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An Efficient Chemoenzymatic Access to Chiral 3,7-Diazabicyclo[3.3.1]nonane Derivatives

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Abstract

Enantiopure 3,7-diazabicyclo[3.3.1]nonane derivatives **4** and **5**, potential precursors of quinolizidine alkaloids, were synthesised in high yields, starting from the biocatalytic asymmetrization of σ-symmetric 3,5-disubstituted piperidines. Their application to the total synthesis of the new pharmacologically active compounds **3** are also described.

Keywords: *alkaloids, aminals, bicyclic heterocyclic compounds, enzyme reactions.*

Quinolizidine alkaloids are widely distributed in various plant families and show an interesting range of biological and chemical properties.[1] For example, (-)-cytisine (**1**) and some of its derivatives act as agonists at the nicotinic receptor and have been the subject of a number of pharmacologic[2] and synthetic[3] studies during the last few years. Another basic component of this class of natural products, (-)-sparteine (**2**), has recently received significant attention due to its use as a chiral chelating base for Li^+ in asymmetric deprotonations with alkyllithium agents.[4]

A notable feature, common to these molecules, is the presence of a chiral 3,7-diazabicyclo[3.3.1]nonane system, on which one or two other rings are fused. This moiety has also been recently incorporated in a number of new pharmacologically active compounds of general structure **3**,[5,6] claimed as cholinergic agents for the prevention and treatment of Alzheimer's disease and other cerebral function disorders (Figure 1). Up to

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now, access to such structures has been secured by a long sequence of reactions starting from 3-bromo-5-carboxypyridine and terminating with an optical resolution step.

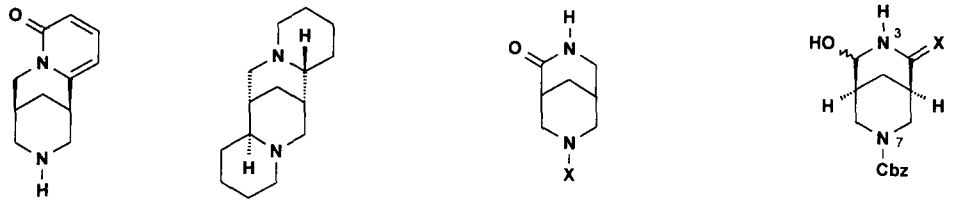
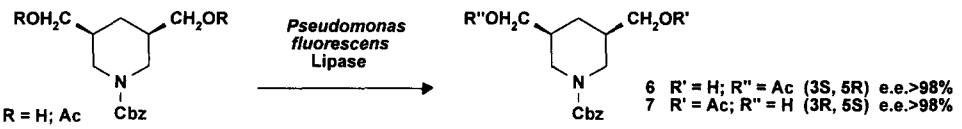


Figure 1

We report here the first enantioselective synthetic entry to (1*S*,2ξ,5*S*)-2-hydroxy-7-benzyloxylcarbonyl-3,7-diazabicyclo[3,3,1]nonane (**4**) and (1*R*,4*R*,5*S*)-2-oxo-4-hydroxy-7-benzyloxylcarbonyl-3,7-diazabicyclo [3.3.1]nonane (**5**), which we envisaged as immediate precursors of compounds of type **3** and as potential advanced intermediates in the stereocontrolled synthesis of tricyclic quinolizidine alkaloids *via* the corresponding imine and acylimine functionalities easily generated by Lewis acid treatment.

Recently, we reported[7] the preparation of *cis*-piperidine-3,5-dimethanol monoacetates **6** and **7**, in high enantiomeric excesses and yields, by means of biocatalytic asymmetrization of the corresponding σ-symmetric diol or diacetate (Scheme 1).

