Synthesis of (1*R*,4*R*,7*S*)- and (1*S*,4*S*,7*S*)-2-(4-Tolylsulfonyl)-5-phenylmethyl-7-methyl-2,5-diazabicyclo[2.2.1]heptanes *via* Regioselective Opening of 3,4-Epoxy-D-proline with Lithium Dimethyl Cuprate

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The synthesis of (1*S*,4*S*,7*S*)- and (1*R*,4*R*,7*S*)-2-(4-tolylsulfonyl)-5-phenylmethyl-7-methyl-2,5-diazabicyclo-[2.2.1]heptanes (**20**) and (**22**) from *trans* 4-hydroxy-L-proline is described.

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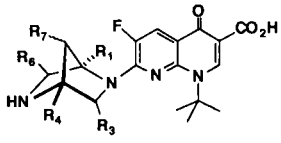
The quinolonecarboxylic acids are a major class of anti-infectives which have been shown to inhibit DNA gyrase [1]. As part of our effort for the synthesis of analogues of 7-[(1*R*,4*R*)-2,5-diazabicyclo[2.2.1]heptan-2-yl]naphthyridone **1** (BMY 40062) (Figure 1) [2] with enhanced antibacterial activity, but with undesired side-effects, we were interested in C-1, C-3, C-4 and C-6 methyl substitution of the bridged piperazine attached at position 7 of the naphthyridone nucleus [3-5].



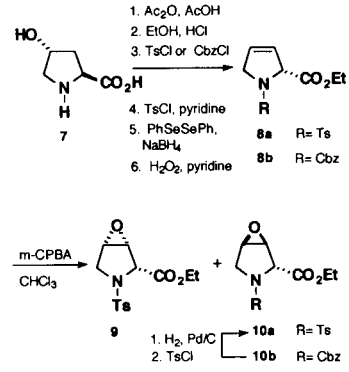
1 R_1, R_3, R_4, R_6, R_7 = H (BMY 40062)
2 R_1 = Me; R_3, R_4, R_6, R_7 = H
3 (3*R* and 3*S*) R_3 = Me; R_1, R_4, R_6, R_7 = H
4 R_4 = Me; R_1, R_3, R_6, R_7 = H
5 (6*R* and 6*S*) R_6 = Me; R_1, R_3, R_4, R_7 = H
6 R_7 = Me; R_1, R_3, R_4, R_6 = H

Figure 1

While some of these *C*-methylated bridged piperazines derivatives led to promising candidates [3], the C-7 substitution of the bridged piperazine still remained to be explored.

The strategy chosen was to start (Scheme I) from the same chiron *trans*-4-hydroxy-L-proline **7**, already used for the synthesis of the unsubstituted 2,5-diazabicyclo[2.2.1]-heptane moiety [2], [6-8] and also the C-1, C-3, C-4 and C-6 methylated analogues **2-5**. From an already known 3,4-epoxyproline, it should be possible to obtain the desired 2-hydroxymethyl-3-methyl-4-hydroxypyrrolidine. This latter compound could give, after cyclization, the desired bridged piperazine. The configuration at C-2 of the starting pyrrolidine should be retained during the synthetic process. The D-proline series should give (1*R*,4*R*)-2,5-diazabicyclo[2.2.1]heptane derivatives while the L-proline series should lead to the (1*S*,4*S*) analogues. To test our reaction scheme, we first prepared the 3,4-epoxy-D-prolines considered to afford the final derivative (1*R*,4*R*) which display better antibacterial activity than the (1*S*,4*S*) analogue [2].

Scheme I

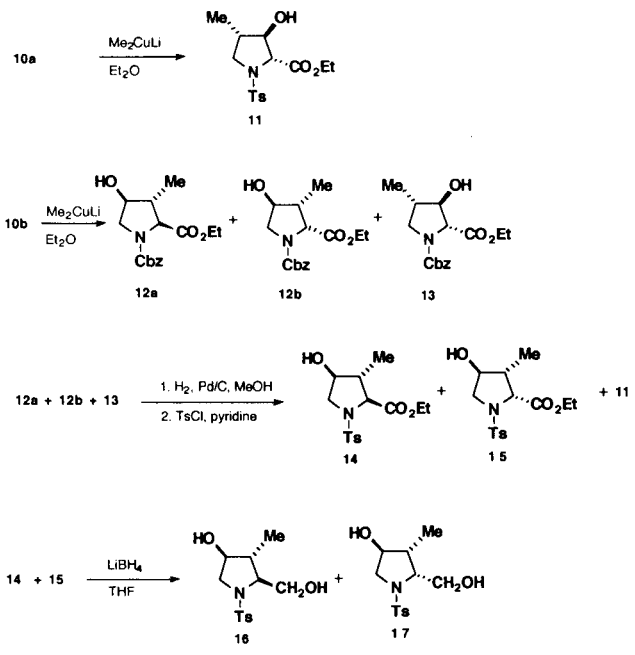


The synthesis commenced with known protocols for inversion and esterification at C-2 of **7**, followed by *N*-protection [2], [4,5], [9]. After *O*-tosylation with 4-toluenesulfonyl chloride and phenylselenoxide elimination with hydrogen peroxide in pyridine as previously reported [10] the 3,4-dehydro-D-prolines **8a** and **8b** were obtained. Epoxidation of **8a** with an excess of *m*-CPBA in refluxing chloroform afforded a 85% yield of a mixture of *cis* and *trans* epoxides **9** and **10a** in a 36:64 ratio as previously described with trifluoroperacetic acid (Scheme I) [11,12]. Both epoxides were readily separated by chromatography. Surprisingly epoxidation of **8b** under the same conditions (excess of *m*-CPBA) afforded only the epoxide **10b** in 45% yield. The epoxidation reaction appeared to be stereoselective as has been reported for the *trans* epoxidation of 3,4-dehydroproline phenacyl ester with *m*-CPBA [13]. This said, however, we have not ruled out of the possibility that the *cis* epoxide was also formed during the reaction [14].

