Synthesis of (1*R*,4*R*)- and (1*S*,4*S*)-2,5-Diazabicyclo[2.2.1]heptanes and Their *N*-Substituted Derivatives

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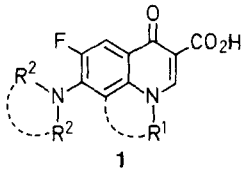
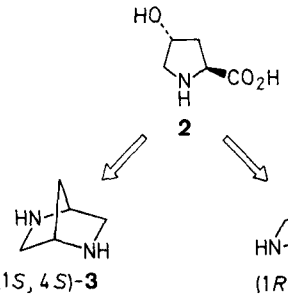
Derivatives of the (1*R*,4*R*)- and (1*S*,4*S*)-2,5-diazabicyclo-[2.2.1]heptane ring system are prepared in enantiomerically pure form from *trans*-4-hydroxy-L-proline (**2**). The target compounds are precursors of antibacterial quinolone carboxyclic acids.

Among the quinolone antibacterial agents[1] chiral compounds have been the subject of several studies.[2-6] In the course of investigations on the antimicrobial activity of chiral 6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acids (**1**), we required both enantiomers **3** and **4** of 2,5-diazabicyclo[2.2.1]heptane and report here their synthesis from *trans*-4-hydroxy-L-proline (**2**).



1

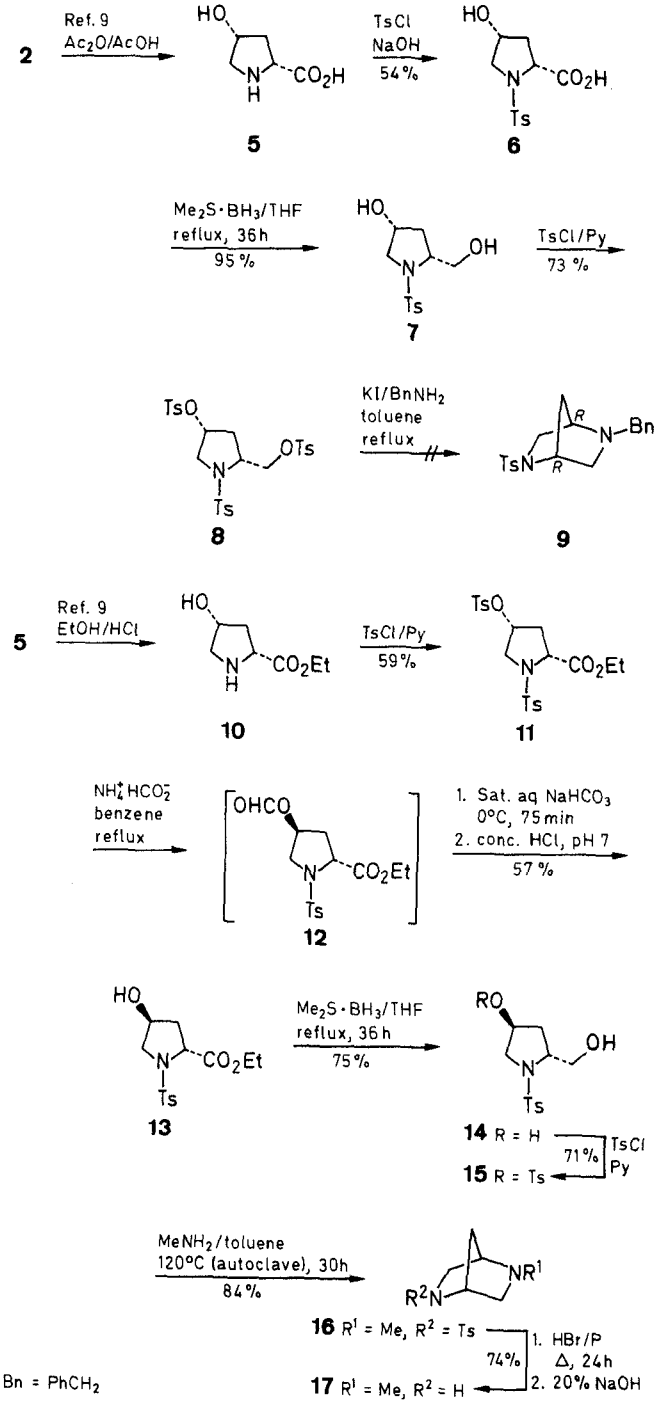


2

(1*S*,4*S*)-**3** (1*R*,4*R*)-**4**

For the synthesis of the 1*R*,4*R*-enantiomer **4**, we initially assumed that it would be sufficient to invert the configuration on carbon 2 of **2** and force the cyclization of the *cis*-tritosyl derivative **8**. However, the desired (1*R*,4*R*)-2,5-diazabicyclo[2.2.1]heptane derivative **9** could not be obtained by refluxing a toluene solution containing **8** with 3 equivalents of benzylamine. Following the suggestion of a reviewer we tried to achieve the *in situ* inversion of carbon 4 by addition of potassium iodide to the reaction mixture and were able to show the formation of **9** from **8** among a series of side products by TLC; however, this pathway proved not to be synthetically useful. Therefore, we decided to prepare the tritosyl *trans*-4-hydroxy-D-prolinol derivative **15**, since the cyclization of its enantiomer *ent*-**15** to (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptane has been reported.[7,8] Thus, **2** was epimerized to **5** according to Stille and coworkers.[9] The purity of **5** was confirmed by TLC on chiral TLC plates, where **2** and **5** could be separated. Tetraethylammonium formate[10] was used to displace the tosyloxy group of **11** to give, upon hydrolysis of the formate **12**, the hydroxy ester **13**. After completion of our work the conversion of **11** to the *N*-tosyl-*O*-acetyl-*trans*-4-hydroxy-D-proline by displacement of the tosylate group with tetraethylammonium acetate was reported by one group to be unsuccessful,[18] by another to proceed in 72% yield.[19]

With both chiral centers of the starting material **2** being inverted, the following steps towards **17** proceeded in analogy to the steps for the synthesis of the 1*S*,4*S*-enantiomer (Scheme A).