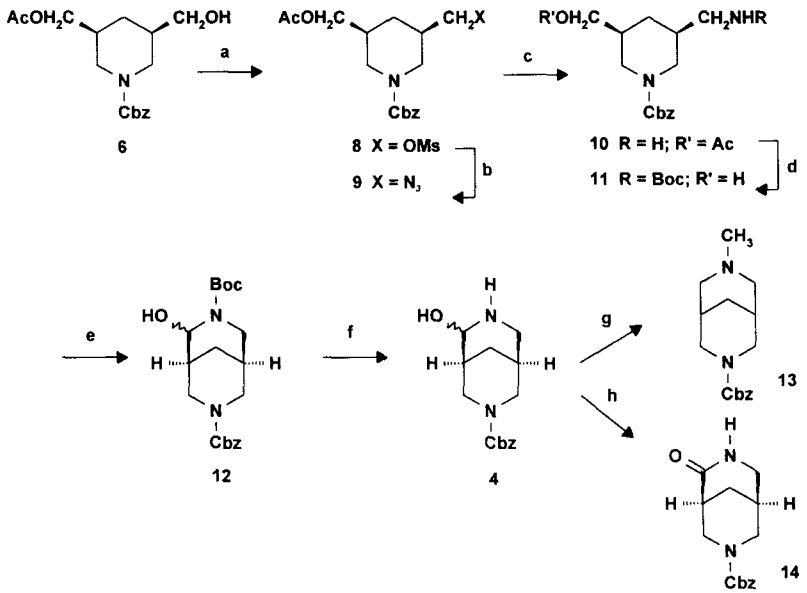


Scheme 1

Prompted by the opportunity to explore the synthetic versatility of these new chiral building blocks, we first planned the preparation of **4**, starting from (3*S*,5*R*)-*N*-benzyloxylcarbonyl-3-acetoxymethyl-5-hydroxymethyl piperidine **6**, as depicted in Scheme 2.

Introduction of the amino functionality was achieved by a three step reaction sequence, starting with treatment of **6** with MsCl to afford the corresponding mesylate **8**; then nucleophilic displacement using sodium azide[8] gave **9** in high yield. Reduction of the azido group of **9** was performed with stannous chloride in methanol as solvent;[9] the reaction was complete within 1 hour and afforded **10** in almost quantitative yield. Then the primary amino group of **10** was protected by means of $(Boc)_2O$ to give the *N*-Boc derivative **11** in which

hydrolysis of the acetate function occurred. Swern oxidation of the hydroxymethyl moiety of **11** gave a mixture of the diastereoisomeric cyclic aminals **12** in nearly quantitative yield. Notably, this cyclization is the result of a fast favoured ring formation occurring in a minor, less stable conformation of the putative intermediate aldehyde in which the C3 and C5 substituents are axially disposed. Epimers corresponding to the structure **12** exchanged slowly at room temperature, giving rise to broad NMR signals. Removal of the *N*-Boc protecting group using TFA, followed by exposure to ice-cold, aqueous sodium hydroxide of the resulting TFA salt and immediate solvent extraction, gave the desired (1*S*,2ξ,5*S*)-2-hydroxy-7-benzyloxylcarbonyl-3,7-diazabicyclo[3.3.1]nonane **4**, in 85% yield from **12**.

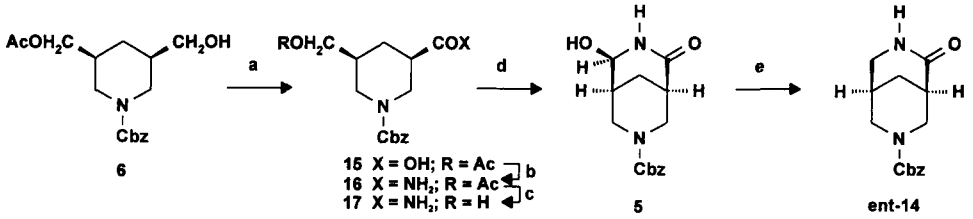


(a) MsCl, Py (98%); (b) NaN_3, DMF, 70 °C (92%); (c) $SnCl_2$, MeOH, reflux (95%);(d) Boc_2O, NaOH(aq), THF (94%); (e) $(COCl)_2$, DMSO, CH_2Cl_2 (90%); (f) TFA, then NaOH(aq), (85%); (g) $NaBH_3CN$, CH_2O, THF (71%); (h) PDC, Celite®, CH_2Cl_2 (65%);

