 H, 3-H), 3.39 (qdd, $J_{2,Me}$ = 6.7 Hz, $J_{2,3}$ = 3.2 Hz, J = 1.2 Hz), 1 H, 2-H), 2.69 - 2.52 (m, 1 H, 5-H_a), 2.14 (dt, $J_{5a,5b}$ = 16.7 Hz, $J_{4a,5b}$ = $J_{4b,5b}$ = 4.9 Hz, 1 H, 5-H_b), 1.85 - 1.65 (m, 2 H, 4-$H_{a,b}$), 1.22 (t, J_{vic} = 7.1 Hz, 3 H, C*H*$_3$-CH_2-), 1.16 (d, $J_{2,Me}$ = 6.7 Hz, 3 H, -C*H*$_3$), 0.87 (s, 9 H, (C*H*$_3$)$_3$CSi-), 0.04 (s, (C*H*$_3$)$_2$Si-).- ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ (ppm) = 170.7 (s, C=O), 161.9 (s, C-6), 79.6 (d, *C*H-CO_2Et), 67.3 (d, C-3), 58.1 (t, CH_3-*C*H_2-), 51.6 (d, C-2), 27.6 (t, C-5), 25.8 (q, 3 C, (*C*H_3)$_3$CSi-), 24.2 (t, C-4), 18.2 (q, *C*H_3-), 18.1 (s, (*C*H_3)$_3$*C*Si-), 14.7 (q, *C*H_3-CH_2-), -4.6 (q, (*C*H_3)$_2$Si-), -4.9 (q, (*C*H_3)$_2$Si-).- IR (KBr): ν (cm^{-1}) = 3280 (N-H), 2960, 2930, 2895, 2860 (C-H), 1645 (C=O), 1605 (C=C), 1245, 1090.- $[\alpha]_D^{20}$ = -12.5 (c = 1.2, $CHCl_3$).- $C_{16}H_{31}NO_3Si$, (313.50): calcd. C 61.30, H 9.96, N 4.47, found C 61.03, H 10.10, N 4.39.

Ethyl (2′*S*, 3′*S*, 6′*S*)-6′-(3′-*tert.*-Butyldimethylsilyloxy-2′-methyl)piperidyl Acetate (14)

A solution of **13** (1.41 g, 4.50 mmol) in ethanol (50 ml) was hydrogenated with 100 mg Pd / C under 60 atm pressure for 36 h at 40°C. The catalyst was separated by filtration and the filtrate was evaporated. The residue was recrystallised from ethanol with ether and pentane. Yield: 1.42 g (99 %), colourless crystals, m.p.: 193-195°C (decomposition).- ^{1}H NMR (CD_3OD, 200 MHz): δ (ppm) = 4.35 (q, J_{vic} = 7.1 Hz, 2 H, CH_3-C*H*$_2$-), 3.97 - 3.94 (m, 1 H, 3′-H), 3.40 - 3.25 (m, 1 H, 6′-H), 3.12 (qd, $J_{2',Me}$ = 6.6 Hz, $J_{2',3'}$ = 1.4 Hz, 1 H, 2′-H), 2.76 - 2.71 (m, 2 H, 2-H), 2.08 - 1.72 (m, 4 H, 4′,5′-H), 1.44 (t, J_{vic} = 7.1 Hz, 3 H, C*H*$_3$-CH_2-), 1.32 (d, $J_{2',Me}$ = 6.6 Hz, 3 H, -C*H*$_3$), 1.13 (s, 9 H, (C*H*$_3$)$_3$CSi-), 0.29 (s, (C*H*$_3$)$_2$Si-).- ^{13}C NMR (CD_3OD, 50.3 MHz): δ (ppm) = 172.7 (s, C=O), 68.7 (d, C-3′), 61.8 (t, CH_3-*C*H_2-), 57.0 (d, C-2′), 54.6 (d, C-6′), 40.4 (t, C-2), 32.6 (t, C-5′), 26.4 (q, 3 C, (*C*H_3)$_3$CSi-), 25.2 (t, C-4′), 19.0 (s, (*C*H_3)$_3$*C*Si-), 18.5 (q, *C*H_3-), 14.6 (q, *C*H_3-CH_2-), -4.4 (q, (*C*H_3)$_2$Si-), -4.7 (q, (*C*H_3)$_2$Si-).- IR (KBr): ν (cm^{-1}) = 3450 - 3340 (N-H), 2950, 2920, 2850 (C-H), 1735 (C=O), 1460, 1245, 1030.- $[\alpha]_D^{20}$ = +5.2 (c = 1.1, EtOH).- $C_{16}H_{33}NO_3Si$ (315.51).- A sample of **14** was stirred with 1.0 eq. of 1.2 M ethanolic hydrochloric acid to provide the corresponding hydrochloride for elemental analysis. $C_{16}H_{34}NO_3ClSi$, (351.97): calcd. C 54.59, H 9.73, N 3.98, found C 54.03, H 9.22, N 4.09.

