Synthesis of an Optically Active Decahydro-6-isoquinolone Scaffold with a Quaternary Stereocenter

Jens Christoffers,*[a] Heiko Scharl,[a] Wolfgang Frey,[a] and Angelika Baro[a]

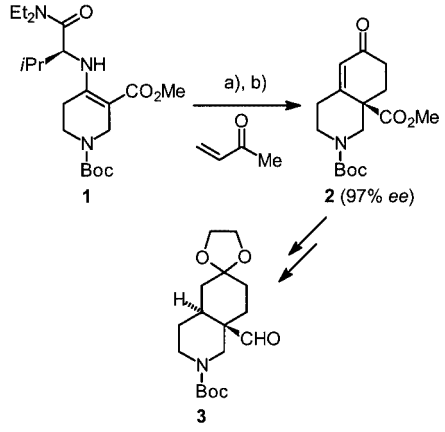
Keywords: Chirality / Isoquinolones / Nitrogen heterocycles / Quaternary stereocenters / Scaffolds

A straightforward synthesis of optically active decahydro-6-isoquinolone derivative **3**, containing a quaternary stereocenter, is reported. The starting (*R*)-configured enantiopure enone **2**, which is readily accessible through a copper-catalyzed, L-valine amide mediated Michael reaction and a subsequent Robinson annulation, was hydrogenated with Pd/C in *i*PrOH to give the decahydroisoquinolone **4**. Treatment of **4** with ethyleneglycol in the presence of PPTS yielded the dioxolane-protected derivative **7**. A sequence of ester reduction with $LiAlH_4$ and subsequent Ley oxidation of the resulting primary alcohol **10** accomplished the synthesis. Enantiomerically pure aldehyde **3**, with three groups for further functionalization, was thus obtained in 63% overall yield.

(© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2004)

Introduction

Piperidines and piperidones are ubiquitous scaffolds in medicinal chemistry.[1] The *trans*-decahydro-6-isoquinolone structural motif,[2] as present in compound **3**, may be regarded as an extended 4-piperidone derivative. We have recently reported a synthetic route to the optically active octahydro-6-isoquinolone derivative **2**, bearing a quaternary stereocenter.[3] Compound **2** was prepared by a sequence consisting of a copper-catalyzed Michael reaction between chiral enamine **1** and methyl vinyl ketone, followed by Robinson annulation (Scheme 1). Use of L-valine diethylamide as the chiral auxiliary gave high enantioselectivity in forming the quaternary stereocenter[4] at ambient temperature.[5]



Scheme 1. Preparation of isoquinolone **2**, the starting material in the synthesis of carbaldehyde **3**; reagents and conditions: a) cat. $Cu(OAc)_2 \cdot H_2O$, methyl vinyl ketone, acetone, 23 °C, 16 h; b) pyrrolidine/AcOH, CH_2Cl_2, 23 °C, 16 h, 97% *ee*, 69% yield over two steps

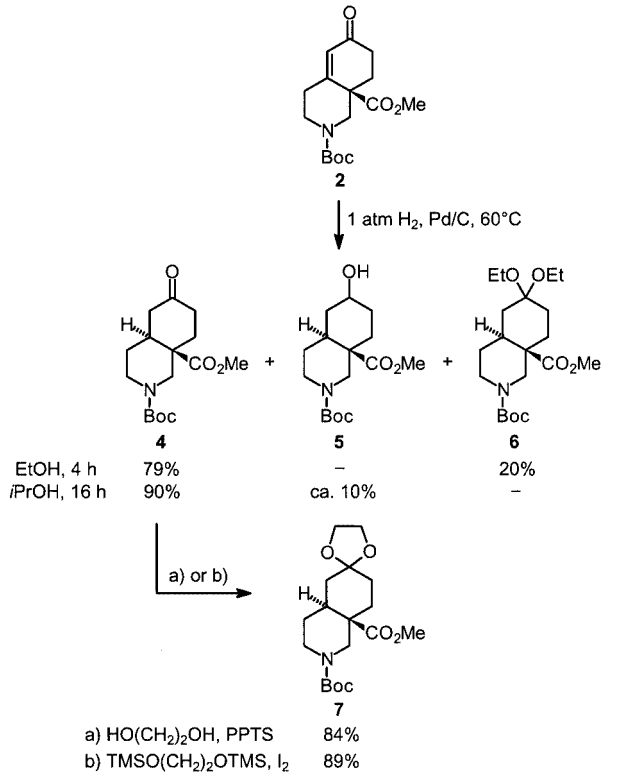
[a] Institut für Organische Chemie der Universität Stuttgart, Pfaffenwaldring 55, 70569 Stuttgart, Germany,
Fax: (internat.) + 49-(0)711-685-4269
E-mail: jchr@oc.uni-stuttgart.de

Although octahydro-6-isoquinolones are well known as racemates,[6] optically active cogeners containing quaternary stereocenters have, to the best of our knowledge, only been reported once.[7] The corresponding enantiopure decahydro-6-isoquinolones are so far unknown. In this work we wish to disclose a straightforward route to protected carbaldehyde **3**, to serve as a building block with further elaboration of the aldehyde function, the secondary amine, and the ketone moiety.