Scheme 2

The proposed structure for **4** was further supported by performing a reduction of the masked aldehydic C-2 followed by a reductive methylation at the N-3 atom by means of $NaBH_3CN$ in the presence of formaldehyde in THF. The high symmetry of the 3-benzyloxylcarbonyl-7-methyl-3,7-diazabicyclo[3.3.1]nonane **13** thus obtained, resulted in very simplified ^1H and ^{13}C NMR spectra. On the other hand, oxidation of **4**, with PDC[10] in dichloromethane afforded the (1*S*,5*S*)-2-oxo-7-benzyloxylcarbonyl-3,7-diazabycyclo[3.3.1]nonane **14**, which represents the heterocyclic motif of the above mentioned compounds of type **3**, in one of its enantiomeric forms.

For the synthesis of (1*R*,4*R*,5*S*)-**5**, the sequence of steps required was modified, as illustrated in Scheme 3.



(a) $KMnO_4$, CH_3COCH_3 (75%); (b) $SOCl_2$, $NH_3(g)$ (98%); (c) NaOH, THF (96%); (d) Dess-Martin periodinane, CH_2Cl_2 (82%); (e) Et_3SiH, BF_3Et_2O, CH_2Cl_2 (52%).

Scheme 3

Oxidation of **6** with $KMnO_4$ in anhydrous acetone led to formation of the carboxylic acid **15**, in 75% yield. Reaction of the acid chloride of **15** with gaseous NH_3 afforded quantitatively the amide **16**, which was easily converted to the corresponding deacetylated compound **17**. Oxidation of **17** was strongly dependent upon the reagent and conditions: reaction with DMSO/pyridine-SO_3 or with DMSO/$(COCl)_2$ gave complex mixtures of products, not easily recoverable after aqueous work up. Instead, oxidation of **17** worked smoothly using Dess-Martin periodinane[11] in CH_2Cl_2, yielding 82% of lactamol **5**, as a single diastereoisomer. Close inspection of the ^1H and ^{13}C NMR (APT) spectra allowed the complete attribution of signals to the whole protonic system; moreover, the configuration at C-4 was ascertained by the presence of a n.O.e. contact between the proton H-4 (δ 5.07, d) and pro*S* H-9 (δ 2.13, br d). The n.O.e. interaction was detectable in a double-chair conformation of **5** in which H-4 and pro*S* H-9 are juxtaposed in a synaxial disposition. Finally, a Lewis acid-catalyzed triethylsilane reduction[12] was performed on **5**, affording **ent-14** in acceptable yield.

In conclusion, we succeeded in developing a convenient enantioselective synthetic entry into 3,7-diazabicyclo[3.3.1]nonane derivatives **4** and **5**, functionalized at the position α to N-3 in such a way to make feasible the subsequent elaboration to tricyclic compounds. Finally, this study has contributed to finding an efficient access to **14** and **ent-14** which represent the core of compounds of type **3**.

Experimental[13]

General

All separations were carried out under flash chromatography (FC) conditions on silica gel 60 (230-400 mesh) using the indicated solvents. The organic extracts were dried over anhydrous Na_2SO_4 prior to solvent removal on a rotary evaporator.