The first attempts to introduce a methyl group by opening of the epoxide **10a** with lithium dimethyl cuprate gave only the regioisomer **11** in poor yield (9%) along with an unidentified mixture of products. We suspect that the *N*-(4-toluenesulfonyl) group of epoxide **10a** may have been cleaved during the reaction. On the other hand, reaction

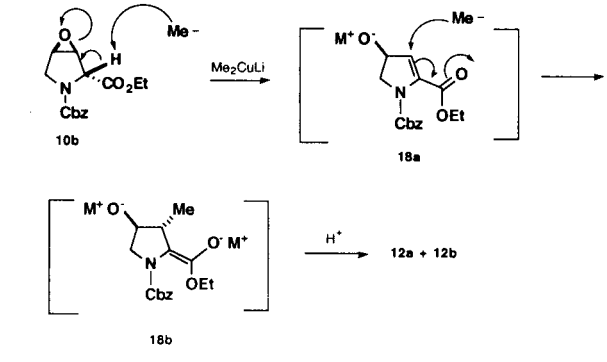
of epoxide **10b** with two equivalents of cuprate gave a difficult to separate mixture of regioisomers **12a**, **12b** and **13** with a 81% total yield (Scheme II).

Scheme II



Attack on epoxide **10b**, by lithium dimethyl cuprate took place specifically and in excellent yield at C-3 of the pyrrolidine ring rather than at C-4 (ratio 8.3:1), even though the C-3 position was more hindered than the C-4 position of the epoxide. One explanation for the regio- and stereoselectivity might be the attack of the methyl anion on the acidic proton at C-2, followed by opening of the epoxide to provide **18a** (Scheme III). The cuprate could

Scheme III



then react stereoselectively in a 1,4 fashion at C-3 of this intermediate leading to a new intermediate similar to **18b**, which upon reprotonation afforded the mixture of diastereoisomers **12a** and **12b**.

The mixture of **12a**, **12b** and **13** was then submitted to catalytic hydrogenation, followed by tosylation to give a mixture of diastereoisomers **14** and **15** (71%) mixed with the regioisomer **11** (9%) which was readily separated by chromatography at this stage [15]. The ester **14** was partially separated from the diastereoisomeric mixture by recrystallization from diisopropyl ether. The *trans* configuration was assigned to the C-2–C-3 substitution by COSY and NOESY experiments.

Lithium borohydride reduction of **14** and **15** provided a mixture of diastereoisomers **16** and **17** which separated upon chromatography (4.5:1 ratio) [16]. The configuration of the diols **16** and **17** could not be clearly assigned because of overlapping nmr signals of protons H-2, H-3, H-5 and CH_2OH. Finally the absolute configuration of **16** (2*S*,3*R*,4*S*) was determined by X-ray crystallographic analysis (Figure 2).

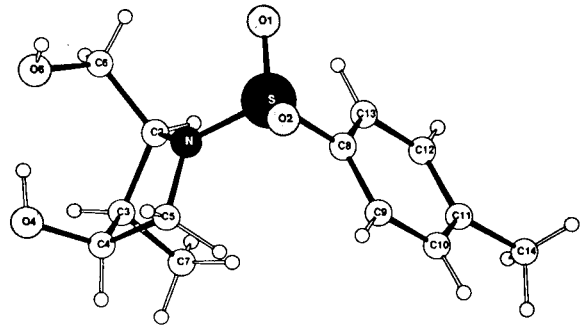


Figure 2. Stereotopic projection of 2*S*,3*R*,4*S*-**16**

Crystallographic Data are shown in Table I. The fractional atom coordinates are given in Table II. Bond distances and bond angles are shown in Table III.

The diol **16** was further tosylated to yield the ditosylate **19** which upon reaction with benzylamine in refluxing xylene afforded in 49% yield the (1*S*,4*S*,7*S*)-2,5-diazabicyclo[2.2.1]heptane derivative **20** (Scheme IV).

Scheme IV

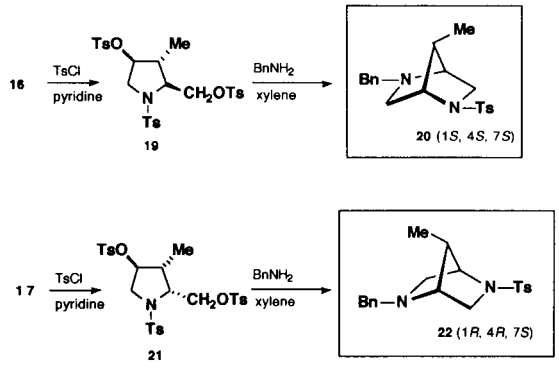


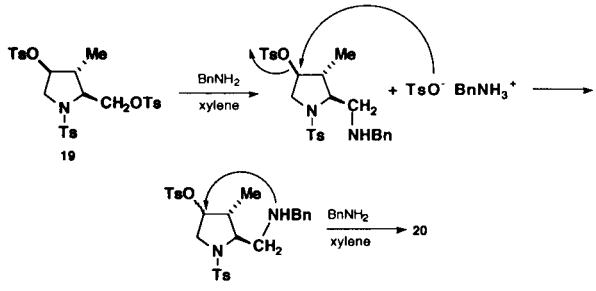
Table I

Crystallographic Data for compound **16**

Formula	$C_{13}H_{19}NO_4S$
Molecular weight	285.35
Crystal System	orthorombic
Space group	$P2_12_12_1$
a, Å	17.082(8)
b, Å	10.955(5)
c, Å	7.619(3)
V, Å^3	1426
Z	4
Radiation (λ, Å)	graphite monochromated CuKα (1.5418)
Reflection measured	±h, +k, +ℓ
Scan type	ω/2θ
Standard Reflections	3 every 3 hours (no significant change)
No. of measured independent Reflections	3015
No. of observed Reflections	2184 with I > 3σ(I)
Crystal Dimensions, mm	0.3 x 0.3 x 0.2
μ, cm^{-1}	3.0
No. of Varied Parameters	124
R	0.0381
R_w	0.0378
w	$[\sigma^2(F)+0.004\,F^2]^{-1}$