Methyl (2′*S*, 3′*S*, 6′*S*)-2′-(3′-Hydroxy-2′-methyl)piperidyl Acetate Hydrochloride (1)

A solution of **14** (840 mg, 2.66 mmol) in methanolic hydrogen chloride was heated at 65°C for 1 h under reflux. The solvent was evaporated, the brown residue was taken up in methanol and stirred with a small amount of charcoal for 30 min at room temperature. After filtration and evaporation of the solvent the residue was recrystallised from methanol with dichloromethane. Yield: 520 mg (87 %), pale crystals, m.p.: 206°C.- ^{1}H NMR (CD_3OD, 200 MHz): δ (ppm) = 3.91 - 3.86 (m, 1 H, 3′-H), 3.75 (s, 3 H, CH_3O-), 3.64 - 3.48 (m, 1 H, 6′-H), 3.41 - 3.30 (m, 1 H, 2′-H), 2.85 (dd, $J_{2a,2b}$ = 16.7 Hz, $J_{2a,6'}$ = 5.4 Hz, 1 H, 2-H_a), 2.70 (dd, $J_{2a,2b}$ = 16.7 Hz, $J_{2b,6'}$ = 7.6 Hz, 1 H, 2-H_b), 2.03 - 1.77 (m, 4 H, 4′,5′-$H_{a,b}$), 1.36 (d, $J_{2',Me}$ = 6.6 Hz, 3 H, -CH_3).- ^{13}C NMR (CD_3OD, 50.3 MHz): δ (ppm) = 171.7 (s, C=O), 65.5 (d, C-3′), 57.9 (d, C-6′), 55.0 (d, C-2′), 52.7 (q, CH_3O-), 38.2 (t, C-2), 30.8 (t, C-4′), 23.6 (t, C-5′), 16.0 (q, CH_3-).- IR (KBr): ν (cm^{-1}) = 3430 - 3280 (O-H), 2950, 2910 (C-H), 2820 (NH_2^+), 1730 (C=O), 1215, 1000.- $[\alpha]_D^{20}$ = +6.3 (c = 0.6, EtOH).- $C_9H_{18}NO_3Cl$, (223.69): calcd. C 48.33, H 8.11, N 6.26, found C 48.47, H 7.96, N 6.29.

Methyl (2′*S*, 5′*S*, 8′*S*)-2′(8′-methyl-6′-oxa-7′-1′-azabicyclo[3.2.1]octanoyl) Acetate (15)