Scheme A

We optimized first the known synthesis of (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptanes. Thus, **2** was tosylated at pH 7.5–8 with a yield of 87–93%. Without this precau-

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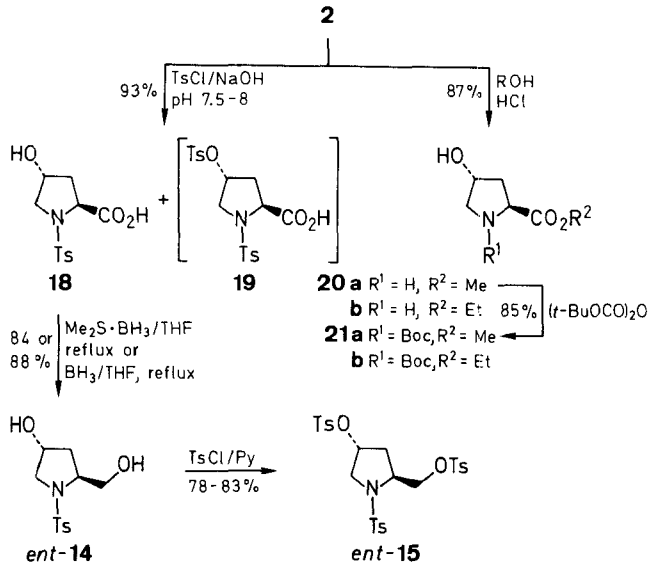
tion[7] the yield dropped to 53–56% on larger scales, as more of the ditosylated product **19** was formed (Scheme **B**). The esterification of **2** to **20b**, followed by protection with *tert*-butoxycarbonylazide to **21b** and reduction with lithium borohydride to **23** has been reported.[9] Furthermore, 4-hydroxy-*N*-tosyl-L-prolinol (*ent*-**14**) has been prepared[7] by esterification of **18** with diazomethane followed by reduction with lithium borohydride. Attempts to reduce the ester with lithium aluminum hydride failed to provide *ent*-**14** in synthetically useful amounts.[7]

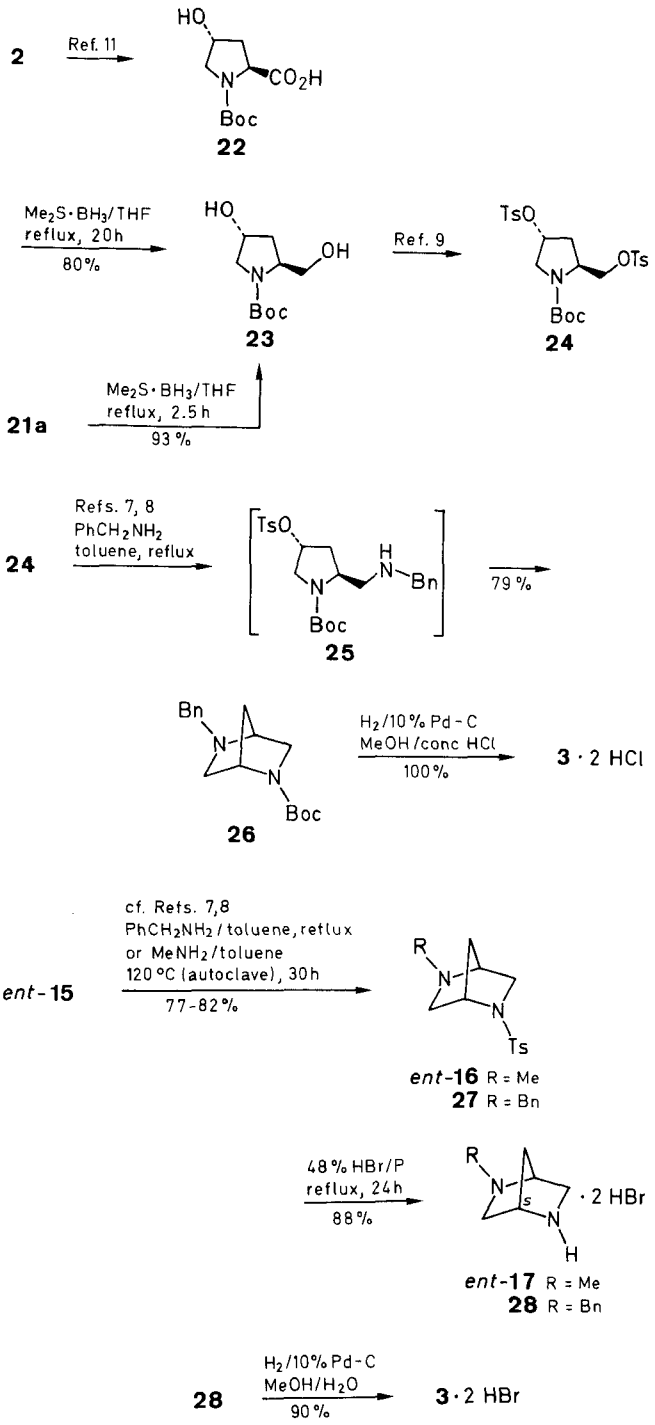
In our hands it proved to be advantageous to convert **2** to **22**[11] and reduce this hydroxy acid with dimethyl sulfide–borane or tetrahydrofuran–borane to the diol **23**. Alternatively, **2** was converted into the protected methyl ester **21a** via **20a** and reduced with dimethyl sulfide–borane complex to **23**.[9] The same reducing agents were used to prepare the tosylated diol *ent*-**14** (Schemes **B** and **C**).