In contrast to previous studies [7] we had been able to force the cyclization of **19** (normally *via* a S_N2 process) even though the C-2 and C-4 substituents were in a *cis* configuration. Nucleophilic substitution could have taken place at C-4 with the 4-toluenesulfonyloxy anion of the salt formed after reaction of benzylamine on the primary tosylate at C-2. The resulting epimerization at C-4 could then have allowed the cyclization (Scheme V).

Scheme V



Cyclization of **21** with benzylamine readily gave in 86% yield the (1*R*,4*R*,7*S*)-2,5-diazabicyclo[2.2.1]heptane derivative **22**.

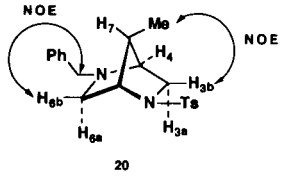


Table II

Final Fractional Coordinates and Equivalent Isotropic Thermal Parameters for Coupound **16**

	X	Y	Z	U
S	5654 (1)	-199 (1)	-1678 (1)	50 (1)
O1	5857 (1)	950 (1)	-2422 (2)	64 (1)
O2	5877 (1)	-1301 (2)	-2538 (3)	68 (1)
N	6036 (1)	-245 (2)	256 (2)	52 (1)
C2	5910 (1)	796 (2)	1479 (3)	56 (1)
C3	5799 (1)	168 (3)	3255 (3)	71 (2)
C4	6237 (1)	-1034 (3)	3083 (4)	81 (2)
O4	7050 (1)	-951 (3)	3459 (3)	100 (2)
C5	6085 (2)	-1408 (3)	1200 (4)	81 (3)
C6	6574 (2)	1709 (3)	1360 (4)	73 (2)
O6	7306 (1)	1207 (2)	1767 (3)	88 (2)
C7	4927 (1)	-47 (4)	3627 (4)	102 (4)
C8	4628 (1)	-222 (2)	-1429 (3)	50 (1)
C9	4239 (1)	-1331 (2)	-1316 (3)	58 (2)
C10	3438 (1)	-1342 (2)	-1155 (4)	68 (2)
C11	3011 (1)	-265 (2)	-1049 (4)	67 (2)
C12	3412 (1)	836 (2)	-1153 (4)	69 (2)
C13	4220 (1)	864 (2)	-1345 (3)	59 (2)
C14	2129 (2)	-288 (3)	-929 (6)	95 (3)
	X	Y	Z	U
H1C7	468	-47	260	250
H2C7	466	75	382	250
H3C7	487	-57	470	250
HC9	454	-211	-135	80
HC10	316	-214	-111	90
HC12	311	162	-109	90
HC13	450	166	-142	80
H114	189	-15	-206	120
H214	197	-108	-33	120
H314	196	28	4	120
HC2	546	123	125	70
HC3	606	56	418	90
HC4	604	-162	386	110
HO4	717	-15	299	130
H1C5	653	-191	75	110
H2C5	551	-184	104	110
H1C6	656	212	30	90
H2C6	646	239	203	90
HO6	753	108	89	110

The stereochemistry (1*S*,4*S*,7*S*) of **20** was confirmed by 2D NOESY experiments (in pyridine-d_5).

A NOE was observed between CH_2Ph and H-6b, and also between H-6a and H-1. A correlation was observed between H-3b and Me-7, and also between H-4 and CH_2-Ph. Differential NOESY experiments (in DMSO-d_6)

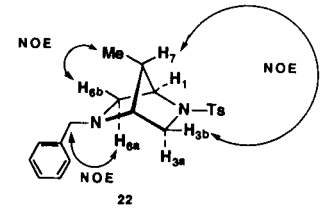


Table III

Bond distances (Å) and Bond Angles (degrees) for Compound **16**

S	-O1	1.423 (2)		C2	-HC2	0.927 (28)	
S	-O2	1.424 (2)		C3	-HC3	0.933 (37)	
S	-N	1.613 (2)		C4	-HC4	0.940 (38)	
S	-C8	1.763 (2)		O4	-HO4	0.975 (48)	
N	-C2	1.488 (3)		C5	-H1C5	0.999 (39)	
N	-C5	1.466 (3)		C5	-H2C5	1.089 (37)	
C2	-C3	1.530 (4)		C6	-H1C6	0.929 (40)	
C2	-C6	1.514 (3)		C6	-H2C6	0.922 (33)	
C3	-C4	1.520 (4)		O6	-HO6	0.783 (48)	
C3	-C7	1.535 (3)		C7	-H1C7	1.000	
C4	-O4	1.421 (3)		C7	-H2C7	1.000	
C4	-C5	1.514 (4)		C7	-H3C7	1.000	
C6	-O6	1.402 (3)		C9	-HC9	1.000	
C8	-C9	1.387 (3)		C10	-HC10	1.000	
C8	-C13	1.381 (3)		C12	-HC12	1.000	
C9	-C10	1.373 (3)		C13	-HC13	1.000	
C10	-C11	1.390 (3)		C14	-H114	0.965 (22)	
C11	-C12	1.390 (3)		C14	-H214	1.018 (26)	
C11	-C14	1.509 (3)		C14	-H314	1.008 (28)	
C12	-C13	1.388 (3)					