To a suspension of powdered **1** (630 mg, 2.82 mmol) in THF (40 ml) DABCO (1.10 g, 9.87 mmol) was added. The mixture was stirred for several hours, until it became a clear solution with a fine colourless precipitate of insoluble ammonium salts. Di-*tert.*-butyl-dicarbonate (1.84 g, 8.46 mmol) was added and slight gas evolution started immediately and went on for several hours. The mixture was allowed to stir for 14 h, then a 2 M solution of sodium chloride (50 ml) was added. The mixture was extracted twice with ether (100 ml) and the combined organic layers were dried with sodium sulfate. The solvent was evaporated, the residue was purified by column chromatography on silica gel with ether. Yield: 409 mg (68 %), colourless crystals, R_f = 0.40 (ether), m.p.: 87 - 88°C.- ^{1}H NMR ($CDCl_3$, 200 and 250 MHz): δ (ppm) = 4.39 (d, $J_{5',4'a}$ = 4.1 Hz, 1 H, 5′-H), 3.65 (s, 3 H, CH_3O-), 3.63 - 3.49 (m, 1 H, 2′-H), 3.14 (q, $J_{8',Me}$ = 6.7 Hz, 1 H, 8′-H), 2.85 (dd, $J_{2a,2b}$ = 16.3 Hz, $J_{2a,2'}$ = 7.0 Hz, 1 H, 2-H_a), 2.38 (dd, $J_{2a,2b}$ = 16.3 Hz, $J_{2b,2'}$ = 7.1 Hz, 1 H, 2-H_b), 2.10 - 1.41 (m, 4 H, 3′,4′-$H_{a,b}$), 1.14 (d, $J_{8',Me}$ = 6.7 Hz, 3 H, CH_3-). - ^{13}C NMR ($CDCl_3$, 50.3 und 62.9 MHz): δ (ppm) = 171.4 (s, C-1), 165.7 (s, C-7′), 80.5 (d, C-5′), 64.0 (d, C-8′), 58.7 (d, C-2′), 51.7 (q, CH_3O-), 38.8 (t, C-2), 27.6 (t, C-3′), 25.2 (t, C-4′), 17.5 (q, CH_3-).- MS (70 eV, EI): *m/z* (%) = 213.2 (12.1) [M^+], 182.1 (17.5) [M^+-OCH_3], 169.2 (47.1) [M^+-CO_2], 154.1 (46.0) [M^+-$C_2H_3O_2$], 128.1 (33.7), 110.2 (51.1), 96.2 (79.4), 95.2 (36.9), 86.1 (35.0), 69.1 (80.6), 68.1 (62.6), 55.1 (50.3), 41.0 (100).- IR (KBr): ν (cm^{-1}) = 3020, 2940, 2860 (C-H), 1765, 1735 (C=O), 1435, 1360, 1195.- $[\alpha]_D^{20}$ = + 81.8 (c = 0.7, $CHCl_3$).- $C_{10}H_{15}NO_4$, (213.23): calcd. C 56.33, H 7.09, N 6.57, found C 56.15, H 7.22, N 6.37.

(2*S*, 5*S*, 8*S*)- 2 (2′-Hydroxyethyl)-8-methyl-6-oxa-1-azabicyclo[3.2.1]octan-7-one (16)

To a solution (-30°C) of **15** 244 mg (1.14 mmol) in THF (10 ml) diisobutylaluminum hydride (3.4 ml, 1 M solution in hexane) was added carefully. After 20 min an additional amount of 0.6 ml DiBAL-H solution was

added and the mixture was allowed to stir for 4 h at -20°C. Remaining hydride was quenched by the addition of a saturated solution of ammonium chloride (10 ml). The mixture was allowed to reach room temperature and 0.5 M hydrochloric acid (20 ml) and dichloromethane (200 ml) were added. The organic layer was separated and dried with sodium sulfate. After evaporation of the solvent the residue was purified by column chromatography on silica gel with ethyl acetate. Yield: 110 mg (52 %), colourless crystals, R_f = 0.32 (EtOAc), m.p.: 33-34°C.- ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) = 4.41 (d, $J_{5,4a}$ = 4.0 Hz, 1 H, 5-H), 3.93 - 3.72 (m, 2 H, 2′-$H_{a,b}$), 3.38 - 3.23 (m, 1 H, 2-H), 3.14 (q, $J_{8,Me}$ = 6.7 Hz, 1 H, 8-H), 2.64 (br, 1 H, OH), 2.14 - 1.88 (m, 2 H, 1′-$H_{a,b}$), 1.84 - 1.40 (m, 4 H, 3,4-$H_{a,b}$), 1.19 (d, $J_{8,Me}$ = 6.7 Hz, 3 H, CH_3-).- ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ (ppm) = 165.5 (s, C-7), 80.7 (d, C-5), 63.9 (d, C-8), 61.3 (d, C-2), 60.3 (t, C-2′), 35.6 (t, C-1′), 27.8 (t, C-3′), 25.9 (t, C-4′), 17.5 (q, CH_3-).- IR (KBr): ν (cm^{-1}) = 3550 - 3280 (O-H), 2930, 2860 (C-H), 1760 (C=O), 1445, 1095.- $[\alpha]_D^{20}$ = + 109.8 (c = 0.4, $CHCl_3$).- $C_9H_{15}NO_3$, (185.21): calcd. C 58.36, H 8.16, N 7.56, found C 57.97, H 8.24, N 7.11.