Scheme **B**

Tosylation of the diols *ent*-**14** and **23** gave the known intermediates *ent*-**15**[7,8] and **24**,[9] respectively, which could be cyclized via **25**[7] to the desired diazanorbonanes *ent*-**16** and **27** (from *ent*-**15**) and **26** (from **24**). For the detosylation of *ent*-**16** or **27** hydrobromic acid, phosphorus and acetic acid was used (Scheme **C**). This procedure (instead of hydroiodic acid[7,8]) bears the additional advantage that the benzyl group of **28** can be removed hydrogenolytically from the hydrobromide without the need to convert the hydroiodide into the hydrochloride by treatment with (expensive) silver chloride.[7]

The use of *tert*-butoxycarbonyl (Boc) as protecting group additionally reduces the number of steps to prepare **3** from **2**, as both the protecting groups are removed during catalytic hydrogenation of **26**. Table 1 summarizes the optical rotations of enantiomeric pairs.



Scheme **C**

Support for the optical purity of **17** and *ent*-**17** was obtained from ^{1}H-NMR analysis using the chiral shift reagent tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato], europium(III) derivative (Eu(tfc)$_3$). In an ^{1}H-NMR spectrum of a mixture of 30 mg of (1*S*,4*S*)-isomer *ent*-**17** and 25 mg of Eu(tfc)$_3$ the C-4 proton was shifted, as a broad singlet, from $\delta = 3.43$ to 5.47 (Figure, spectrum B). Addition of 5 mg of 1*R*,4*R*-isomer **17** to the same sample gave a singlet at $\delta = 5.12$ for the C-4 proton of **17** (Figure, spectrum C). Further addition of 5-mg of Eu(tfc)$_3$ and 10 mg **17** proved that the C-4 proton of **17** appeared at a lower chemical shift compared to C-4 proton of *ent*-**17** (Figure, spectrum D). In a separate

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experiment, an ^{1}H-NMR of a solution of 30 mg of pure 1*R*,4*R*-isomer **17** and 30 mg of Eu(tfc)$_3$ gave a broad singlet for C-4 proton of **17** at $\delta = 5.76$ (Figure, spectrum E). Since the ^{1}H-NMR spectra B, E and F (Figure) of *ent*-**17** or **17** did not show any visible contamination by the other enantiomer, compounds *ent*-**17** and **17** were considered to be optically pure.

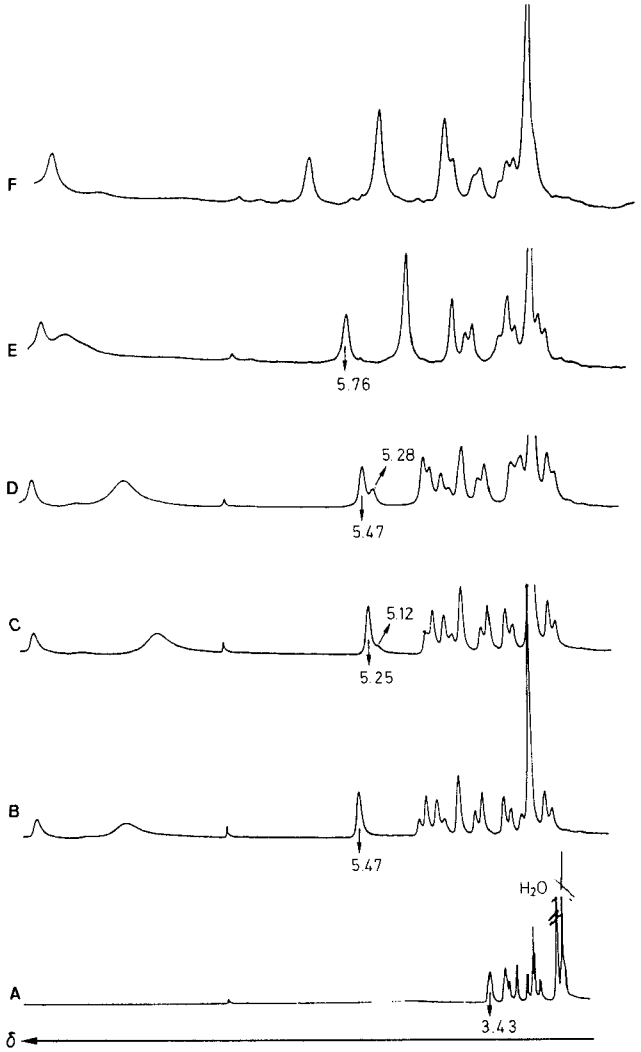


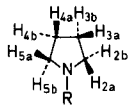
Figure. ^{1}H-NMR spectra of **17** and *ent*-**17** in the presence of Eu(tfc)$_3$

^{1}H-NMR data for 2,5-diazabicyclo[2.2.1]heptane derivatives are listed in Table 3. The chemical shifts and the coupling constants were deducted from spin decoupling experiments and confirmed by assignment of similar bridged compounds.