Results and Discussion

Catalytic hydrogenation of enone **2** with Pd/C in EtOH at 60 °C proceeded with quantitative conversion, although diethylacetal **6** was obtained as a by-product (20%) together with the major product **4** (79%) (Scheme 2). The EtOH solvent was therefore replaced by *i*PrOH, and **2** was again completely converted after 16 h, the major product **4** now being isolated in 90% yield. The secondary alcohol **5** was formed in about 10% yield as a by-product, the result of over-hydrogenation of ketone **4**.

Compounds **4** and **5** were separated by column chromatography on SiO_2. Both by-products **5** and **6** were obtained as single diastereomers, as determined by ^1H NMR spectroscopy. The relative configuration of the secondary alcohol in by-product **5** is so far unknown. The major product **4** was isolated as a 95:5 mixture of *trans* and *cis* diastereoisomers, independently of the solvent used. The minor *cis* isomer was separated and finally lost in the purification of the three subsequent synthetic steps. The relative *trans*



Scheme 2. Hydrogenation of compound **2** and subsequent protection of derivative **4**; reagents and conditions: a) $HO(CH_2)_2OH$ (4 equiv.), PPTS (0.3 equiv.), benzene, Dean–Stark trap, 80 °C, 16 h; b) $TMSO(CH_2)_2OTMS$ (1.4 equiv.), I_2 (0.2 equiv.), 23 °C, 5 d

configuration of the major isomer was already indicated by ^{1}H NMR spectroscopy and was finally established by single-crystal X-ray analysis of compound **4** in the racemic series (Figure 1).[8]

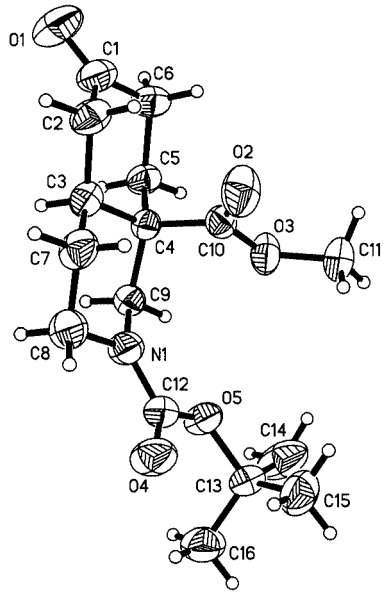
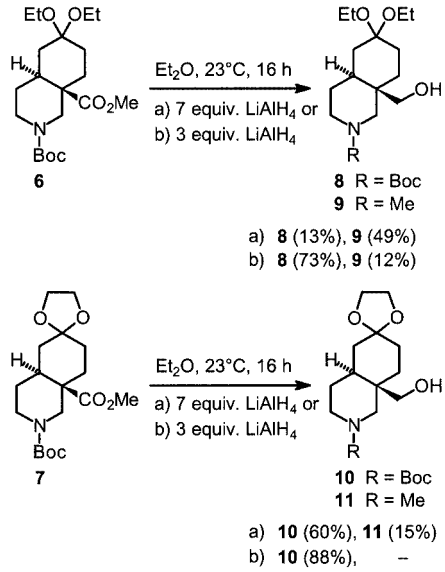


Figure 1. ORTEP view of methyl 3-(*tert*-butyloxycarbonyl)-8-oxo-3-azabicyclo[4.4.0]decane-1-carboxylate (*rac*-**4**), showing the relative *trans* configuration of the decalin backbone

Protection of ketone **4** with ethyleneglycol proceeded in the presence of catalytic amounts of PPTS in benzene as solvent in a Dean–Stark trap to give dioxolane derivative **7** in 84% yield (Scheme 2).[9] The yield was not improved significantly (89%) by use of bis(TMS) glycol and catalytic amounts of I_2.[10] The NMR spectra of **7** reveal a single signal set (> 98% *de*).

Both acetals, diethoxy derivative **6** and dioxolane **7**, were subjected to ester reduction with $LiAlH_4$. When 7 equiv. of $LiAlH_4$ were used, the two primary alcohols with the carbamate protective group reduced to NMe – compounds **9** and **11**, respectively – were obtained (Scheme 3). With 3 equiv. of $LiAlH_4$, the *N*-Boc alcohol **8** became the major product in the diethoxy series. For dioxolane **7**, 3 equiv. of $LiAlH_4$ gave the primary alcohol **10** as the only isolated product in 88% yield. Over-reduction was not observed in this case.



Scheme 3. Reduction of the ester function in compounds **6** and **7**

The molecular structures in the racemic series of the two compounds *rac*-**10** and *rac*-**11** were established by single-crystal X-ray analysis (Figures 2 and 3).[8]

Finally, a clean Ley oxidation[11] converted the primary alcohol **10** into aldehyde **3** in 90% yield (Scheme 4). Initial attempts to reduce carboxylate **7** directly always gave mixtures of primary alcohol **10** and aldehyde **3**, which could be separated only with difficulty.