O1	-S	-N	107.0 (1)	O1	-S	-O2	120.1 (1)
O2	-S	-N	106.6 (1)	O1	-S	-C8	107.3 (1)
N	-S	-C8	107.6 (1)	O2	-S	-C8	107.6 (1)
S	-N	-C5	119.9 (2)	S	-N	-C2	119.3 (1)
N	-C2	-C3	103.1 (2)	C2	-N	-C5	111.5 (2)
N	-C2	- HC2	113.3 (17)	N	-C2	-C6	111.1 (2)
C3	-C2	-HC2	107.4 (17)	C3	-C2	-C6	116.3 (2)
C2	-C3	-C4	104.6 (2)	C6	-C2	-HC2	105.8 (17)
C2	-C3	-HC3	113.5 (22)	C2	-C3	-C7	110.6 (2)
C4	-C3	-HC3	103.4 (22)	C4	-C3	-C7	111.1 (2)
C3	-C4	-O4	114.1 (2)	C7	-C3	-HC3	113.0 (22)
C3	-C4	-HC4	110.8 (23)	C3	-C4	-C5	103.4 (2)
O4	-C4	-HC4	105.9 (23)	O4	-C4	-C5	112.1 (3)
C4	-O4	-HO4	101.3 (28)	C5	-C4	-HC4	110.6 (23)
N	-C5	-H1C5	110.5 (23)	N	-C5	-C4	103.8 (2)
C4	-C5	-H1C5	110.0 (23)	N	-C5	-H2C5	105.7 (20)
H1C5	-C5	-H2C5	114.1 (31)	C4	-C5	-H2C5	112.0 (20)
C2	-C6	-H1C6	111.1 (22)	C2	-C6	-O6	113.3 (2)
O6	-C6	-H1C6	113.7 (22)	C2	-C6	-H2C6	110.4 (21)
H1C6	-C6	-H2C6	94.7 (30)	O6	-C6	-H2C6	112.1 (21)
C3	-C7	-H1C7	109.5 (3)	C6	-O6	-HO6	108.9 (32)
C3	-C7	-H3C7	109.5 (3)	C3	-C7	-H2C7	109.5 (3)
H1C7	-C7	-H3C7	109.5 (4)	H1C7	-C7	-H2C7	109.5 (4)
S	-C8	-C9	119.7 (2)	H2C7	-C7	-H3C7	109.5 (4)
C9	-C8	-C13	120.6 (2)	S	-C8	-C13	119.7 (2)
C8	-C9	-HC9	120.3 (2)	C8	-C9	-C10	119.4 (2)
C9	-C10	-C11	121.4 (2)	C10	-C9	-HC9	120.3 (2)
C11	-C10	-HC10	119.3 (3)	C9	-C10	-HC10	119.3 (3)
C10	-C11	-C14	120.9 (2)	C10	-C11	-C12	118.3 (2)
C11	-C12	-C13	121.0 (2)	C12	-C11	-C14	120.7 (2)
C13	-C12	-HC12	119.5 (3)	C11	-C12	-HC12	119.5 (3)
C8	-C13	-HC13	120.4 (2)	C8	-C13	-C12	119.2 (2)
C11	-C14	-H114	111.3 (16)	C12	-C13	-HC13	120.4 (2)
C11	-C14	-H314	108.9 (15)	C11	-C14	-H214	108.1 (15)
H114	-C14	-H314	115.7 (22)	H114	-C14	-H214	115.1 (22)
				H214	-C14	-H314	96.7 (22)

showed correlation between CH_2Ph and H-6a, and also that H-6a is correlated with H-1, H-6b with Me-7, H-3b with H-7, H-4 with CH_2Ph, thus giving the 1*R*,4*R*,7*S* configuration to **22**.

In summary, we have discovered a practical synthesis of (1*S*,4*S*,7*S*) and (1*R*,4*R*,7*S*)-7-methyl bridged piperazines **20** and **22** from the sole chiral *trans*-4-hydroxy-L-proline. Deprotection and condensation of these derivatives with 7-chloro-6-fluoro-1-(1,1-dimethylethyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid ethyl ester are in progress.

EXPERIMENTAL

General Procedures.

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Melting points were taken in a Büchi 510 capillary apparatus and are uncorrected. Elemental analysis was performed by the Microanalytical Laboratory, operated by the Bristol-Myers Squibb Analytical Department. Infrared spectra were recorded on a Nicolet FT-IR SXC spectrophotometer. The ^{1}H nmr spectra were recorded on a Bruker AC 200 spectrometer. Chemical shifts are expressed in δ (ppm) relative to internal tetramethylsilane. Optical rotations were measured in a 1-dm cell with a Perkin-Elmer model 241 polarimeter at concentration of 0.5% in methanol unless otherwise noted.

Crystallography.

Crystals of **16** were grown by slow cooling and filtration at room temperature of a refluxing benzene solution of the compound. The crystal selected for X-ray analysis was sealed to a glass fiber and transferred directly to an automatic Nonius single-crystal diffractometer. All measurements were carried out at room temperature, under the conditions listed in Table I. The intensities were corrected for Lorentz and polarization effects, and empirical absorption correction, based on the ψ scan, was applied. The space group was determined uniquely from a survey of systematic absences.