(2′*S*, 5′*S*, 8′*S*)-2′(8′-methyl-6′-oxa-1′-azabicyclo[3.2.1]octan-7′-oyl)ethanal (17)

To a solution (-50°C) of trifluoroacetic anhydride (120 mg, 0.57 mmol) in dichloromethane (4 ml) a solution of dry dimethyl sulfoxide (0.63 mmol) in dichloromethane (2 ml) was added within 2 min. The mixture was stirred for 5 min at -50°C, then a solution of **16** (85 mg, 0.46 mmol) was added. The mixture was stirred for another 30 min at -50°C and dry triethylamine (1 ml) was added. The reaction mixture was allowed to reach room temperature within 30 min and was washed with water (30 ml). The organic layer was separated, the aqueous one was extracted with dichloromethane (40 ml). The combined organic layers were dried with sodium sulfate. The solvent was evaporated and the residue was purified by column chromatography on silica gel with ethyl acetate. Yield: 49 mg (59 %), colourless crystals, R_f = 0.48 (EtOAc), m.p.: 36-38°C.- ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) = 9.82 (s, 1 H, 1-H), 4.43 (d, $J_{5',4'a}$ = 4.1 Hz, 1 H, 5′-H), 3.73 - 3.58 (m, 1 H, 2′-H), 3.18 (q, $J_{8',Me}$ = 6.7 Hz, 1 H, 8′-H), 3.09 (dd, $J_{2a,2b}$ = 17.8 Hz, $J_{2a,2'}$ = 7.3 Hz, 1 H, 2-H_a), 2.51 (dd, $J_{2a,2b}$ = 17.8 Hz, $J_{2b,2'}$ = 6.5 Hz, 1 H, 2-H_b), 2.16 - 1.36 (m, 4 H, 3′,4′-$H_{a,b}$), 1.20 (d, $J_{8',Me}$ = 6.7 Hz, 3 H, CH_3-).- ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ (ppm) = 200.6 (d, C-1), 165.8 (s, C-7′), 80.7 (d, C-5′), 64.1 (d, C-8′), 57.1 (d, C-2′), 47.9 (t, C-2), 27.8 (t, C-3′), 25.7 (t, C-4′), 17.6 (q, CH_3-).- IR (neat): ν (cm^{-1}) = 2970, 2920, 2730 (C-H), 1760, 1720 (C=O), 1445, 1355, 1315.- $C_9H_{13}O_3N$, (183.20).

(2*S*, 5*S*, 8*S*)-2-Allyl-8-methyl-6-oxa-1-azabicyclo[3.2.1]octan-7-one (18)

To a suspension (-40°C) of methyltriphenylphosphonium bromide (116 mg, 0.325 mmol) in ether (15 ml) sodium hexamethyldisilazide (0.32 ml, 1 M solution in THF) was added and the mixture was stirred for 1 h at -40°C. A solution of **17** (36 mg, 0.196 mmol) in THF (2 ml) was added and stirring was continued for 30 min at -40°C and 2 h at room temperature. The solvent was evaporated, the residue was partly solved in ether. Insoluble triphenylphosphine oxide was separated by suction. The filtrate was evaporated and the residue was purified by column chromatography on silica gel with hexane / ether (2 : 1). Yield: 17 mg (48 %), colourless oil, R_f = 0.21

(hexane / ether 2:1).- ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) = 5.84 (dddd, J_{trans} = 17.2 Hz, J_{cis} = 10.1 Hz, $J_{1'a,2'}$ = 7.8 Hz, $J_{1'b,2'}$ = 6.1 Hz, 1 H, 2'-H), 5.10 ("dq", J_{trans} = 17.1 Hz, $J_{gem} = {}^4J \approx 1.6$ Hz, 1 H, 3'-H_a), 5.04 ("dm", J_{cis} = 10.1 Hz, 1 H, 3'-H_b), 4.40 (d, $J_{4a,5}$ = 4.1 Hz, 1 H, 5-H), 3.17 - 3.02 (m, 1 H, 2-H), 3.10 (q, $J_{8,Me}$ = 6.7 Hz, 1 H, 8-H), 2.65 - 2.50 (m, 1 H, 1'-H_a), 2.26 - 2.03 (m, 2 H, 1'-H_b, 4-H_a), 1.91 - 1.54 (m, 3 H, 4-H_b, 3-$H_{a,b}$), 1.21 (d, $J_{8,Me}$ = 6.7 Hz, CH_3-). - ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ (ppm) = 165.8 (s, C-7), 134.8 (d, C-2'), 117.0 (t, C-3'), 80.6 (d, C-5), 64.2, 62.7 (2 d, C-2,8), 38.7 (t, C-1'), 27.9, 25.6 (2 t, C-3,4), 17.6 (q, CH_3-).- $C_{10}H_{15}NO_2$, (181.23).