Comparison of their X-ray crystal structures reveals that compounds **4**, **10**, and **11** crystallized as racemates in primitive centrosymmetric space groups (Table 1). The six-membered ring systems have chair conformations. In the Boc-protected derivatives **4** and **10**, nitrogen is of course planarized with a shortened distance of 1.36 Å to the carbonyl C-atom, whereas the methyl-substituted nitrogen atom in **11** shows, as would be expected, a pyramidalization with a distance to the methyl group of 1.46 Å. The molecules of **4** stack in a face-to-face orientation along the *b*-axis with an

 © 2004 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

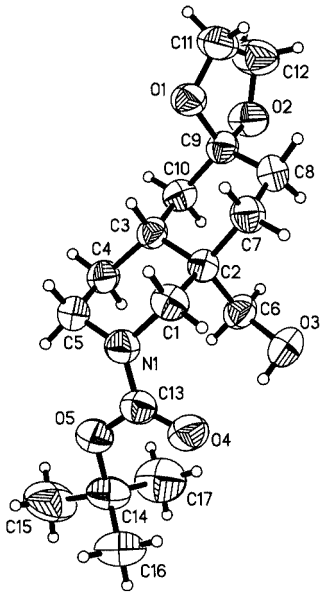


Figure 2. ORTEP view of *rac*-**10**

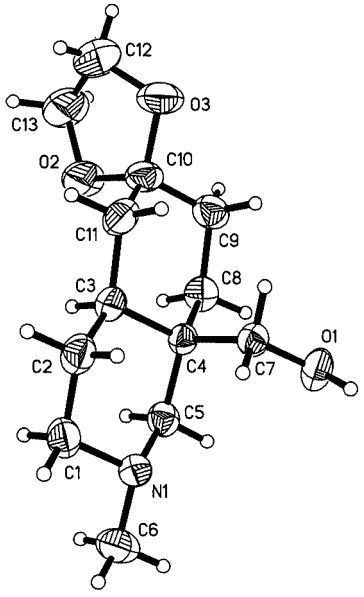
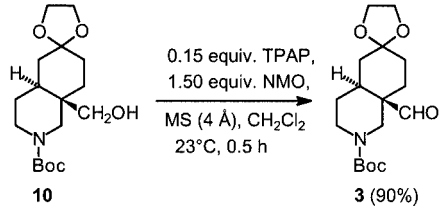


Figure 3. ORTEP view of *rac*-**11**



Scheme 4. Ley oxidation of alcohol **10** to decahydro-6-isoquinolone derivative **3**

antiparallel orientation along the *a*-axis. These properties result in nonpolar channels involving the terminal methyl groups of the ester functions.

Table 1. X-ray crystallographic data for **4**, **10**, and **11**

	rac-**4**	*rac*-**10**	*rac*-**11**
Empirical formula	$C_{16}H_{25}NO_5$	$C_{17}H_{29}NO_5$	$C_{13}H_{23}NO_3$
Formula mass [g·mol^{-1}]	311.37	327.41	241.32
Crystal system	monoclinic	triclinic	monoclinic
Space group	$P2_1/c$	$P\bar{1}$	$P2_1/c$
T [K]	293(2)	293(2)	293(2)
Wavelength [Å]	1.54178	1.54178	0.71073
a [Å]	10.7296(17)	6.6276(4)	14.212(2)
b [Å]	6.9893(12)	9.8514(5)	8.235(2)
c [Å]	22.898(3)	14.1792(12)	11.396(3)
α [°]	90	97.215(5)	90
β [°]	98.306(14)	100.387(7)	96.440(17)
γ [°]	90	97.353(6)	90
Z	4	2	4
V [Å^3]	1699.2(5)	892.57(10)	1352.4(6)
$\delta_{calcd.}$ [g·cm^{-3}]	1.217	1.218	1.209
R_w (F^2)	0.2723	0.1972	0.1498
$R(F)$ [$I > 2\sigma(I)$]	0.0851	0.0601	0.0701

In compound **10**, an intramolecular hydrogen bond is observed between the donor hydroxy function and the carbonyl oxygen atom of the Boc group. The O3−O4 and the H3−O4 distances are 2.85 Å and 1.99 Å, respectively. A nearly linear hydrogen bond with an O3−H3···O4 angle of 160° is found for the free refined H3. In the cell-plot of **10**, the same packing pattern and direction as in **4** is obtained, because the hydrogen bonds have no intermolecular influence. The packing pattern of **11** shows an antiparallel orientation of the molecules along the *c*-axis. Intermolecular hydrogen bonds are formed by one molecule working as donor (hydroxy group) and one molecule working as acceptor (nitrogen atom) and vice versa. The distance between the oxygen donor O1 and the nitrogen acceptor N1 is 2.84 Å and the H1···N1 distance is 1.88 Å. The angle of O1−H1···N1 is 170°. The crystal morphologies of the compounds do not correlate with the lack or the presence of intermolecular hydrogen bonds.

Conclusion

The first synthesis of an optically active decahydro-6-isoquinolone scaffold **3** with a quaternary stereocenter has been achieved, in four steps and 63% overall yield, starting from bicyclic compound **2**. After suitable deprotection, compound **3** might be further elaborated by aldehyde, ketone, and secondary amine transformation.

Experimental Section

General: Compounds **1** and **2** were prepared by literature procedures.[3] Column chromatography was carried out on Merck SiO_2 60 with hexanes (PE, b.p. 40−60 °C) and EtOAc (EA) as eluents. ^{13}C NMR multiplicities were determined with DEPT experiments.