Materials

(3*S*,5*R*)-3-Acetoxymethyl-5-hydroxymethyl-piperidine-1-carboxylic acid benzyl ester (**6**) was obtained in 78% yield and >98% ee by enzymatic acetylation of the corresponding diol as previously described.[7b]

(3S,5R)-3-Acetoxymethyl-5-aminomethyl-piperidine-1-carboxylic acid benzyl ester ***10***

Mesyl chloride (1.36 ml, 13.9 mmol) was added to a solution of **6** (3.7 g, 11.6 mmol) in pyridine (30 ml) at 0°C. After 4 h at rt, the reaction mixture was quenched by addition of sat. aq. $NaHCO_3$ at 0°C, acidified by 1N HCl and extracted with CH_2Cl_2. The combined organic extracts were washed with water, dried, and concentrated. FC (AcOEt : hexane 7:3) of the residue gave **8** (4.5 g, 98%): oil; R_f (AcOEt) 0.50; ^{1}H NMR (300 MHz, $CDCl_3$, 50 °C) δ 7.34 (m, 5H), 5.13 (s, 2H), 4.30 (m, 2H), 4.11 (dd, 1H, *J*=10.0, 5.0 Hz), 4.04 (1H, dd, *J*=10.0, 5.0 Hz), 3.98 (dd, 1H, *J*=11.2, 5.7 Hz), 3.89 (dd, 1H, *J*=11.2, 6.8 Hz), 2.98 (s, 3H), 2.43 (t, 1H, *J*=12.5 Hz), 2.37 (t, 1H, *J*=12.5 Hz), 2.03 (s, 3H), 2.00-1.83 (m, 3H), 1.01 (q, 1H, *J*=11.9 Hz); EIMS *m/z* (relative intensity) 399 (10, M^+), 354 (22), 339 (5), 250 (100). Sodium azide (950 mg, 14.6 mmol) was added in one portion to a solution of the mesylate **8** (2.20 g, 5.5 mmol) in DMF (30 ml) at rt. After heating at 75 °C for 8 h, the reaction mixture was partitioned between ether and water. The combined organic layers were dried and concentrated in vacuo to provide the almost pure crude azide **9** (1.70 g, 92%): oil; R_f(AcOEt) 0.65; IR ($CHCl_3$) 2150, 1300 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 50 °C) δ 7.35 (m, 5H), 5.12 (s, 2H), 4.26 (br d, 2H, *J*=12.0 Hz), 3.97 (dd, 1H, *J*=11.2, 5.2 Hz), 3.86 (dd, 1H, *J*=11.2, 6.4 Hz), 3.22 (m, 2H), 2.40 (t, 2H, *J*=12.6 Hz), 2.05 (s, 3H), 1.98-1.64 (m, 3H), 0.95 (q, 1H, *J*=12.5 Hz); EIMS *m/z* (relative intensity) 318 (3, M^+-28), 183 (15), 91(100). To a stirred suspension of $SnCl_2$ (3.2 g, 9.53 mmol) in 33 ml of methanol was added dropwise a solution of the crude azide **9** (3.3 g, 9.53 mmol) in methanol (10 ml). The reaction was exothermic and N_2 gas was evolved. The resulting mixture was stirred at rt for 1h and then evaporated in vacuo. The residue was partitioned between ether (20 ml) and 5% NH_4OH solution (aq, 20 ml) and the precipitated inorganic material filtered off. The aq. portion was saturated with NaCl and further extracted with ether (5 x 5 ml). The combined organic layers were dried and concentrated to give, after FC ($CHCl_3$: methanol 19:1) of the residue, the amine **10** (2.9 g, 95 %): oil; ; R_f($CHCl_3$: MeOH 9:1) 0.10; $[\alpha]_D^{25}$ – 5.4 (*c* 1, $CHCl_3$); IR ($CHCl_3$) 3400, 1725 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 50 °C) δ 7.35 (m, 5H), 5.14 (s, 2H), 4.30 (br d, 2H, *J*=12.0 Hz), 4.00 (dd, 1H, *J*=11.4, 5.7 Hz), 3.88 (dd, 1H, *J*=11.4, 6.9 Hz), 2.65 (d, 2H, *J*=7.2 Hz), 2.40 (q, 2H, *J*=12.3 Hz), 2.04 (s, 3H), 2.00-1.79 (m, 2H), 1.78-1.50 (m, 1H), 0.85 (q, 1H, *J*=12.6 Hz); EIMS *m/z* (relative intensity) 320 (3, M^+), 156 (48), 91(100); Anal. Calcd for $C_{17}H_{24}N_2O_4$: C, 63.73; H, 7.55; N, 8.74. Found: C, 63.84; H, 7.35; N, 8.76.