(2*R*, 5*S*, 8*S*)- 8-Methyl-6-oxa-2-propyl-1-azabicyclo[3.2.1]octan-7-one (19)

A solution of **18** (17 mg, 93.8 μmol) in ethanol was hydrogenated with 10 mg Pd / C under 15 atm pressure for 18 h at room temperature. The catalyst was separated by filtration and the filtrate was evaporated. Yield: 13 mg (76 %), colourless oil.- ^{1}H NMR (CD_3OD, 200 MHz): δ (ppm) = 4.39 (d, $J_{4a,5}$ = 3.6 Hz, 1 H, 5-H), 3.18 (q, $J_{8,Me}$ = 6.7 Hz, 1 H, 8-H), 3.14 - 3.02 (m, 1 H, 2-H), 1.93 - 1.13 (m, 8 H, 3,4-$H_{a,b}$, 1',2'-H), 1.07 (d, $J_{8,Me}$ = 6.7 Hz, 3 H, CH_3-), 0.84 (t, $J_{2',3'}$ = 7.1 Hz, 3 H, 3'-H). - ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ (ppm) = 165.3 (s, C-7), 82.9 (d, C-5), 65.2, 64.0 (2 d, C-2,8), 37.2 (t, C-1'), 28.7, 27.1 (2 t, C-3,4), 20.2 (t, C-2'), 17.6 (q, CH_3-), 14.2 (q, C-3').- IR (neat): ν (cm^{-1}) = 2950, 2920 (C-H), 1740 (C=O), 1440, 1260 (C-O).- $C_{10}H_{15}NO_2$, (183.24).

(2*S*, 3*S*, 6*R*)-6-Propyl-3-hydroxy-2-methylpiperidine Hydrochloride (20)

A solution of **19** (13 mg, 70.9 μmol) in methanol (3 ml) and concentrated hydrochloric acid (1 ml) was stirred for 18 h at room temperature, then it was heated to 45°C for 2 h. The solvent was evaporated, the semicrystalline residue was crystallised from ethanol with ether. Yield: 13 mg (quantitative), m.p.: 129°C.- ^{1}H NMR (CD_3OD, 200 MHz): δ (ppm) = 4.01 - 3.99 (m, 1 H, 3-H), 3.83 - 3.70 (m, 1 H, 2-H), 3.46 - 3.28 (m, 1 H, 6-H), 2.38 - 2.31 (m, 1 H, 1'-H_a), 2.15 - 2.09 (m, 1 H, 1'-H_b), 1.92 - 1.30 (m, 9 H, 2'-H, 4,5-H, CH_3-), 1.17 (t, $J_{2',3'}$ = 6.6 Hz, 3 H, 3'-H).- ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ (ppm) = 73.3 (d, C-3), 58.2, 55,7 (2 d, C-2,6), 36.6 (t, C-1'), 28.0 (t, C-4), 23.8 (t, C-5), 19.6 (t, C-2'), 15.5 (q, CH_3-), 14.1 (q, C-3').- MS (70 eV, CI): *m/z* (%) = 175.1 (11.4) [M+NH_4^+-HCl], 172.1 (45.5), 157.1 (1.0) [M^+-HCl], 154.2 (2.3), 140.1 (12.8) [$C_9H_{18}N^+$], 96.1 (100) [$C_6H_{10}N^+$].- $[\alpha]_D^{20}$ = + 81.8 (c = 0.7, $CHCl_3$).- $C_9H_{20}NOCl$, (193.70).

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