The synthetic route discussed in this communication appears to be generally useful for the preparation of enantiomeric pairs or norbornane structures of known absolute configuration, in which heteroatoms are part of the bicyclic structure and are located at the 2- and/or 5-position.[12]

While working on the revised manuscript Braish[19] published the preparation of **17** and *ent*-**17** via the tosylates **15** and *ent*-**15** using a very similar approach as described here.

Melting points were obtained on Kofler melting point apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL FX90Q (90 MHz) or Brucker WM 250 (250 MHz) spectrometers with TMS as the internal standard. Optical rotations at the Na-D line were measured using a Perkin-Elmer 241 polarimeter. Elemental analysis were determined by Dr. J. Zak at the Microanalytical Laboratory of the Institute of Physical Chemistry, University of Vienna. TLC was performed with Merck TLC plates (alumina and Kieselgel 60 F_{254}) and compound visualization was effected with a 5% solution of molybdatophosphoric acid in EtOH, or a 0.25% solution of ninhydrin in BuOH. For flash chromatography Merck silica gel 60 (0.04–0.63 mm, Art No. 9385) was used. Tosyl chloride was purified as described.[14,15] Numbering of protons in proline derivatives is as follows:



The analytical and spectral data of compounds prepared are assembled in Table 4.

cis-4-Hydroxy-D-proline hydrochloride **(5)** and its corresponding ethyl ester **(10)** were prepared according to literature and the purity checked[9] by TLC on chiral plates (Macherey–Nagel) using $CH_3CN/MeOH/H_2O$ (4:1:1). $[\alpha]_D^{20}$ for **10**, +28.5° (c = 2, H_2O) (Lit.[9] not reported). *trans*-N-(*tert*-Butoxycarbonyl)-4-hydroxy-L-proline **(22)**,[11] (2*R*,4*S*)-*N*-(*tert*-Butoxycarbonyl)-4-tosyloxy-2-tosyloxymethylpyrrolidine **(24)**,[9] and (1*S*,4*S*)-5-benzyl-2-tosyl-2,5-diazabicyclo[2.2.1]heptane **(27)**[7,8] were prepared as reported.

***cis*-4-Hydroxy-*N*-tosyl-D-proline (6):**

To a mechanically stirred solution of **5** (20 g, 0.12 mol) in 2N NaOH is added tosyl chloride (28 g, 0.147 mol). After stirring at r.t. for 3 h, the mixture is extracted with CH_2Cl_2 (6 × 40 mL). The combined extracts are dried (Na_2SO_4) and evaporated *in vacuo* at r.t. The residue is dissolved in water, acidified with conc HCl and the white precipitate collected by filtration, dried and recrystallized from a small amount of MeOH to give **6**; yield: 18.7 g (54%).

***cis*-4-Hydroxy-*N*-tosyl-D-prolinol [(2*R*,4*R*)-4-Hydroxy-*N*-tosyl-2-pyrrolidinemethanol, 7]:**

To a solution of **6** (18 g, 0.0632 mol) in anhydrous THF (100 mL) is added dropwise a solution of $Me_2S \cdot BH_3$ (25 mL, 0.329 mol) in anhydrous dry THF (100 mL). The mixture is refluxed for 36 h,

Table 1. Optical Rotations of Enantiomeric Pairs

D-Series	$[\alpha]_D^{20}$	L-Series	$[\alpha]_D^{20}$	(*c*, solvent)
14	+46.8	*ent*-**14**	−46.6	1.86, EtOH
15	+55.8	*ent*-**15**	−55.06[a]	1.92, acetone
16	−8.5	*ent*-**16**	+8.7	1.96, 1 N HCl
17	−10.95	*ent*-**17**	+11.08	7.50, H_2O

[a] Lit.[7] $[\alpha]_D^{23}$ −52.5° (1.92, acetone).

Table 2. Compositions of Ingredients (in mg) Present in the Spectra in the Figure

Spectrum	1*S*,4*S*-Isomer *ent*-**17**	Eu(tfc)$_3$	1*R*,4*R*-Isomer **17**
A	30	–	–
B	30	25	–
C	30	25	5
D	30	30	15
E	–	30	30
F	–	30	35

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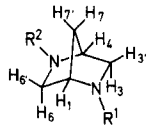
Table 3. ^{1}H-NMR-Data for 2,5-Diazabicyclo[2.2.1]heptane Derivatives [$CDCl_3$, δ, J(Hz)][a,b]

Compound	H-1	H-3	H-3′	H-4	H-6	H-6′	H-7	H-7′
16, *ent*-**16**	3.09 (m)	2.44 (dd)	2.66 (dd)	3.95 (m)	3.31 (dd)	2.81 (dd)	1.54 (dm)	1.05 (dm)
17, *ent*-**17**	3.04 (m)	2.26 (dd)	2.65 (dd)	3.24 (m)	2.94 (dd)	2.58 (dd)	1.67 (dm)	1.42 (dm)
26	3.37 (br)	2.46 (d)	2.81 (dd)	4.08 (br)	3.40 (d)	3.02 (dd)	1.78 (d)	1.59 (dd)
27	3.33 (m)	2.59 (d)	2.82 (dd)	4.19 (m)	3.55 (d)	2.98 (dd)	1.66 (dm)	1.09 (dm)
28	3.35 (br)	2.29 (d)	2.79 (dd)	3.19 (br)	3.07 (d)	2.67 (dd)	1.74 (d)	1.44 (d)