(3S,5R)-3-Hydroxymethyl-5-(t-butyloxycarbonyl)aminomethyl-piperidine-1-carboxylic acid benzyl ester ***11***

To a stirred solution of **10** (2.90 g, 9.0 mmol) in THF (20 ml) and NaOH 1N (10 ml) $(Boc)_2O$ (2.40 g, 10.8 mmol) was added. After 6h at rt, the reaction mixture was poured into water and extracted with Et_2O; the organic phase was washed with brine, dried and concentrated to give pure **11** (3.24 g, 94%): oil; R_f(AcOEt) 0.40; $[\alpha]_D^{25}$ – 6.2 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 50 °C) δ 7.35 (m, 5H), 5.12 (s, 2H), 4.50 (br s, 1H), 4.24 (m, 2H), 3.52 (dd, 1H, *J*=11.8, 5.6 Hz), 3.48 (dd, 1H, *J*=11.8, 6.0 Hz), 3.01 (t, 2H, *J*=6.4 Hz), 2.42 (m, 2H), 1.88 (br d, 1H, *J*=12.0 Hz), 1.80-1.60 (m, 2H), 1.45 (s, 9H), 0.88 (q, 1H, *J*=12.0 Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 156.0, 155.3, 137.1, 128.5, 127.9, 127.8, 67.1, 65.3, 47.9, 47.1, 43.9, 38.6, 36.9, 31.7, 28.3; EIMS *m/z* (relative intensity) 378 (2, M^+), 158 (77), 91(100); HRMS calcd for $C_{20}H_{30}N_2O_5$ 378.2155, found 378.2169.

(1S,2ξ,5S)-2-Hydroxy-3-t-butyloxycarbonyl-7-benzyloxycarbonyl-3,7-diazabicyclo[3.3.1]nonane ***12*** *(mixture of diastereomers)*

At –70°C, a solution of oxalyl chloride (480 µl, 5.5 mmol) in CH_2Cl_2 (5 ml) was treated dropwise within 1h with a solution of DMSO (790 µl, 11.0 mmol) in CH_2Cl_2 (5 ml). After stirring for 50 min, the resulting mixture was treated dropwise with a solution of **11** (1.0 g, 2.75 mmol) in CH_2Cl_2 (5 ml), stirred for 1h at –70°C and then treated with Et_3N (2 ml). After 1h at –70°C, the mixture was warmed

at rt and washed with water; the organic phase was dried and concentrated to give, after FC (AcOEt:exane 1:2) of the residue, pure **12** (880 mg, 90%): foam; R_f(AcOEt:hexane 1:1) 0.60; IR ($CHCl_3$) 1725, 1700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 50 °C) δ 7.35 (m, 5H), 5.20-5.07 (m, 3H), 4.60 (br s, 1H), 4.41 (br d, 1H, *J*=12.2 Hz), 4.18 (br d, 1H, *J*=12.2 Hz), 3.05 (m, 2H), 2.74 (m, 1H), 2.45 (m, 2H), 2.15 (br d, 1H, *J*=13.1 Hz), 1.75 (m, 1H), 1.22 (br d, 1H, *J*=13.1 Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 156.0, 155.0, 136.5, 128.4, 127.9, 127.7, 67.2, 58.7, 48.0, 47.5, 43.7, 36.3, 33.6, 28.5, 28.3; FABMS *m/z* 377 (MH^+); Anal. Calcd for $C_{20}H_{28}N_2O_5$: C, 63.81; H, 7.50; N, 7.44. Found: C, 63.95; H, 7.37; N, 7.41.