The structure was resolved by direct methods by means of the SHELX-86 program [17], and were refined through full-matrix least-squares calculations with $\Sigma_w (|F_O| - |F_C|)^2$ being minimized [18]. All non-hydrogen atoms were treated anisotropically. The hydrogen atoms were located by means fo ΔF Fourier maps and were refined isotropically (with common temperature factors for hydrogens bonded to the same carbon atom, except for hydrogens of C-7 methyl, which are probably disorganized and were drawn in Figure 2 with a shift of the conformation of this methyl group). Least-squares refinement of these models led to final conventional R factors of 0.0381. The highest residual on the final, featureless ΔF Fourier maps are reported in Table I. Because recording of data was made on the two octants (h, k, l) and (-h, k, l) independent from the anomal diffusion point of view, it was possible to determine the absolute configuration of **16**. For the sulfur atom, the anomal diffusion value was $\Delta f' = 0.319$ and $\Delta f'' = 0.557$ electron. One can expect an effect in a scale of size of 0.5 electron to establish the absolute configuration. Using a pro-

gram of C. Riche (BIJVOET) the differences $\Delta_C = F_C(hkl) - F_C(-hkl) > 0.6$ electron were classified by decreasing values. (F_C represents the calculated structure factor, F_O the observed structure factor). This list was compared to that of the differences $\Delta_O = F_O(hkl) - F_O(-hkl)$. At first we noted that all the signs of these differences were opposite, then the postulated absolute configuration applied during the resolution of the structure needed to be inverted. This made all the signs coincide. The absolute configuration was therefore 2*S*,3*R*,4*S*.

(2*R*,2*S*,4*R*) and (2*R*,3*R*,4*S*)-1-(4-Toluenesulfonyl)-3,4-epoxy-2-pyrrolidinecarboxylic Acid Ethyl Ester (**9**) and (**10a**).

Under nitrogen, a solution fo 25.22 g (106 mmoles) of *m*-CPBA in 100 ml of chloroform was added dropwise to a mixture of 8.85 g (30 mmoles) of **8a** and 0.96 g (4.3 mmoles) of 2,6-di-*tert*-butyl-4-phenol in 70 ml of chloroform. The mixture was stirred under reflux for 7 hours, cooled and filtered. The filtrate was washed with 3 x 100 ml of 10% sodium bicarbonate, dried (magnesium sulfate), and evaporated under reduced pressure to yield 19 g of crude material which upon chromatography (hexane/ethyl acetate 80:20 to 60:40) gave 1.2 g of unreacted material, 4.7 g (58% on the reacted material) of **10a** and 2.2 g (27% on reacted material) of **9**, mp 126-128°; $[\alpha]_D = +134.7°$; ^{1}H nmr (deuteriochloroform): δ 1.33 (t, J = 7.1 Hz, 3H, Me ester), 2.43 (s, 3H, Me Ts), 3.46 (dd, J = 1.82 Hz, J = 11.2 Hz, 1H, H-5β), 3.60 (d, J = 11.2 Hz, 1H, H-5α), 3.77 (dd, J = 1.82 Hz, J = 2.6 Hz, 1H, H-4), 3.97 (dd, J = 2.1 Hz, J = 2.6 Hz, 1H, H-3), 4.30 (q, J = 7.1 Hz, 2H, CH_2 ester), 4.46 (d, J = 2.1 Hz, 1H, H-2), 7.32 (d, J = 8.2 Hz, 2H, *m*-Ar Ts), 7.84 (d, J = 8.2 Hz, 2H, *o*-Ar Ts).

Anal. Calcd. for $C_{14}H_{17}NO_5S$: C, 54.01; H, 5.50; N, 4.49. Found: C, 54.22; H, 5.21; N, 4.77.

Compound **10a**.

This compound had mp 89-91°; $[\alpha]_D = +121.6°$; ^{1}H nmr (deuteriochloroform): δ 1.30 (t, J = 7.1 Hz, 3H, Me ester), 2.43 (s, 3H, Me Ts), 3.59 (dd, J = 1.9 Hz, J = 12.4 Hz, 1H, H-5β), 3.60 (dd, J = 1.9 Hz, J = 2.8 Hz, 1H, H-4), 3.71 (d, J = 2.8 Hz, 1H, H-3), 3.76 (d, J = 12.4 Hz, 1H, H-5α), 4.24 (q, J = 7.1 Hz, 2H, CH_2 ester), 4.56 (s, 1H, H-2), 7.30 (d, J = 8.2 Hz, 2H, *m*-Ar Ts), 7.68 (d, J = 8.2 Hz, 2H, *o*-Ar Ts).

Anal. Calcd. for $C_{14}H_{17}NO_5S$: C, 54.01; H, 5.50; N, 4.49. Found: C, 54.30; H, 5.31; N, 4.81.

(2*R*,3*R*,4*S*)-1-(Benzyloxycarbonyl)-3,4-epoxy-2-pyrrolidinecarboxylic Acid Ethyl Ester (**10b**).

This compound was prepared according to the same procedure described for the preparation of **9** and **10a** as a single isomer (45%), was obtained as an oil, **10b**; $[\alpha]_D = +80.8°$; ir (potassium bromide): 2981, 1747, 1712, 1423, 1328, 1189, 1114 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 1.19 (t, J = 7.0 Hz, 3H, Me ester), 3.45 (d, J = 12.6 Hz, 1H, H-5α), 3.79 (d, J = 12.6 Hz, 1H, H-5β), 3.84 (d, J = 2.8 Hz, 1H, H-4), 3.89 (d, J = 2.8 Hz, 1H, H-3), 4.32 (q, J = 7.0 Hz, 2H, CH_2 ester), 4.54 (s, 1H, H-2), 5.09 (m, 2H, CH_2Ar), 7.33 (m, 5H, Ar). The nmr spectrum was performed at 70° to obtain only one rotamer (two rotamers were observed at 25°).

Anal. Calcd. for $C_{15}H_{17}NO_5$: C, 61.84; H, 5.88; N, 4.81. Found: C, 61.67; H, 5.62; N, 4.96.

(2*R*,3*R*,4*S*)-1-(4-Toluenesulfonyl)-3-hydroxy-4-methyl-2-pyrrolidinecarboxylate Acid Ethyl Ester (**11**).