	$J_{1,6'}$	$J_{1,7}$	$J_{1,7'}$	$J_{3,3'}$	$J_{3',4}$	$J_{4,7}$	$J_{4,7'}$	$J_{3,7'}$	$J_{6,7}$	$J_{7,7'}$	Others
16, *ent*-**16**	2.5	≈1	≈1	9	2.5	< 1	< 1	< 1	1.5	9.5	2.16 (NCH_3), 2.27 ($ArCH_3$), 7.17, 7.58 (Ar)
17, *ent*-**17**	2	≈1	≈1	9	2	1	1	≈1	≈1	10	2.21 (NCH_3)
26	≈2	n.o.	n.o.	9	≈2	n.o.	n.o.	n.o.	n.o.	10	1.43 (t-C_4H_9), 3.58 ($PhCH_2$), 7.04 (C_6H_5)
27	2.5	≈1	≈1	9.5	2.5	< 1	< 1	n.o.	n.o.	10	2.40 ($ArCH_3$), 3.58 ($PhCH_2$), 7.17, 7.58 (Ar)
28	2.5	n.o.	n.o.	9	2.5	n.o.	n.o.	n.o.	n.o.	10	3.57 ($PhCH_2$), 7.04 (C_6H_5)

[a] 

[b] n.o. = Not observed.

Table 4. Analytical and Spectral Data of Compounds Prepared

Product	Yield (%)	mp (°C)	$[\alpha]_D^{20}$ (c, solvent)	Molecular Formula[a] or Lit. Data	^{1}H-NMR[b,c] δ, J (CH_2)
3 · 2 HBr	90	272–280	+40 (1.17, H_2O)	mp 272–278 °C[7] $[\alpha]_D^{23}$ + 41 (c = 1.17, H_2O)[7]	2.32 (s, 2H, H-7), 3.63 (dd, 4H, CH_2N), 4.78 (br s, 2H, H-1, 4)
6	54	183–185	+26.5 (1, EtOH)	$C_{12}H_{15}NO_5S \cdot H_2O$ (303.3)	1.94 (m, 2H, H-3a, 3b), 2.35 (s, 3H, CH_3), 3.08 (d, 1H, H-5b, J = 10), 3.47 (dd, 1H, H-5a, J = 4.3, 10), 4.04 (dd, 1H, H-2a, J = 8,8), 4.22 (m, 1H, H-4a), 4.89 (br, 1H, OH), 7.38 (d, 2H_{arom}, J = 8), 7.66 (d, 2H_{arom}), J = 8), 12.50 (br, 1H, CO_2H)
7	95	76–79	+11.56 (1.6, MeOH)	$C_{12}H_{17}NO_4S$ (271.3)	1.49 (m, 1H, H-3a), 1.95 (m, 1H, H-3b), 2.40 (s, 3H, CH_3), 2.92 (dd, 1H), 3.41 (br, 2H), 3.57 (m, 2H), 4.22 (m, 1H), 4.79 (m, 2H), 7.38 (d, 2H_{arom}, J = 8), 7.68 (d, 2H_{arom}, J = 8)
8	73	152–153	+104.5 (2, acetone)	$C_{26}H_{29}NO_3S_3$ (579.9)	1.46 (m, 1H, H-3b), 1.86 (m, 1H, H-3a), 2.10 (m, 1H), 2.50 (s, 6H, CH_3), 2.55 (s, 3H, CH_3), 2.98 (m, 1H), 3.55–3.58 (m, 3H), 4.35 (m, 1H), 7.39–7.68 (12H_{arom})
11	58	122–124	+30.5 (1, acetone)	$C_{21}H_{25}NO_7S_2$ (383.5)	1.21 (t, 3H, CH_2CH_3, J = 7), 2.21 (m, 2H, H-3a, 3b), 2.30 (s, 6H, $ArCH_3$), 3.36 (dd, 1H, H-5a, J = 3, 12), 3.68 (dd, 1H, H-5b, J = 5, 12), 4.00 (q, 2H, CH_2CH_3, J = 7), 4.42 (dd, 1H, H-2a, J = 4, 8), 4.86 (m, 1H, H-4a), 7.17 (d, 4H_{arom}, J = 8), 7.50 (d, 2H_{arom}, J = 8), 7.60 (d, 2H_{arom}, J = 8)
13	57	oil	+126 (1, MeOH)	$C_{14}H_{19}NO_5S$ (313.8)	1.28 (t, 3H, CH_2CH_3, J = 7), 2.08 (ddd, 1H, H-3a, J = 5, 8, 14), 2.19 (m, 1H, H-3b), 2.41 (s, 3H, $ArCH_3$), 2.54 (s, 1H, OH), 3.33 (d, 1H, H-5a, J = 11), 3.55 (dd, 1H, H-5b, J = 3, 7, 11), 4.13 (q, 2H, CH_2CH_3, J = 7), 4.31 (dd, 1H, H-2a, J = 7,7), 4.39 (m, 1H, H-4b), 7.21 (d, 2H_{arom}, J = 8), 7.64 (d, 2H_{arom}, J = 8)
14	75	131–132	+46.8 (1.86, EtOH)[d]	$C_{12}H_{17}NO_4S$ (271.3)	1.49 (m, 1H, H-3a), 1.95 (m, 1H, H-3b), 2.40 (s, 3H, CH_3), 3.41 (br, 1H), 3.34 (m, 2H), 3.57 (m, 2H), 4.22 (m, 1H, H-4a), 7.38 (d, 2H_{arom}, J = 8), 7.68 (d, 2H_{arom}, J = 8)
ent-**14**	77–84[e] 88[f]	127–131 130–131	−46.6 (1.86, EtOH)	mp 131–133 °C[7] $[\alpha]_D^{23}$ − 42.8° (c = 1.96, EtOH)[7]	1.87 (m, 2H, H-3a, 3b), 2.38 (s, 3H, CH_3), 3.25 (m, 1H, H-5a or H-5b), 3.51–3.87 (m, 3H, CH_2O + H-5a or H-5b), 4.22 (m, 1H, H-4a), 7.16 (d, 2H_{arom}, J = 8), 7.61 (d, 2H_{arom}, J = 8)
15	71	130–132	+53.8 (1.92, acetone)[g]	$C_{26}H_{29}NO_8S_3$ (579.7)	2.07 (m, 2H, H-3a, 3b), 2.44 (s, 6H, 2 × $ArCH_3$), 2.45 (s, 3H, $ArCH_3$), 3.51 (m, 2H, CH_2O), 3.82 (m, 1H, H-4a), 4.13 (dd, 1H, H-5a, $J_{4a,5a}$ = 6, $J_{5a,5b}$ = 10), 4.32 (dd, 1H, H-5b, $J_{4a,5b}$ = 3, $J_{5a,5b}$ = 10), 4.76 (m, 1H, H-2b, J_{2a,CH_2O} = 3, $J_{2a,3ab}$ = 4), 7.39–7.68 (m, 12H_{arom})