Hydrogenation of Enone 2. a) in EtOH: A suspension of *rac*-**2** (2.00 g, 6.46 mmol) and Pd (5% on C, 100 mg) in EtOH (10 mL)

 © 2004 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

was stirred at 23 °C for 30 min. The reaction mixture was then degassed, flushed with H_2 (1 atm), and subsequently stirred at 60 °C for 4 h. The solution was filtered through SiO_2 (PE/EA, 1:5) and subsequently chromatographed (SiO_2; PE/EA, 5:1) to give two fractions. The first fraction contained by-product *rac*-**6** (R_f = 0.25, 502 mg, 1.30 mmol, 20%) as a colorless oil. In a second fraction, compound *rac*-**4** was isolated (R_f = 0.10, 1.581 g, 5.08 mmol, 79%). **b) in *i*PrOH:** A suspension of (1*R*)-**2** (1.00 g, 3.23 mmol) and Pd (5% on C, 50 mg) in *i*PrOH (6 mL) was stirred at 23 °C for 30 min. The reaction mixture was then degassed, flushed with H_2 (1 atm), and stirred at 60 °C for 24 h. The solution was filtered through SiO_2 (PE/EA, 1:5), and subsequently chromatographed on SiO_2 (PE/EA, 2:1) to give (1*R*,6*S*)-**4** (902 mg, 2.90 mmol, 90%) as a colorless solid, m.p. 74 °C. Elution with EA gave by-product (1*R*,6*S*)-**5** (100 mg, 0.32 mmol, 10%) as a colorless solid.

Methyl (1*R*,6*S*)-3-(*tert*-Butoxycarbonyl)-8-oxo-3-azabicyclo[4.4.0]-decane-1-carboxylate (4): R_f (PE/EA, 2:1) = 0.23. $[\alpha]_D^{20}$ = −15.4 (*c* = 1.55, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.36−1.49 (m, 10 H), 1.55 (dt, *J* = 13.6, *J* = 4.7 Hz, 1 H), 1.76 (tt, *J* = 13.6, *J* = 4.0 Hz, 1 H), 2.05−2.20 (m, 1 H), 2.22−2.32 (m, 3 H), 2.39−2.56 (m, 2 H), 2.60−2.80 (m, 1 H), 2.83−2.98 (m, 1 H), 3.74 (s, 3 H), 4.10−4.36 (m, 1 H), 4.55−4.72 (br. s, 1 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ = 28.59 (CH_2), 28.69 (CH_3), 33.33 (CH_2), 38.95 (CH_2), 43.86 (CH), 45.07 (CH_2), 47.36 (C), 52.24 (CH_3), 52.91 (CH_2), 53.80 (CH_2), 80.07 (C), 154.61 (C), 173.48 (C), 209.65 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2973 (m), 2924 (m), 2842 (m), 1729 (s), 1715 (s), 1678 (s), 1423 (s), 1367 (m), 1338 (m), 1235 (m), 1167 (s), 1140 (s), 1115 (s) cm^{-1}. MS (CI, CH_4): *m*/*z* (%) = 312 (40) [M^+ + H], 284 (8), 256 (100), 254 (60), 238 (28), 210 (56), 152 (24), 57 (26). $C_{16}H_{25}NO_5$ (311.38): calcd. C 61.72, H 8.09, N 4.50; found C 61.73, H 8.17, N 4.46.

Methyl *trans*-3-(*tert*-Butoxycarbonyl)-8-hydroxy-3-azabicyclo[4.4.0]-decane-1-carboxylate (*rac*-5): R_f (PE/EA, 1:5) = 0.24. M.p. 88 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.11−1.23 (m, 2 H), 1.29−1.38 (m, 2 H), 1.42 (s, 9 H), 1.71−1.85 (m, 2 H), 1.92−1.96 (m, 1 H), 2.03−2.25 (m, 3 H), 2.36−2.45 (m, 1 H), 2.58−2.76 (m, 1 H), 3.60−3.70 (m, 4 H), 4.05−4.30 (m, 1 H), 4.40−4.53 (m, 1 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 28.04 (CH_2), 28.23 (CH_3), 32.14 (CH_2), 37.85 (CH_2), 42.26 (CH), 43.79 (CH_2), 47.30 (C), 51.38 (CH_3), 53.81 (CH_2), 70.24 (CH), 79.37 (C), 154.03 (C), 173.53 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2955 (m), 2925 (m), 2860 (m), 2359 (m), 1724 (s), 1691 (s), 1421 (s), 1366 (m), 1260 (m), 1159 (m) cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 313 (20) [M^+], 256 (74), 212 (56), 196 (76), 154 (36), 57 (100). $C_{16}H_{27}NO_5$ (313.39): calcd. C 61.32, H 8.68, N 4.47; found C 60.90, H 8.57, N 4.42.