*(1S,2ξ,5S)-2-Hydroxy-7-benzyloxycarbonyl-3,7-diazabicyclo[3.3.1]nonane **4** (mixture of diastereomers)*

At 0°C, **12** (880 mg, 2.3 mmol) was dissolved in TFA (5 ml) and stirred for 1h. Then the solution was poured into ice-cold, aq. NaOH 10% and immediatly extracted with CH_2Cl_2, to give **4** (546 mg, 85%): oil; R_f(19:1 $CHCl_3$ / MeOH) 0.43; $[\alpha]_D^{25}$ – 9.3 (*c* 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 50°C) δ 7.35 (m, 5H), 5.08 (m, 2H), 5.02 (s, br, 1H), 4.24 (m, 2H), 3.28 (m, 2H), 3.00 (d, br, 1H, *J* =13.0 Hz), 2.91 (d, br, 1H, *J* =13.0 Hz), 2.39 (m, 1H), 1.99 (m, 2H), 1.75 (m, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 156.5, 136.0, 129.0, 128.6, 68.4, 66.0, 59.2, 49.1, 44.8, 33.8, 28.9, 24.1; FABMS *m/z* 277 (MH^+); HRMS calcd for $C_{15}H_{20}N_2O_3$ 276.1474, found 276.1482.

*3-Benzyloxycarbonyl-7-methyl-3,7-diazabicyclo[3.3.1]nonane **13***

A solution of **4** (180 mg, 0.6 mmol) in THF (5 ml) was treated with $NaBH_3CN$ (164 mg, 2.6 mmol) and then with a solution of 37% aq. CH_2O. After stirring for 1h at rt, the mixture was partitioned between AcOEt and aq. $NaHCO_3$ 5%; the combined organic layers were dried and concentrated to give, after FC ($CHCl_3$: MeOH 85:15), pure **13** (127 mg, 71%): oil; R_f(4:1 $CHCl_3$ / MeOH) 0.18; ^1H NMR (300 MHz, $CDCl_3$, 50°C) δ 7.35 (s, 5H), 5.13 (s, 2H), 4.23 (dd, 2H, *J* =13.5, 2.2 Hz), 3.09 (ddd, 2H, *J* =13.5, 3.5, 2.2 Hz), 2.95 (d, br, 2H, *J* =12.0 Hz), 2.24 (dt, br, 2H, *J* =12.0, 2.0 Hz), 2.14 (s, 3H), 2.05-1.84 (m, 2H), 1.81 (m, 1H), 1.65 (m, 1H); FABMS 275 *m/z* (MH^+).

*(1S,5S)-2-Oxo-7-benzyloxycarbonyl-3,7-diazabycyclo[3.3.1]nonane **14***

To a solution of **4** (200 mg, 0.7 mmol) in CH_2Cl_2 (3 ml) pyridinium dichromate (376 mg, 1 mmol) was added. After stirring at rt for 3h, the mixture was diluted with Et_2O, the inorganic material was filtered off and the filtrate was evaporated, to give, after FC (AcOEt:hexane 2:1), pure **14** (118 mg, 65%): oil; R_f(2:1 EtOAc / *n*-hexane) 0.45; $[\alpha]_D$= - 8.4 (*c* 1, $CHCl_3$); IR ($CHCl_3$) 1725, 1650 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 50°C) δ 7.37 (m, 5H),), 5.17 and 5.08 (AB system, *J* = 12.2 Hz), 4.48 (br d, 1H, *J* =13.5 Hz), 4.20 (m, 1H), 3.47 (dd, 1H, *J* = 12.0, 6.8 Hz), 3.26 (br d, *J* = 12.0 Hz), 3.08 (m, 2H), 2.53 (m, 1H), 2.08 (m, 1H), 1.97 (br d, 1H, *J* = 14.5 Hz), 1.71 (br d, 1H, *J* = 14.5 Hz); FABMS *m/z* 275 (MH^+); HRMS calcd for $C_{15}H_{18}N_2O_3$ 274.1317, found 274.1327.