To a suspension of 3.96 g (20.8 mmoles) of cuprous iodide in 50 ml of dry ether cooled at -10° was carefully added 25.5 ml of 1.6*M* methyl lithium in ether (41 mmoles), the temperature being kept under -5°. After stirring the mixture for 20 minutes at -10°, 2.6 g (8.3 mmoles) of **10a** in 123 ml of dry ether was added dropwise below -2°. The reaction mixture was stirred 1 hour at 0°, quenched with 50 ml of water and diluted with 70 ml of dichloromethane. The mixture was filtered over a celite pad, the organic layer was decanted, dried (magnesium sulfate) and evaporated *in vacuo* to provide 0.32 g of crude material which was purified over silica gel (chloroform/methanol 96:4) giving 0.25 g of **11** (9.2%), mp 102-103°; $[\alpha]_D = +115.1°$; ir (potassium bromide): 3489, 2964, 2935, 2878, 1741, 1734, 1596, 1342, 1199, 1158 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 0.98 (d, J = 6.7 Hz, 3H, Me-4), 1.20 (t, J = 7.0 Hz, 3H, Me ester), 1.92 (m, J = 6.8 Hz, J = 7.7 Hz, 1H, H-4), 2.39 (s, 3H, Me Ts), 3.00 (dd, J = 8.7 Hz, J = 10.3 Hz, 1H, H-5α), 3.58 (dd, J = 7.7 Hz, J = 10.3 Hz, 1H, H-5β), 3.93 (m, J = 5.6 Hz, J = 6.8 Hz, 1H, H-3), 4.01 (d, J = 5.6 Hz, 1H, H-2), 4.22 (q, J = 7.0 Hz, 2H, CH_2 ester), 7.28 (d, J = 8.2 Hz, 2H, *m*-Ar Ts), 7.39 (d, J = 8.2 Hz, 2H, *o*-Ar Ts).

Anal. Calcd. for $C_{15}H_{21}NO_5S$: C, 55.03; H, 6.47; N, 4.28. Found: C, 54.93; H, 6.45; N, 4.21.

The COSY experiments (in DMSO-d_6) indicated that H-3 is coupled with OH, and also coupled with H-4, which is coupled with Me-4 and H-5α, indicating that the methyl group is in position 4 of the pyrrolidine ring. Differential NOESY experiments showed that there is a correlation between H-2 and H-4, as well as correlations between H-4 and OH, H-2 and OH, H-3 and Me-4 and finally H-5α and Me-4 (absolute configuration for **11** is 2*R*,3*R*,4*S*).

(2*R*,3*R*,4*S*) and (2*S*,3*R*,4*S*)-1-(Benzyloxycarbonyl)-3-methyl-4-hydroxy-2-pyrrolidinecarboxylic Acid Ethyl Ester (**12a** and **12b**) and (2*R*,3*R*,4*S*)-1-(Benzyloxycarbonyl)-3-hydroxy-4-methyl-2-pyrrolidinecarboxylic Acid Ethyl Ester (**13**).

To a suspension of 19.4 g (102 mmoles) of cuprous iodide in 250 ml of dry ether cooled at -10° was carefully added 125 ml of 1.6*M* methyl lithium in ether (205 mmoles), the temperature being kept under -5°. After stirring the mixture for 20 minutes at -10°, 12.7 g (43 mmoles) of **10b** in 90 ml of dry ether was added dropwise below -2°. The reaction mixture was stirred 1 hour at -10°, quenched with 80 ml of water and diluted with 100 ml of dichloromethane. The mixture was filtered over a celite pad, the organic layer was decanted, dried (magnesium sulfate) and evaporated *in vacuo* to provide 11.15 g of an inseparable mixture of **12a**, **12b** and **13** in 83% yield which was used without further purification.

(2*S*,3*R*,4*S*) and (2*R*,3*R*,4*S*)-1-(4-Toluenesulfonyl)-3-methyl-4-hydroxy-2-pyrrolidinecarboxylic Acid Ethyl Ester (**14**) and (**15**) and (2*R*,3*R*,4*S*)-1-(4-Toluenesulfonyl)-3-hydroxy-4-methyl-2-pyrrolidinecarboxylic Acid Ethyl Ester (**12**).

A suspension of 7 g of 10% Pd/C and 21.6 g (70 mmoles) of the mixture of **12a**, **12b** and **13** in 400 ml of methanol was hydrogenated over 1.5 hours at normal pressure. The catalyst was filtered and the filtrate was evaporated *in vacuo* to give 11.3 g of the *N*-deprotected mixture of pyrrolidines (95%). To a solution of the above mixture of 11.3 g (65 mmoles) of pyrrolidines in 135 ml of dry pyridine, cooled to 5°, was added portionwise 13.86 g (72 mmoles) of 4-toluenesulfonyl chloride and the reaction mixture stirred at 5° for 24 hours. The solvent was evaporated *in vacuo* at 40°. The residue was poured into ice water, extracted with ethyl