Methyl *trans*-3-(*tert*-Butoxycarbonyl)-8,8-diethoxy-3-azabicyclo-[4.4.0]decane-1-carboxylate (*rac*-6): ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.15 (t, *J* = 7.1 Hz, 3 H), 1.20 (t, *J* = 7.0 Hz, 3 H), 1.25−1.34 (m, 3 H), 1.42 (s, 9 H), 1.55−1.64 (m, 1 H), 1.75−1.82 (m, 1 H), 1.91−2.00 (m, 3 H), 2.05−2.20 (m, 1 H), 2.39−2.56 (m, 1 H), 2.59−2.82 (m, 1 H), 3.37−3.44 (m, 2 H), 3.46−3.51 (m, 2 H), 3.65 (s, 3 H), 4.10−4.31 (m, 1 H), 4.35−4.56 (m, 1 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 15.88 (CH_3), 28.25 (CH_2), 28.71 (CH_3), 30.71 (CH_2), 37.06 (CH_2), 40.56 (CH), 44.26 (CH_2), 48.25 (C), 51.79 (CH_3), 54.15 (CH_2), 55.44 (CH_2), 55.52 (CH_2), 79.70 (C), 100.28 (C), 154.55 (C), 174.11 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2974 (m), 2930 (m), 2866 (m), 1728 (m), 1690 (s), 1424 (s), 1365 (m), 1240 (m), 1165 (s), 1137 (s), 1054 (s), 1011 (m) cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 385 (38) [M^+], 284 (56), 256 (48), 210 (44), 129 (100), 57 (78). $C_{20}H_{35}NO_6$ (385.50): calcd. C 62.31, H 9.15, N 3.63; found C 62.55, H 9.09, N 3.69.

Methyl (1*R*,6*S*)-3-(*tert*-Butoxycarbonyl)spiro[3-azabicyclo[4.4.0]-decane-8,2′-[1,3]dioxolane]-1-carboxylate (7): A solution of (1*R*,6*S*)-**4** (2.69 g, 8.64 mmol, 1.0 equiv.), absolute ethyleneglycol (2.145 g, 34.65 mmol, 1.93 mL, 4.0 equiv.), and pyridinium 4-toluenesulfonate (PPTS, 651 mg, 2.59 mmol, 0.3 equiv.) in benzene (12 mL) was heated at reflux in a Dean−Stark trap for 20 h. H_2O (15 mL) and CH_2Cl_2 (15 mL) were then added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was chromatographed (SiO_2; PE/EA, 2:1; R_f = 0.26) to give **7** (270 mg, 0.76 mmol, 84%) as a colorless oil. $[\alpha]_D^{20}$ = −13.2 (*c* = 0.58, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.25−1.36 (m, 1 H), 1.42 (s, 9 H), 1.44−1.46 (m, 1 H), 1.49 (dd, *J* = 14.2, *J* = 3.2 Hz, 1 H), 1.54 (dt, *J* = 13.2, *J* = 3.1 Hz, 1 H), 1.63−1.73 (m, 2 H), 1.96−2.20 (m, 3 H), 2.37−2.54 (m, 1 H), 2.60−2.80 (m, 1 H), 3.66 (s, 3 H), 3.90−3.98 (m, 4 H), 4.06−4.31 (m, 1 H), 4.40−4.56 (m, 1 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ = 27.94 (CH_2), 28.28 (CH_3), 31.17 (CH_2), 32.15 (CH_2), 37.91 (CH_2), 41.26 (CH), 43.69 (CH_2), 47.38 (C), 51.40 (CH_3), 53.70 (CH_2), 64.16 (CH_2), 64.31 (CH_2), 79.24 (C), 108.61 (C), 154.08 (C), 173.46 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2950 (m), 2929 (m), 2868 (m), 1729 (s), 1688 (vs), 1424 (s), 1364 (m), 1191 (m), 1141 (s), 1068 (m) cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 355 (24) [M^+], 298 (100), 254 (72), 210 (36), 196 (20), 99 (88), 57 (55). $C_{18}H_{29}NO_6$ (355.43): calcd. C 60.83, H 8.22, N 3.94; found C 60.81, H 8.14, N 3.91.

Reduction of the Ester *rac*-6: A solution of *rac*-**6** (516 mg, 1.34 mmol, 1.0 equiv.) in Et_2O (6 mL) was added dropwise to $LiAlH_4$ (152 mg, 4.02 mmol, 3.0 equiv.) in Et_2O (6 mL). After the mixture had been stirred at 23 °C for 16 h, the reaction was terminated with 0.1% KOH/H_2O solution and filtered. The filtrate was extracted with CH_2Cl_2 (3 × 80 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was chromatographed (SiO_2; PE/EA, 3:1) to give *rac*-**8** (350 mg, 0.98 mmol, 73%) as a colorless oil. Elution with MeOH gave *rac*-**9** (R_f = 0.13, 42 mg, 0.16 mmol, 12%) as a colorless solid.