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Table 4. (continued)

Product	Yield (%)	mp (°C)	$[\alpha]_D^{20}$ (*c*, solvent)	Molecular Formula[a] or Lit. Data	^{1}H-NMR[b,c] δ, *J* (CH_2)
16	84	96–98	−8.5 (1.96, 1N HCl)	$C_{13}H_{16}N_2O_2S \cdot \frac{1}{6}H_2O$ (272.4)	1.08, 1.76 (2d, 1H each, $J = 11.5$), 2.37 (s, $ArCH_3$), 2.53–3.65 (m, 6H, CH_2N + CHN), 3.61 (s, 3H, NCH_3), 7.17, 7.58 (2d, 2H each, $J = 8$)
ent-**16**	84	96–98	+8.7 (1.96, 1N HCl)	$C_{13}H_{16}N_2O_2S$ (272.4)	–
17 · 2HBr	74	220–225	−10.95 (7.5, H_2O)	$C_6H_{12}N_2 \cdot 2HBr$ (274.0)	–
ent-**17** · 2HBr	74	220–225	+11.08 (7.5, H_2O)	$C_6H_{12}N_2 \cdot 2HBr$ (274.0)	–
18	87–93	153–155	−105 (2, EtOH)	mp 153–155 °C[7] $[\alpha]_D^{23}$ − 105.4° (*c* = 2, EtOH)[7]	1.97 (m, 2H, H-3a, 3b), 2.35 (s, 3H, CH_3), 3.10 (d, 1H, H-5b, $J = 10$), 3.46 (dd, 1H, H-5a, $J = 4, 10$), 4.06 (dd, 1H, H-2a, $J = 8, 8$), 4.22 (m, 1H, H-4a), 4.87 (br, 1H, OH), 7.38 (d, $2H_{arom}$, $J = 8$), 7.66 (d, $2H_{arom}$, $J = 8$), 12.5 (br, 1H, CO_2H)
20a	87	156–160	−30 (2, H_2O)	$C_6H_{11}NO_3$ (145.2)	2.15–2.55 (m, 2H, H-3a, 3b), 3.48 (m, 2H, H-5a, 5b), 3.85 (br, 4H, OCH_3 + H-4a), 4.60 (m, 1H, H-2b)
21a	75–84	130–132/ 0.05	−50 (1.56, EtOH)	$C_{11}H_{19}NO_5$ (245.3)	1.45 (s, 9H, *t*-C_4H_9), 1.80–2.40 (m, 2H, H-3a, 3b), 3.40–3.60 (m, 2H, H-5a, 5b)
23	93[h] 80[i]	oil	–	oil[9]	1.10–2.00 (m, 2H, H-3a, 3b), 1.48 (s, 9H, *t*-C_4H_9), 3.30–4.20 (m, 6H, CH_2OH + H-2b, 4a, 5a, 5b), 4.40 (br, 2H, OH)
26	79	52–57	+8.92 (1.02, MeOH)	$C_{17}H_{24}N_2O_2 \cdot \frac{1}{2}H_2O$ (297.4)	–
28 · 2HBr	88	260	+6.1 (3, H_2O)	$C_{12}H_{16}N_2 \cdot 2HBr$ (350.3)	–

[a] Satisfactory microanalyses obtained: C ± 0.38, H ± 0.3, N ± 0.24.

[b] Solvents: D_2O for **3** · 2HCl (250 MHz), **20a** (90 MHz); $CDCl_3$ for **8**, **13**, **16** (250 MHz), **11**, **15**, **23** 90 MHz and 21a (60 MHz); $CDCl_3/D_2O$ for **14** (250 MHz); $CDCl_3$/DMSO-d_6/H_2O for *ent*-**14**; DMSO-d_6 for **6**, **7**, **18** (250 MHz).

[c] ^{13}C-NMR:
3 · 2HCl (D_2O): δ = 57.47 (C-7), 59.89 (C-3, 5), 76.63 (C-1, 4).
5 ($CDCl_3$): δ = 37.90 (C-3), 53.76 (C-5), 58.34 (C-2), 68.92 (C-4), 171.03 (C=O).
20a (D_2O): δ = 37.49 (C-3), 54.34 (C-5 or $CO_2\underline{C}H_3$), 59.11 (C-2), 70.05 (C-4), 170.66 (C=O).
23 ($CDCl_3$): δ = 28.40 (*t*-C_4H_9), 37.24 (C-3), 54.98 (C-5), 55.45 (C-2), 65.91 (CH_2OH), 68.66 (C-4), 80.23 (*t*-$C_4H_9\underline{C}$), 154.84 (C=O).
26 ($CDCl_3$): δ = 28.3 (*t*-C_4H_9), 35.2 (C-7), 46.4 (C-6), 57.4 (C-4), 58.0 ($Ph\underline{C}H_2$), 59.8 (C-1 or C-3), 60.5 (C-1 or C-3), 78.9 (*t*-$C_4H_9\underline{C}$), 126.6, 128.0, 128.1, 139.4 (C_{arom}), 154.0 (C=O).
28 ($CDCl_3$): δ = 34.95 (C-7), 47.68 (C-6), 56.40 (C-4), 57.8 ($Ph\underline{C}H_2$), 60.1 (C-1 or C-3), 62.0 (C-1 or C-3), 126.1, 127.5, 127.8, 139.2 (C_{arom}).

[d] Temp.: 23 °C.

[e] Yield from the reduction of **22** with $Me_2S \cdot BH_3$.

[f] Yield from the reduction of **22** with THF · BH_3.

[g] Temp.: 29 °C.

[h] Yield from **21a**.

[i] Yield from **22**.

cooled and anhydrous MeOH is added dropwise. After evaporation of the solvent under reduced pressure, the residue is dissolved in anhydrous MeOH (100 mL), reevaporated, and triturated with warm petroleum ether (bp 40–60 °C) to afford **7** as colorless crystals; yield: 16.26 g (95%).

(2*R*,4*R*)- and (2*R*,4*S*)-*N*-Tosyl-4-tosyloxy-2-tosyloxymethylpyrrolidine (8 and 15):
To a stirred solution of **7** or *ent*-**14** (0.061 mol) in anhydrous pyridine (50 mL) at −5 °C is added solid tosyl chloride (34.66 g, 0.182 mol). The mixture is stored in the refrigerator for 3 d and then poured onto ice/2N HCl (300 mL). The precipitated yellow solid is filtered, washed with water, and recrystallized from methanol.

Ethyl (2*R*,4*R*)-*N*-Tosyl-4-tosyloxy-2-pyrrolidinecarboxylate (11):
To a stirred solution of **10** (30 g, 0.153 mol) in anhydrous pyridine (500 mL) at −5 °C is added tosyl chloride (87.7 g, 0.46 mol). The mixture is stored in the refrigerator for 5 d and then poured onto ice (1 kg) and 2N HCl (1 L). The precipitated solid is filtered, washed with water, dried and recrystllized from EtOH; yield: 42.1 g (58%).

Ethyl (2*R*,4*S*)-4-Hydroxy-*N*-tosyl-2-pyrrolidinecarboxylate (13):
Tetraethylammonium hydroxide (30 mL, 20%) is neutralized in the presence of phenolphthalein indicator with 98–100% HCO_2H. After removal of the water by rotary evaporation, the residue is dried azeotropically by refluxing overnight with benzene. To this crude tetraethylammonium formate in benzene, ditosylate **11** (2.0 g, 4.28 mmol) is added and refluxed for 3 h. After cooling to r.t., the crystalline tetraethylammonium tosylate is filtered and the solvent evaporated. The resulting oil is dissolved in MeOH (200 mL), sat. aq $NaHCO_3$ solution (200 mL) added at 0 °C, and stirred for 75 min. The pH is adjusted to 7 by dropwise addition of conc HCl at 0 °C. After concentrating to one half of the volume by rotary evaporation, the residue is extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts are dried (Na_2SO_4), filtered, evaporated to dryness and the crude yellow oil purified by chromatography (eluent: CH_2Cl_2/MeOH, 98:2) to give **13** as a thick pale yellow oil; yield: 0.77 g (57%).

(2*S*,4*R*)-4-Hydroxy-*N*-tosyl-2-pyrrolidinemethanol (14 and *ent*-14):
Method A: To a solution of $Me_2S \cdot BH_3$ (50 mL, 0.52 mol) in anhydrous THF (~ 300 mL) is added a solution of **22** (62.14 g, 0.218 mol) in anhydrous THF (300 mL) over a period of 30 min. The reaction becomes exothermic and a gelatinous precipitate is formed within a short-time. After refluxing for 48 h with mechanical stirring in the presence of glass beads excess $Me_2S \cdot BH_3$ is destroyed by dropwise addition of anhydrous MeOH (50 mL). The

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solvent is evaporated to dryness, the residue is dissolved in anhydrous MeOH, re-evaporated to dryness, and recrystallized from a small amount of EtOAc.

Method B: To a mechanically stirred solution of BH_3 in THF (0.7 M, 250 mL, 175 mmol) is added dropwise a solution of **22** (27 g, 96 mmol) in anhydrous THF (300 mL). The mixture is refluxed for 10 h under N_2 and the excess BH_3 is destroyed by dropwise addition of anhydrous MeOH (50 mL). Removal of solvent and trituration of the residue with petroleum ether (bp 30–60 °C) gives crystalline product, which is filtered and recrystallized from EtOAc.

(1*R*,4*R*)- and (1*S*,4*S*)-5-Methyl-2-tosyl-2,5-diazabicyclo[2.2.1]-heptane (16 and *ent*-16):
A solution of **15** or *ent*-**15** (20.7 mmol) and dry $MeNH_2$ (1.92 g, 4 equiv.) in toluene (50 mL) is heated in an autoclave for 30 h at 120 °C. After cooling, the filtrate from the reaction mixture is washed with 4N NaOH and water, dried (Na_2SO_4), and *evaporated* to dryness to give the crystalline product.

Detosylation with 48% Hydrobromic Acid and Red Phosphorus, Preparation of (1*R*,4*R*)- and (1*S*,4*S*)-2-Methyl-2,5-diazabicyclo-[2.2.1]heptanes (17 and *ent*-17), and (1*S*,4*S*)-2-Benzyl-2,5-diazabicyclo[2.2.1]heptane (28); General Procedure:
A mixture of **16**, *ent*-**16** or **27** (66.3 mmol), red P (7.5 g), 48% aq HBr (200-mL), and water (40 mL) is heated under reflux for 24 h. The hot reaction mixture is filtered and the filtrate evaporated to dryness. The residual solid is triturated with Et_2O (100 mL) and MeOH (50 mL), filtered and dried *in vacuo* to give the dihydrobromides.

The corresponding free bases **17**, *ent*-**17** and **28** are obtained by continous extraction of a solution of the dihydrobromides in 20% NaOH with Et_2O followed by distillation.

17: bp 44–54 °C/10 Torr; *ent*-**17**: bp 45–52 °C/torr.

***trans*-4-Hydroxy-*N*-tosyl-L-proline [(2*S*,4*R*)-4-Hydroxy-*N*-tosyl-2-pyrrolidinecarboxylic Acid, 18]:**
Tosyl chloride (200 g, 1.05 mol) is added with stirring to a solution of **2** (131.0 g, 1 mol) in 2N NaOH (2 L) and the pH maintained at 7.5–8 by addition of 2N NaOH. After stirring for 4 h conc HCl is added till pH becomes 3, the precipitate filtered and recrystallized from MeOH; yield: 248–265 g (87–93%).

Methyl (2*S*,4*R*)-4-Hydroxy-2-pyrrolidinecarboxylate Hydrochloride Salt (20a):
A slurry of *trans*-4-hydroxy-L-proline (**2**; 131 g, 1 mol) in anhydrous MeOH (1 L) is treated with dry HCl until homogeneous. MeOH is evaporated and the residue triturated with Et_2O to give the solid product; yield: 158 g (87%).

Methyl (2*S*,4*R*)-*N*-*tert*-Butoxycarbonyl-4-hydroxy-2-pyrrolidinecarboxylate (21a):
A stirred mixture of **20a** (240 g, 132.8 mol), *tert*-butoxycarbonyl azide (21.0 mL, 151 mol), Et_3N (33 mL, 237 mol), water (155 mL) and *p*-dioxane (150 mL) is heated under N_2 at 50 °C for 15 h. The mixture is reduced in volume by half on a rotary evaporator and extracted with Et_2O (4 × 50 mL). The combined extracts are washed with brine, dried (Na_2SO_4), concentrated under reduced pressure, and distilled, using a Kugelrohr apparatus; yield: 23–27 g (75–84%).

(2*S*,4*R*)-*N*-tert-Butoxycarbonyl-4-hydroxy-2-pyrrolidinemethanol (23):
From **21a**: To an ice-cold solution of **21a** (4.6 g, 18.8 mmol) in anhydrous THF is added dropwise $Me_2S \cdot BH_3$ (4 mL, 52.6 mmol) in anhydrous THF (15 mL). After stirring for 30 min at r.t. mixture is refluxed for 2.5 h. Excess BH_3 is destroyed by dropwise addition of 10 mL of anhydrous MeOH. After removal of the solvent and coevaporation with a second portion of anhydrous MeOH, the product is obtained as an oil, which is used without further purification as it decomposed on distillation under high vacuum; yield: 3.8 g (93%).

From **22**: To a solution of $Me_2S \cdot BH_3$ (830 mg, 10.9 mmol) in anhydrous THF (10 mL) is added a solution of **22** (1 g, 4.33 mmol) in anhydrous THF (10 mL). The mixture is refluxed for 20 h and worked up as described above; yield: 751 mg (80%).

(1*S*,4*S*)-5-Benzyl-2-*tert*-butoxycarbonyl-2,5-diazabicyclo[2.2.1]-heptane (26):
A mixture of **24**[9] (3.0 g, 5.71 mmol) and dry benzylamine (1.74 g, 16.3 mmol) in toluene (50 mL) is heated under reflux for 18 h. After cooling, the mixture is filtered and the filtrate evaporated to leave an oil, which is purified by Kugelrohr distillation; yield: 1.3 g (79%).

(1*S*,4*S*)-2,5-Diazabicyclo[2.2.1]heptane (3):
From **28** · 2HBr: A solution of **28** · 2HBr (6 g; 17.1 mmol) in MeOH (75 mL) and water (25 mL) is hydrogenated in the presence of 10% Pd-C as catalyst (2 g), at 70 psi for 24 h. The catalyst is removed, the solvent evaporated to dryness and the residue washed with anhydrous acetone to give **3** as the dihydrobromide; yield: 3.57 g (90%).

From **26**: 10% Pd-C (500 mg) is added to a solution of **26** (800 mg, 2.77 mmol) in MeOH (30 mL) and conc HCl (2 mL). After hydrogenolysis (80 psi, 3 h, r.t.) the catalyst is filtered and the solvent removed *in vacuo*. The residue is washed with acetone and dried to give **3** · 2HCl; yield: 375 mg (100%).

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