acetate, dried (magnesium sulfate) and evaporated *in vacuo* to give 20 g of crude material. Chromatographic purification (dichloromethane/ethyl acetate 95:5 to 85:15) afforded 1.8 g (9%) of **11** $[\alpha]_D$ = +110.7° and 14.75 g of a mixture of **14** and **15** (71%). Double recrystallization of 2.31 g of the mixture of **14** and **15** from diisopropyl ether provided 0.83 g of pure **14**, mp 92-94°; $[\alpha]_D$ = -92.3°; ir (potassium bromide): 3528, 3480, 2971, 2930, 1750, 1329, 1159, 1095 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.84 (t, J = 7.2 Hz, 3H, Me-3), 1.31 (t, J = 7.0 Hz, 3H, Me ester), 2.36 (m, J = 2.3 Hz, J = 7.2 Hz, J = 2.5 Hz, 1H, H-3), 2.44 (s, 3H, Me Ts), 3.49 and 3.50 (double q, J = 10.5 Hz, J = 3.4 Hz, J = 3.9 Hz, 2H, H-5α and H-5β), 3.80 (m, J = 2.3 Hz, J = 3.4 Hz, J = 3.9 Hz, 1H, H-4), 3.91 (d, J = 2.5 Hz, 1H, H-2), 4.24 (q, J = 7.0 Hz, 2H, C*H*$_2$ ester), 7.34 (d, J = 8.2 Hz, 2H, *m*-Ar Ts), 7.78 (d, J = 8.2 Hz, 2H, *o*-Ar Ts). The regio- and stereochemistry of **14** was confirmed by COSY and 2D NOE studies. A NOE was observed between H-2 and Me-3, H-3 and OH, OH and H-5β, H-4 and H-5α and also between H-5β and H-3, thus giving the 2*S*,3*R*,4*R* configuration.

Anal. Calcd. for $C_{15}H_{21}NO_5S$: C, 55.03; H, 6.46; N, 4.28. Found: C, 54.93; H, 6.40; N, 4.37.

(2*S*,3*R*,4*S*) and (2*R*,3*R*,4*S*)-1-(4-Toluenesulfonyl)-3-methyl-4-hydroxy-2-hydroxymethylpyrrolidine (**16**) and (**17**).

Under nitrogen, to a solution of 14.75 g (45 mmoles) of the mixture of **14** and **15** in 150 ml of dry THF at 0° was added portionwise 3.4 g (157 mmoles) of lithium borohydride. The reaction mixture was stirred 1 hour at 0°, 3 hours at room temperature, cooled to 5° and the *p*H brought to 7 with 12*N* hydrochloric acid. After evaporation under reduced pressure, the residue was partitioned between ethyl acetate and water, washed with water, dried (magnesium sulfate) and evaporated *in vacuo* to give 13 g of crude material. Chromatography over silica gel (dichloromethane/methanol 96:4) afforded 1.9 g (13%) of starting material **14** and **15**, 8.04 g of **16** (63%) and 2 g of **17** (16%).

Compound **16**.

This compound had mp 119-121°; $[\alpha]_D$ = -55.4°; ir (potassium bromide): 3252, 2958, 2924, 2868, 1595, 1471, 1346, 1165, 1089, 1054 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.56 (t, J = 7.2 Hz, 3H, Me-3), 2.14 (m, 1H, H-3), 2.44 (s, 3H, Me Ts), 3.26 (m, 1H, H-5), 3.35 (dd, J = 3.6 Hz, J = 8.0 Hz, 1H, C*H*$_2$OH), 3.49 (dd, J = 1.6 Hz, J = 8.0 Hz, 1H, C*H*$_2$OH), 3.62-3.72 (m, 4H, H-2, H-5, 4-O*H*, CH$_2$O*H*), 4.09 (m, J = 2.2 Hz, 1H, H-4), 7.34 (d, J = 8.2 Hz, 2H, *m*-Ar Ts), 7.73 (d, J = 8.2 Hz, 2H, *o*-Ar Ts).

Compound **17**.

This compound had mp 125-126°; $[\alpha]_D$ = +0.8°; ir (potassium bromide): 3252, 2958, 2924, 2868, 1595, 1471, 1346, 1165, 1089, 1051, 1016 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.01 (t, J = 7.0 Hz, 3H, Me-3), 1.54 (m, 2H, 4-OH and CH$_2$O*H*), 1.81 (m, J = 7.0 Hz, J = 7.6 Hz, 1H, H-3), 2.44 (s, 3H, Me Ts), 2.98 (dd, J = 6.4 Hz, J = 10.0 Hz, 1H, H-5α), 3.63-3.89 (m, 4H, H-2, H-5β, C*H*$_2$OH), 4.09 (dt, J = 6.2 Hz, J = 7.7 Hz, 1H, H-4), 7.34 (d, J = 8.2 Hz, 2H, *m*-Ar Ts), 7.75 (d, J = 8.2 Hz, 2H, *o*-Ar Ts).

Anal. Calcd. for $C_{13}H_{19}NO_4S$: C, 54.72; H, 6.71; N, 4.91. Found: C, 54.97; H, 6.79; N, 4.89.

(2*S*,3*R*,4*S*)-1-(4-Toluenesulfonyl)-2-(4-toluenesulfonyloxymethyl)-3-methyl-4-(4-toluenesulfonyloxy)pyrrolidine (**19**).

To a cooled solution of 8 g (28 mmoles) of **16** in 20 ml of dry pyridine was added portionwise 12.65 g (65 mmoles) of 4-toluenesulfonyl chloride. The reaction mixture was stirred at room temperature overnight and the usual work-up provided 16.95 g of crude material which upon chromatographic purification (dichloromethane/ethyl acetate 95:5) yielded 14.90 g (93%) of **19**, mp 109-110°; $[\alpha]_D$ = -54° (c 0.5, acetone); ir (potassium bromide): 3433, 3059, 2973, 1598, 1358, 1165, 1094 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.45 (t, J = 7.2 Hz, 3H, Me-7), 2.36 (m, 1H, H-3), 2.43 (s, 3H, Me N-Ts), 2.45 (s, 6H, MeO-Ts), 3.37 (m, 3H, H-5β, H-5α, H-2), 4.01 (dd, J = 5.6 Hz, J = 10.50 Hz, 1H, C*H*$_2$OTs), 4.05 (dd, J = 2.6 Hz, J = 10.50 Hz, 1H, C*H*$_2$OTs), 4.23 (m, 1H, H-4), 7.30 (m, 6H, Ar Ts), 7.57 (d, J = 8.2 Hz, 2H, Ar Ts), 7.64 (d, J = 8 Hz, 2H, Ar Ts), 7.75 (d, J = 8 Hz, 2H, Ar Ts).