***tert*-Butyl 8,8-Diethoxy-1-(hydroxymethyl)-3-azabicyclo[4.4.0]-decane-3-carboxylate (*rac*-8):** ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.99 (dt, *J* = 13.2, *J* = 4.0 Hz, 1 H), 1.16 (t, *J* = 7.1 Hz, 3 H), 1.19 (t, *J* = 7.1 Hz, 3 H), 1.22−1.27 (m, 2 H), 1.35−1.47 (m, 1 H), 1.47 (s, 9 H), 1.66−1.83 (m, 5 H), 1.92−1.99 (m, 1 H), 2.21 (d, *J* = 13.6 Hz, 1 H), 2.84 (t, *J* = 12.6 Hz, 1 H), 3.10−3.20 (m, 1 H), 3.36−3.46 (m, 2 H), 3.49 (dq, *J* = 7.1, *J* = 1.6 Hz, 2 H), 3.60 (t, *J* = 11.0 Hz, 1 H), 4.03−4.18 (m, 2 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 15.90 (CH_3), 15.96 (CH_3), 27.24 (CH_2), 27.89 (CH_2), 28.78 (CH_3), 29.27 (CH_2), 36.01 (CH_2), 39.44 (C), 40.30 (CH), 46.30 (CH_2), 51.79 (CH_2), 55.35 (CH_2), 55.46 (CH_2), 57.38 (CH_2), 80.59 (C), 100.46 (C), 156.72 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2972 (s), 2930 (s), 2873 (s), 1688 (s), 1661 (vs), 1428 (vs), 1364 (s), 1298 (m), 1238 (s), 1147 (vs), 1048 (vs) cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 357 (8) [M^+], 312 (50), 311 (49), 281 (20), 228 (35), 225 (44), 129 (100), 57 (44). $C_{19}H_{35}NO_5$ (357.49): calcd. C 63.84, H 9.87, N 3.92; found C 63.59, H 9.86, N 3.73.

8,8-Diethoxy-1-(hydroxymethyl)-3-methyl-3-azabicyclo[4.4.0]decane (*rac*-9): M.p. 88 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.10−1.21 (m, 2 H), 1.16 (t, *J* = 7.0 Hz, 3 H), 1.18 (t, *J* = 7.0 Hz, 3 H), 1.31−1.37 (m, 2 H), 1.43−1.49 (m, 1 H), 1.57 (t, *J* = 13.4 Hz, 1 H), 1.81−1.88 (m, 3 H), 1.95−2.04 (m, 1 H), 2.01 (d, *J* = 9.5 Hz, 1 H), 2.22 (s, 3 H), 2.89−2.91 (m, 2 H), 3.40 (q, *J* = 7.0 Hz, 2 H), 3.47−3.54 (m, 3 H), 4.18 (dd, *J* = 10.8, *J* = 2.5 Hz, 1 H), 6.60 (s, 1 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 15.89 (CH_3), 15.95 (CH_3), 29.18 (CH_2), 29.36 (CH_2), 32.38 (CH_2), 35.85 (CH_2),

 © 2004 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

36.75 (C), 39.33 (CH_3), 46.21 (CH), 55.34 (CH_2), 55.44 (CH_2), 56.49 (CH_2), 67.13 (CH_2), 67.74 (CH_2), 100.67 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3152 (br.), 2923 (s), 2856 (s), 2799 (s), 1440 (s), 1360 (m), 1251 (m), 1098 (s), 1045 (vs) cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 271 (24) [M^+], 242 (16), 226 (56), 196 (100), 166 (4), 58 (30). $C_{15}H_{29}NO_3$ (271.40): calcd. C 66.38, H 10.77, N 5.16; found C 66.17, H 10.71, N 4.99.

Reduction of (1*R*,6*S*)-7 to *tert*-Butyl (1*R*,6*S*)-1-(Hydroxymethyl)spiro[3-azabicyclo[4.4.0]decane-8,2′-[1,3]dioxolane]-3-carboxylate (10): A solution of (1*R*,6*S*)-**7** (3.280 g, 9.29 mmol, 1.0 equiv.) in Et_2O (20 mL) was added dropwise to $LiAlH_4$ (1.410 g, 37.15 mmol, 3.0 equiv.) in Et_2O (18 mL) in a Schlenk flask. After the mixture had been stirred at 23 °C for 16 h, 0.1% KOH/H_2O solution (15 mL) was added, and the reaction mixture was stirred for a further 20 min and filtered. The filtrate was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was chromatographed (SiO_2; PE/EA, 1:1; R_f = 0.21) to give **10** (2.667 g, 8.15 mmol, 88%) as a colorless solid. M.p. 109 °C. $[\alpha]_D^{20}$ = −3.4 (*c* = 0.50, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.09 (dt, *J* = 13.5, *J* = 4.4 Hz, 1 H), 1.25 (br. d, *J* = 13.1 Hz, 1 H), 1.39−1.47 (m, 3 H), 1.47 (s, 9 H), 1.68−1.71 (m, 1 H), 1.79−1.90 (m, 3 H), 2.21 (d, *J* = 13.4 Hz, 1 H), 2.84 (t, *J* = 12.3 Hz, 1 H), 3.15−3.27 (m, 1 H), 3.43 (d, *J* = 12.0 Hz, 1 H), 3.60 (d, *J* = 9.2 Hz, 1 H), 3.93−3.98 (m, 4 H), 4.05−4.16 (m, 2 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 27.32 (CH_2), 27.63 (CH_3), 30.53 (CH_2), 37.19 (CH_2), 38.77 (C), 41.06 (CH), 45.79 (CH_2), 51.27 (CH_2), 56.75 (CH_2), 64.22 (CH_2), 64.33 (CH_2), 80.21 (C), 108.85 (C), 156.32 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3440 (m), 2934 (m), 2885 (m), 2853 (m), 1657 (s), 1476 (m), 1421 (s), 1366 (m), 1307 (m), 1250 (m), 1234 (m), 1145 (m) cm^{-1}. MS (FAB, glycerol): *m*/*z* (%) = 328 (62) [M^+ + H], 272 (100), 228 (8), 182 (2), 166 (2). $C_{17}H_{29}NO_5$ (327.42): calcd. C 62.36, H 8.93, N 4.28; found C 62.43, H 8.87, N 4.23.