*(3R,5S)-3-Carboxyl-5-acetoxymethyl-piperidine-1-carboxylic acid benzyl ester **15***

To a solution of **6** (200 mg, 0.62 mmol) in acetone (6 ml), $KMnO_4$ (200 mg, 1.27 mmol) was added in portions, at 0°C and the mixture was stirred for 1h at 0°C and for 2h at rt. EtOH (3 ml) was added and, after stirring for 1h, the brown precipitate was filtered through Celite®. The filtrate was evaporated and the residue was partitioned between Et_2O and $NaHCO_3$ 5%; the aq. phase was acidified with H_2SO_4 10% and extracted with AcOEt, to give **15** (156 mg, 75%): amorphous solid; R_f(AcOEt) 0.29; $[\alpha]_D$= - 7.5 (*c* 1, $CHCl_3$); IR ($CHCl_3$) 1780, 1725 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 50°C) δ 7.35 (m, 5H),), 5.12 (s, 2H), 4.46 (br d, 1H, *J* =12.7 Hz), 4.28 (br d, 1H, *J* = 12.7 Hz), 3.98 (dd, 1H, *J* = 12.0, 5.5 Hz), 3.90 (dd, 1H, *J* = 12.0, 6.7 Hz), 2.79 (t, 1H, *J* = 12.0 Hz), 2.46 (t, 1H, *J* =12.0 Hz), 2.18 (br d, 1H, *J* =12.4 Hz), 2.03 (s, 3H), 1.91 (m, 2H), 1.37 (q, 1H, *J* = 12.4 Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 177.5,

170.9, 155.1, 136.4, 128.5, 128.1, 127.9, 67.5, 65.9, 46.7, 45.4, 40.9, 35.0, 30.3, 20.7; EIMS *m/z* (relative intensity) 335 (28, M^+), 275 (54), 232 (100); Anal. Calcd for $C_{17}H_{21}N_1O_6$: C, 60.88; H, 6.32; N, 4.18. Found: C, 60.95; H, 6.47; N, 4.05.

(3R,5S)-3-Carboxyamido-5-acetoxymethyl-piperidine-1-carboxylic acid benzyl ester ***16***

A solution of **15** (232 mg, 0.70 mmol) in $SOCl_2$ (10 ml) was heated at reflux for 4h. Thionyl chloride was evaporated, the residue was dissolved in dioxane (10 ml), cooled at 0°C and saturated with gas. NH_3. After 3h at 0°C, the solution was concentrated, acidified with aq. H_2SO_4 10% and extracted with AcOEt, to give pure **16** (229 mg, 98%): oil; R_f(AcOEt) 0.26; $[\alpha]_D$= - 6.0 (*c* 1, $CHCl_3$); IR ($CHCl_3$) 1725, 1680 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 50°C) δ 7.35 (m, 5H), 5.43 (br s, 2H), 5.12 (s, 2H), 4.33 (br d, 1H, *J* =13.0 Hz), 4.24 (br d, 1H, *J* = 13.0 Hz), 4.00 (dd, 1H, *J* = 11.2, 5.4 Hz), 3.90 (dd, 1H, *J* = 11.2, 6.8 Hz), 2.87 (dd, 1H, *J* = 13.6, 11.8 Hz), 2.53 (br t, 1H, *J* =13.6 Hz), 2.35 (m, 1H), 2.03 (s, 3H), 2.01 (m, 1H), 1.88 (m, 1H), 1.54 (q, 1H, *J* = 12.0 Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 175.8, 170.9, 155.2, 136.3, 128.5, 128.0, 127.7, 127.3, 67.4, 65.9, 46.6, 42.1, 34.4, 30.3, 20.7; FABMS *m/z* 335 (MH^+).