Anal. Calcd. for $C_{27}H_{31}NO_8S_3$: C, 54.62; H, 5.26; N, 2.36. Found: C, 54.69; H, 5.20; N, 2.31.

(1*R*,3*R*,4*S*)-1-(4-Toluenesulfonyl)-2-(4-tolylsulfonyloxymethyl)-3-methyl-4-(4-toluenesulfonyloxy)pyrrolidine (**21**).

According to a procedure similar to that described for **19**, derivative **21** was obtained in 94% yield, mp 113-115°; $[\alpha]_D$ = -5.6° (c 0.5, acetone); ^1H nmr (deuteriochloroform): δ 0.77 (t, J = 7.1 Hz, 3H, Me-7), 2.03 (m, 1H, H-3), 2.41 (s, 3H, Me-Ar N-Ts), 2.44 (s, 6H, Me-Ar O-Ts), 3.10 (dd, J = 2.06 Hz, J = 11.21 Hz, 1H, H-5α), 3.58 (dd, J = 6.0 Hz, J = 11.21 Hz, 1H, H-5β), 3.67 (m, 1H, H-2), 4.07 (dd, J = 6.2 Hz, J = 10.50 Hz, 1H, C*H*$_2$OTs), 4.26 (dd, J = 2.6 Hz, J = 10.50 Hz, 1H, C*H*$_2$OTs), 4.48 (q, J = 5.6 Hz, 1H, H-4), 7.30 (m, 6H, Ar Ts), 7.57 (d, J = 8.2 Hz, 2H, Ar Ts), 7.64 (d, J = 8 Hz, 2H, Ar Ts), 7.75 (d, J = 8 Hz, 2H, Ar Ts).

Anal. Calcd. for $C_{27}H_{31}NO_8S_3$: C, 54.62; H, 5.26; N, 2.36. Found: C, 54.69; H, 5.32; N, 2.40.

(1*S*,4*S*,7*S*)-2-(4-Toluenesulfonyl)-5-phenylmethyl-7-methyl-2,5-diazabicyclo[2.2.1]heptane (**20**).

A mixture of 2.3 g (3.87 mmoles) of **19** and 1.24 g (11.62 mmoles) of benzylamine in 8 ml of *o*-xylene was heated under reflux for 25 hours. The solvent was evaporated *in vacuo* to give 1.6 g of crude material which upon chromatographic purification (dichloromethane/ethyl acetate 90:10) afforded 0.7 g (51%) of **20**, mp 96-97°; $[\alpha]_D$ = -37.2°; ir (potassium bromide): 3420, 2967, 2930, 2876, 2808, 1490, 1452, 1342, 1284, 1160, 1098, 1065 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.98 (t, J = 6.7 Hz, 3H, Me-7), 2.42 (q, J = 6.7 Hz, 1H, H-7), 2.53 (s, 3H, Me-Ar Ts), 2.64 (d, J = 9.8 Hz, 1H, H-6a), 2.96 (dd, J = 1.92 Hz, J = 9.8 Hz, 1H, H-6b), 3.25 (m, 1H, H-1), 3.28 (dd, J = 2.06 Hz, J = 9.0 Hz, 1H, H-3b), 3.65 (q, J = 13.4 Hz, 2H, C*H*$_2$Ph), 3.69 (d, J = 9.0 Hz, 1H, H-3a), 7.29 (m, 5H, Ar benzyl), 7.41 (d, J = 8 Hz, 2H, *m*-Ar Ts), 7.86 (d, J = 8 Hz, 2H, *o*-Ar Ts).

Anal. Calcd. for $C_{20}H_{24}N_2O_2S$: C, 67.39; H, 6.79; N, 7.86. Found: C, 67.29; H, 6.63; N, 7.68.

(1*R*,4*R*,7*S*)-2-(4-Toluenesulfonyl)-5-phenylmethyl-7-methyl-2,5-diazabicyclo[2.2.1]heptane (**22**).

According to a procedure similar to that described for **20** in refluxing xylene, derivative **22** was obtained in 12 hours in 86% yield, mp 167-169°; $[\alpha]_D$ = +12.6° (c 0.25, methanol 0.1*N* hydrochloric acid 50:50); ir (potassium bromide): 3420, 2960, 2882, 2810, 1594, 1450, 1342, 1160, 1096 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.03 (d, J = 6.7 Hz, 3H, Me-7), 1.63 (m, J = 6.7 Hz, 1H, H-7), 2.35 (d, J = 9.7 Hz, 1H, H-6a), 2.41 (s, 3H, Me-Ar Ts), 3.00 (d, J = 9.7 Hz, 1H, H-6b), 3.06 (d, J = 9.4 Hz, 1H, H-3b), 3.09

(m, 1H, H-4), 3.67 (q, J = 13.6 Hz, 2H, CH_2Ph), 3.69 (d, J = 9.4 Hz, 1H, H-3a), 3.88 (m, 1H, H-1), 7.19 (m, 5H, Ar benzyl), 7.29 (d, J = 8 Hz, 2H, *m*-Ar Ts), 7.70 (d, J = 8 Hz, 2H, *o*-Ar Ts).

Anal. Calcd. for $C_{20}H_{24}N_2O_2S$: C, 67.39; H, 6.79; N, 7.86. Found: C, 67.34; H, 6.92; N, 7.67.

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[16] Reduction of pure **14** with lithium borohydride afforded a pure compound, mp 119-120°, with an optical rotation of -54.4° (compared to **16**, $[\alpha]_D$ = -55.4°, mp 119-121°), thus indicating that lithium borohydride did not induce racemization at C-2.

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