Reduction of *rac*-7 with $LiAlH_4$ (7 equiv.): A solution of *rac*-**7** (5.607 g, 15.78 mmol, 1.0 equiv.) in Et_2O (20 mL) was added dropwise to $LiAlH_4$ (4.191 g, 110.44 mmol, 7.0 equiv.) in Et_2O (15 mL) in a Schlenk flask. After the mixture had been stirred at 23 °C for 16 h, 0.1% KOH/H_2O solution (30 mL) was added, and the mixture was stirred for a further 20 min and filtered. The filtrate was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was chromatographed (SiO_2; PE/EA, 1:1; R_f = 0.21) to give *rac*-**10** (3.105 g, 9.48 mmol, 60%) as a colorless solid, m.p. 81 °C. Elution with MeOH gave *rac*-**11**.

1-(Hydroxymethyl)-3-methylspiro[3-azabicyclo[4.4.0]decane-8,2′-[1,3]dioxolane] (*rac*-11): Yield 580 mg, 2.40 mmol, 15% as a colorless solid. R_f(MeOH) = 0.07. M.p. 71 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.15−1.25 (m, 1 H), 1.32−1.37 (m, 2 H), 1.53−1.59 (m, 4 H), 1.72 (d, *J* = 13.5 Hz, 1 H), 1.82 (dd, *J* = 11.2, *J* = 2.1 Hz, 1 H), 1.97 (dq, *J* = 12.2, *J* = 3.4 Hz, 1 H), 1.99 (d, *J* = 9.2 Hz, 1 H), 2.23 (s, 3 H), 2.90 (d, *J* = 6.6 Hz, 1 H), 2.93 (d, *J* = 11.0 Hz, 1 H), 3.55 (d, *J* = 10.7 Hz, 1 H), 3.89−3.97 (m, 4 H), 4.16 (dd, *J* = 10.9, *J* = 2.2 Hz, 1 H), 6.39 (br. s, 1 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 29.41 (CH_2), 31.17 (CH_2), 33.29 (CH_2), 36.52 (C), 37.41 (CH_2), 40.46 (CH), 46.24 (CH_3), 56.36 (CH_2), 64.60 (CH_2), 64.72 (CH_2), 67.41 (CH_2), 67.94 (CH_2), 109.53 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3144 (br., m), 2939 (s), 2855 (s), 2798 (s), 1463 (m), 1445 (m), 1360 (m), 1282 (m), 1188 (m) cm^{-1}. MS (FAB, glycerol): *m*/*z* (%) = 242 (100) [M^+ + H], 210 (4), 196 (4), 122 (1). $C_{13}H_{23}NO_3$ (241.33): calcd. C 64.70, H 9.61, N 5.80; found C 64.62, H 9.18, N 5.70.

3-*tert*-Butyl (1*R*,6*S*)-1-Formylspiro[3-azabicyclo[4.4.0]decane-8,2′-[1,3]dioxolane]-3-carboxylate (3): Compound (1*R*,6*S*)-**10** (100 mg, 0.31 mmol, 1.0 equiv.), *N*-methylmorpholine *N*-oxide (NMO, 62 mg, 0.46 mmol, 1.5 equiv.), and molecular sieves (4 Å) in CH_2Cl_2 (1 mL) were stirred at 23 °C for 5 min. Tetrapropylammonium perruthenate (TPAP, 5 mg, 0.02 mmol, 0.05 equiv.) was then added, and the mixture was stirred at 23 °C for a further 30 min and finally filtered through SiO_2 (PE/EA, 2:1; R_f = 0.19) to give **3** (90 mg, 0.28 mmol, 90%) as a colorless solid, m.p. 90 °C. $[\alpha]_D^{20}$ = −16.8 (*c* = 0.29, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.43 (s, 10 H), 1.45−1.60 (m, 3 H), 1.69−1.74 (m, 1 H), 1.75−1.82 (m, 1 H), 1.83−1.88 (m, 1 H), 1.94 (dq, *J* = 13.4, *J* = 5.1 Hz, 1 H), 1.97−2.07 (m, 1 H), 2.38−2.57 (m, 1 H), 2.66−2.80 (m, 1 H), 3.94 (s, 4 H), 4.07−4.52 (m, 2 H), 9.56 (s, 1 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 27.77 (CH_2), 28.39 (CH_3), 31.51 (CH_2), 37.47 (CH_2), 39.78 (CH), 44.86 (CH_2), 50.12 (C), 51.55 (CH_2), 64.30 (CH_2), 64.41 (CH_2), 80.02 (C), 108.59 (C), 154.48 (C), 203.74 (CH) ppm. IR (KBr): $\tilde{\nu}$ = 2981 (m), 2924 (m), 2865 (m), 1714 (m), 1674 (s), 1465 (m), 1418 (s), 1364 (m), 1297 (m), 1263 (m), 1238 (s), 1164 (s), 1142 (s), 1112 (s), 1086 (s), 1070 (s), 1032 (m) cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 326 (25) [M^+ + H], 297 (92), 270 (100), 252 (54), 241 (100), 197 (21), 180 (11), 57 (17). $C_{17}H_{27}NO_5$ (325.40): calcd. C 62.75, H 8.36, N 4.30; found C 62.69, H 8.35, N 4.21.