(3R,5S)-3-Carboxyamido-5-hydroxymethyl-piperidine-1-carboxylic acid benzyl ester ***17***

To a stirred solution of **16** (150 mg, 0.45 mmol) in THF (3 ml), aq. NaOH 0.5 N (1.35 ml, 0.68 mmol) was added. After 2h at rt, usual work up gave pure **17** (121 mg, 92%): oil; R_f($CHCl_3$:MeOH 9:1) 0.44; IR ($CHCl_3$) 1680, 1603 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 50°C) δ 7.10 (m, 5H), 6.53 (br s, 1H), 5.60 (br s, 1H), 4.89 (s, 2H), 4.07 (m, 2H), 3.57 (br s, 1H), 3.17 (m, 2H), 2.60 (t, 1H, *J* = 12.0 Hz), 2.32-2.09 (m, 2H), 1.78 (br d, 1H, *J* =13.0 Hz), 1.46 (m, 1H), 1.16 (q, 1H, *J* = 13.0 Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 175.5, 154.9, 136.6, 128.2, 127.7, 127.5, 66.7, 64.3, 46.6, 46.2, 42.0, 38.0, 30.8; EIMS *m/z* (relative intensity) 292 (2, M^+), 157 (47), 91 (100); HRMS calcd for $C_{15}H_{20}N_2O_4$ 292.1423, found 292.1418.

(1R,4R,5S)-2-Oxo-4-hydroxy-7-benzyloxycarbonyl-3,7-diazabicyclo[3.3.1]nonane ***5***

Freshly prepared Dess-Martin reagent[11] (310 mg, 0.73 mmol) was added to a stirred solution of **17** (165 mg, 0.56 mmol) in CH_2Cl_2 (20 ml). The solution turned yellow, and after 10 min, a colourless precipitate formed. Filtration through Celite® after 25 min gave a pale yellow filtrate, from which part of the solvent was removed by vacuum evaporation. FC (CH_2Cl_2:MeOH 95:5) of the residue gave pure **5** (128 mg, 82%) as a single epimer (from 300 MHz ^1H NMR). **5**: amorphous solid; R_f(CH_2Cl_2:MeOH 9:1) 0.46; $[\alpha]_D$ = - 3.3 (*c* 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 50°C) δ 7.35 (s, 5H), 6.70 (br s, 1H), 5.14 and 5.06 (AB system, *J*= 12.1 Hz), 5.07 (d, 1H, *J* =5.7 Hz), 4.54 (br d, 1H, *J* =14.2 Hz), 4.43 (br d, 1H, *J* =13.5 Hz), 3.11 (br d, 1H, *J* =13.5 Hz), 2.92 (dd, 1H, *J* =14.2, 3.0 Hz), 2.49 (m, 1H), 2.19-2.08 (m, 2H), 1.96 (ddd, 1H, *J* =14.5, 4.4, 3.0 Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 173.5, 168.1, 143.0, 128.4, 128.1, 78.7, 68.2, 48.0, 43.8, 37.6, 32.7, 27.8; EIMS *m/z* (relative intensity) 290 (4, M^+), 272 (22), 166 (65), 91 (100); Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.05; H, 6.25; N, 9.65. Found: C, 62.02; H, 6.17; N, 9.48.

(1R,5R)-2-Oxo-7-benzyloxycarbonyl-3,7-diazabicyclo[3.3.1]nonane ***ent-14***

At –40°C, Et_3SiH (40 μl, 0.25 mmol) and BF_3OEt_2 (31 μl, 0.25 mmol) were added dropwise to a solution of **5** (60 mg, 0.21 mmol) in 3 ml of CH_2Cl_2. The resulting mixture was warmed at rt, stirred for 5h and then treated with sat. aq. Na_2CO_3. Normal work up, followed by FC (AcOEt:hexane 2:1) of the residue gave **ent-14** (28 mg, 52% yield).

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References and notes

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