Acknowledgments

The authors acknowledge the generous support from Aventis Pharma Deutschland GmbH and the Fonds der Chemischen Industrie.

[1] [1a] P. M. Weintraub, J. S. Sabol, J. M. Kane, D. R. Borcherding, *Tetrahedron* **2003**, *59*, 2953−2989. [1b] M. Eguchi, R. Y. W. Shen, J. P. Shea, M. S. Lee, M. Kahn, *J. Med. Chem.* **2002**, *45*, 1395−1398. [1c] J. R. Dimmock, M. P. Padmanilayam, R. N. Puthucode, A. J. Nazarali, N. L. Motaganahalli, G. A. Zello, J. W. Quail, E. O. Oloo, H.-B. Kraatz, J. S. Prisciak, T. M. Allen, C. L. Santos, J. Balzarini, E. De Clercq, E. K. Manavathu, *J. Med. Chem.* **2001**, *44*, 586−593. [1d] P. S. Watson, B. Jiang, B. Scott, *Org. Lett.* **2000**, *2*, 3679−3681. [1e] C. R. Ganellin, R. G. W. Spickett, *J. Med. Chem.* **1965**, *8*, 619−625.

[2] [2a] D. I. MaGee, M. L. Lee, A. Decken, *J. Org. Chem.* **1999**, *64*, 2549−2554. [2b] C. Simon, J.-F. Peyronel, J. Rodriguez, *Org. Lett.* **2001**, *3*, 2145−2148. [2c] C. Simon, F. Lieby-Muller, J.-F. Peyronel, T. Constantieux, J. Rodriguez, *Synlett* **2003**, 2301−2304.

[3] J. Christoffers, H. Scharl, *Eur. J. Org. Chem.* **2002**, 1505−1508.

[4] Reviews: [4a] I. Denissova, L. Barriault, *Tetrahedron* **2003**, *59*, 10105−10146. [4b] J. Christoffers, A. Baro, *Angew. Chem.* **2003**, *115*, 1726−1728; *Angew. Chem. Int. Ed.* **2003**, *42*, 1688−1690. [4c] J. Christoffers, A. Mann, *Angew. Chem.* **2001**, *113*, 4725−4732; *Angew. Chem. Int. Ed.* **2001**, *40*, 4591−4597. [4d] E. J. Corey, A. Guzman-Perez, *Angew. Chem.* **1998**, *110*, 402−415; *Angew. Chem. Int. Ed.* **1998**, *37*, 388−401. [4e] K. Fuji, *Chem. Rev.* **1993**, *93*, 2037−2066. [4f] S. F. Martin, *Tetrahedron* **1980**, *36*, 419−460.

[5] [5a] J. Christoffers, A. Mann, *Angew. Chem.* **2000**, *112*, 2871−2874; *Angew. Chem. Int. Ed.* **2000**, *39*, 2752−2754. [5b] J. Christoffers, A. Mann, *Chem. Eur. J.* **2001**, *7*, 1014−1027. [5c] J. Christoffers, B. Kreidler, H. Oertling, S. Unger, W. Frey, *Synlett* **2003**, 493−496. [5d] J. Christoffers, B. Kreidler, S. Unger, W. Frey, *Eur. J. Org. Chem.* **2003**, 2845−2853. [5e] J. Christoffers, K. Schuster, *Chirality* **2003**, *15*, 777−782. Review: [5f] J. Christoffers, *Chem. Eur. J.* **2003**, *9*, 4862−4867. Review on a

 © 2004 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

similar method: [5g] J. d′Angelo, D. Desmaële, F. Dumas, A. Guingant, *Tetrahedron: Asymmetry* **1992**, *3*, 459−505.

[6] [6a] A. G. Schultz, R. D. Lucci, J. J. Napier, H. Kinoshita, R. Ravichandran, P. Shannon, Y. K. Yee, *J. Org. Chem.* **1985**, *50*, 217−231. [6b] T. A. Crabb, J. R. Wilkinson, *J. Chem. Soc., Perkin Trans. 1* **1977**, 953−959. [6c] T. A. Crabb, J. R. Wilkinson, *J. Chem. Soc., Perkin Trans. 1* **1976**, 644−651.

[7] M. M. Barth, J. L. Binet, D. M. Thomas, D. C. de Fornel, S. Samreth, F. J. Schuber, P. P. Renaut, *J. Med. Chem.* **1996**, *39*, 2302−2312.

[8] CCDC-229854 (**4**), -229853 (**10**), and -229855 (**11**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

[9] R. Sterzycki, *Synthesis* **1979**, 724−725.

[10] B. Karimi, B. Golshani, *Synthesis* **2002**, 784−788.

[11] S. V. Ley, J. Norman, W. P. Griffith, S. P. Marsden, *Synthesis* **1994**, 639−666.

Received January 29, 2004

 © 2004 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim