

PREPARATION OF (1*R*,4*R*)-1-METHYL-2-(*p*-TOLUENESULFONYL)-5-PHENYL-METHYL-2,5-DIAZABICYCLO[2.2.1]HEPTANE, INTERMEDIATE IN A SYNTHESIS OF NEW NAPHTHYRIDONES

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Abstract-An efficient chiral synthesis of the (1*R*,4*R*)-1-methyl-2-(*p*-toluenesulfonyl)-5-phenylmethyl-2,5-diazabicyclo[2.2.1]-heptane (**2b**) was performed using *trans*-4-hydroxy-L-proline as starting material. This bridged piperazine was used in the preparation of new naphthyridones (**16**) and (**17**).

In the course of our investigations on the synthesis of new quinolones, BMY 40062¹ (**1a**) (Figure 1) was found to be a potent antibacterial agent. The chiral (1*R*,4*R*)-(6*R*)- and (6*S*)-2-*p*-toluenesulfonyl-5-phenylmethyl-6-methyl-2,5-diazabicyclo[2.2.1]heptane groups have already been used for substitution on other antimicrobial naphthyridones (**1b**) and (**1c**).² After substitution at C₃ and C₆ on the chiral bridged piperazine of **1a**, we were interested in the addition of a methyl group at other positions like C₁ and C₄.

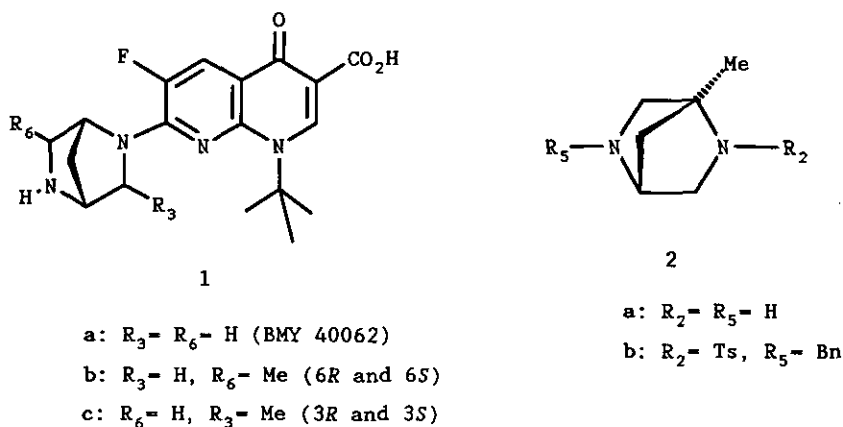
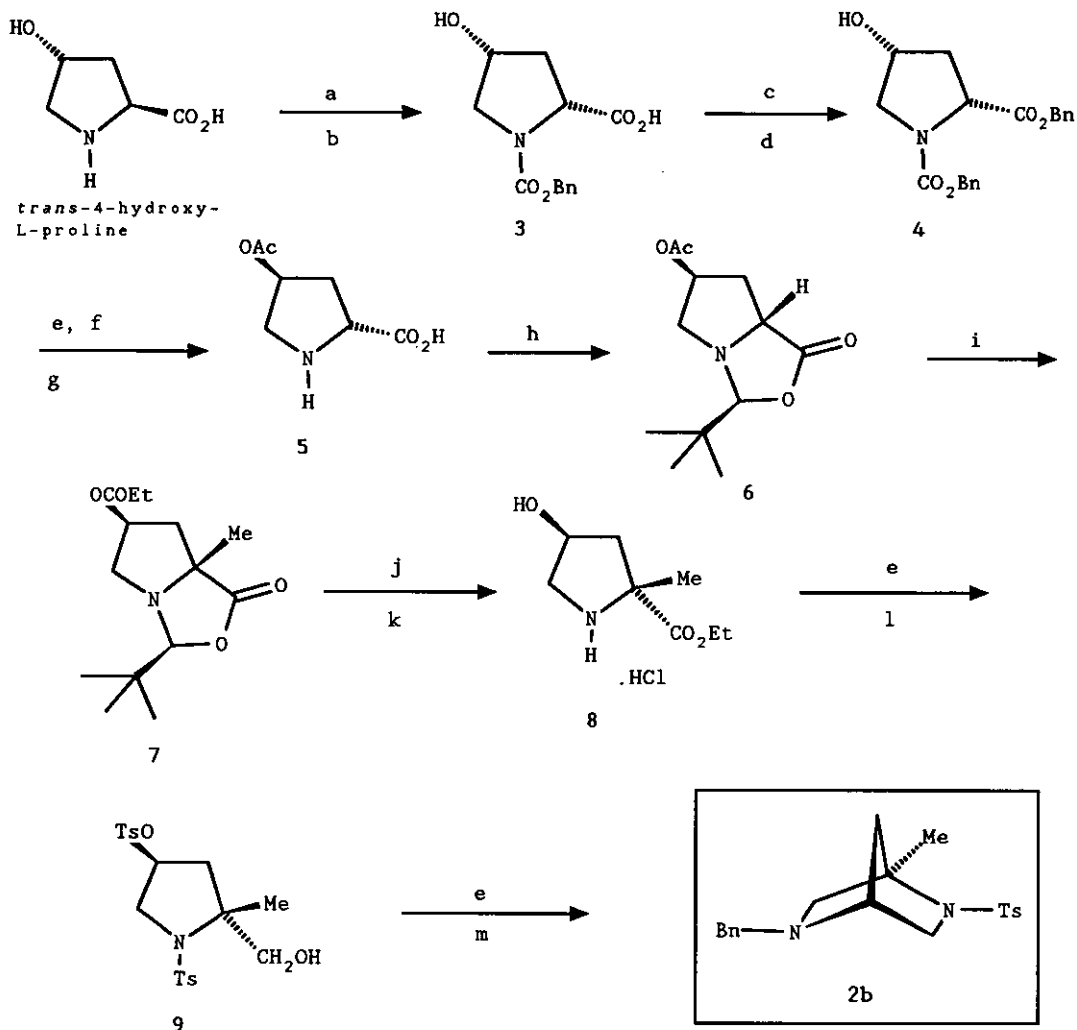


Figure 1

The synthesis commenced with inversion at C_2 and N -protection of *trans*-4-hydroxy-L-proline to afford the proline (3) (Scheme 1).¹ The anhydrous potassium salt of 3, after reaction with benzyl bromide in dimethylacetamide, gave 4 (37% yield from the *trans*-4-hydroxy-L-proline).³ O -Tosylation of 4, followed by inversion of configuration at C_4 with tetraethylammonium acetate, provided the *trans*-4-acetoxy- N -benzyloxycarbonyl-D-proline benzyl ester. The latter was hydrogenolyzed with 10% Pd on C to give 5 in 50% yield from 4.

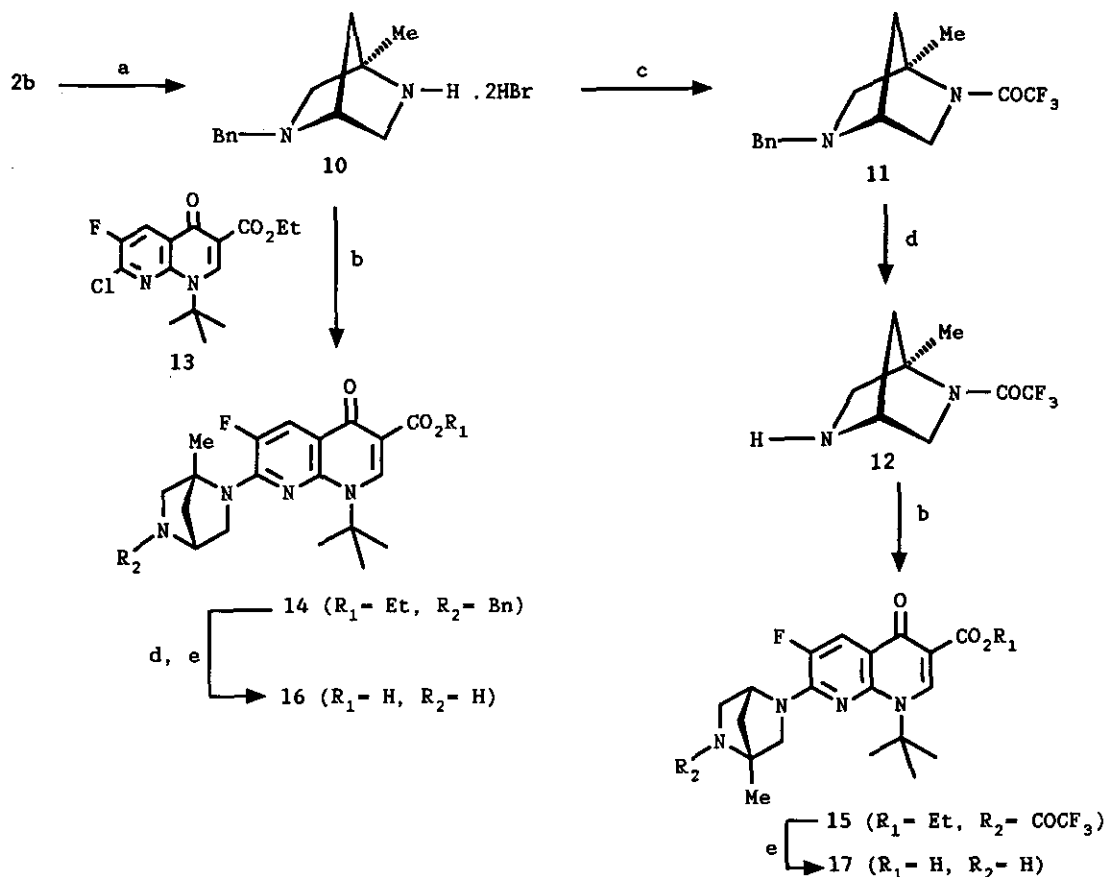
The chiral acid (5)⁴ was converted to the instable adduct (6)⁵ according to literature procedures⁶ with trimethylacetaldehyde in presence of a catalytic amount of trifluoroacetic acid in 90% yield. Deprotonation of 6 with lithium diisopropylamide, followed by alkylation with methyl iodide, gave the propionate (7) with complete retention of configuration in 55% yield after silica gel chromatography. Hydrolysis of 7 with 6N HCl and esterification in EtOH gave the alcohol (8) in 64% yield.⁷ O -Protection with *p*-toluenesulfonyl chloride and reduction of the ester function with lithium borohydride provided the alcohol (9) in 58% yield.⁸ Tosylation of the primary alcohol and finally cyclization with benzylamine in refluxing xylene for 12 hours yielded the expected bridged piperazine (2b) after column chromatography over silica gel (10% total yield from 9).⁹ Detosylation of 2b was performed using 33% HBr in acetic acid to provide 10 in 100% yield (as a dihydrobromide salt)¹⁰ (Scheme 2). The latter was N -protected with tri-



a) Ac_2O , AcOH ; b) ClCO_2Bn , K_2CO_3 ; c) KOH ; d) BrBn , DMA ; e) TsCl , pyridine ;
 f) $\text{Et}_4\text{N}^+\text{AcO}^-$; g) H_2 , 10% Pd/C ; h) $(\text{CH}_3)_3\text{CHO}$, TFA , CH_2Cl_2 ; i) LDA , MeI ; j) 6N HCl ;
 k) HCl_g , EtOH ; l) LiBH_4 , THF ; m) BnNH_2 , xylene .

Scheme I

fluoroacetic acid anhydride to provide 11. Hydrogenolysis of 11 with 10% Pd on C gave the bridged piperazine (12) as a trifluoroacetate salt in 37% yield from 10. The bridged piperazines (10) and (12) were condensed with 7-chloronaphthyridine (13) with DBU to yield the derivatives (14) and (15) in 26 and 50% yield respectively.^{11,12} The naphthyridine (14) was successively



a) 33% HBr, AcOH; b) 13, DBU, MeCN; c) (CF₃CO)₂O, CH₂Cl₂; d) H₂, 10% Pd on C;
 e) 1N NaOH or 1N HCl, EtOH.

Scheme 2

hydrogenolyzed and hydrolysed with 1N NaOH to provide the compound (16) in 30% yield.¹³ The naphthyridine (15) was hydrolysed with 1N NaOH in EtOH to give the derivative (17) in 53% yield.¹⁴

The naphthyridine (17) showed a 4- to 16-fold better *in vitro* antibacterial activity than the naphthyridine (16). *In vitro*, 1a was found better than 17 against either Gram-negative or Gram-positive organisms.

REFERENCES AND NOTES

1. D. Bouzard, P. Di Cesare, M. Essiz, J.P. Jacquet, R. Kiechel, P. Remuzon, A. Weber, T. Oki, M. Masuyoshi, R. E. Kessler, J. Fung-Tomc, and J. Desiderio, *J. Med. Chem.*, 1990, **33**, 1344.
2. P. Remuzon, D. Bouzard, C. Dussy, J. P. Jacquet, and M. Massoudi, *Heterocycles*, 1992, **34**, 241.
3. **4**: oil; $[\alpha]_D +34.2^\circ$ ($c = 0.5$, MeOH). The (2*S*,4*R*) analogue was prepared in a similar manner: A. G. Barrett and D. Pilipauskas, *J. Org. Chem.*, 1991, **56**, 2787.
4. **5**: mp 176-178 °C; $[\alpha]_D +28^\circ$ ($c = 0.86$, 0.5 N HCl); lit.⁶: mp 171-173 °C, $[\alpha]_D -26.6^\circ$ ($c = 0.865$, 0.5 N HCl) for the (2*S*,4*R*) isomer.
5. **6**: mp 100 °C; $[\alpha]_D +11^\circ$ ($c = 0.5$, CHCl₃); lit.⁶: mp 95.5-96.5 °C, $[\alpha]_D = -18.4^\circ$ ($c = 0.5$, CHCl₃) for the **6** enantiomer analogue.
6. T. Weber and D. Seebach, *Helv. Chim. Acta*, 1985, **68**, 155.
7. **8** (as a base): mp 50 °C; $[\alpha]_D +14.5^\circ$ ($c = 0.5$, MeOH); nmr (CDCl₃) δ : 1.28 (t, $J = 7$ Hz, 3H, CH₃ ester); 1.50 (s, 3H, Me-2); 1.71-1.79 (dd, $J = 1.6$ Hz, $J = 14$ Hz, 1H, H-3); 2.53 and 2.60 (dd, $J = 6.2$ Hz, $J = 14$ Hz, 1H, H-3'); 3.01-3.03 (m, 2H, H-5 and H-5'); 4.17 (q, $J = 7$ Hz, 2H, CH₂ ester); 4.34 (m, 1H, H-4).
8. **9**: oil; nmr (CDCl₃) δ : 1.26 (s, 3H, Me-2); 1.80-1.90 (m, 1H, H-3); 2.42-2.46 (m, 7H, Me, tosyl and H-3'); 3.30-3.71 (m, 3H, CH₂OH and H-5); 3.93 (d, $J = 12$ Hz, 1H, H-5'); 4.97 (m, 1H, H-4); 7.27-7.34 (m, 4H, Ar, tosyl); 7.66-7.77 (m, 4H, Ar, tosyl).
9. **2b**: mp 77 °C; $[\alpha]_D +8^\circ$ ($c = 0.5$, MeOH); nmr (CDCl₃) δ : 1.62 (s, 3H, Me-1); 1.76 (d, $J = 9.6$ Hz, 1H, H-7); 1.86 (d, $J = 9.6$ Hz, 1H, H-7'); 2.40 (m, 1H, H-6); 2.46 (s, 3H, Me, tosyl); 2.54 (m, 1H, H-6'); 3.35-3.41 (m, 2H, H-3 and H-4); ; 3.55 (q, $J = 13.4$ Hz, 2H, CH₂Ph); 3.75-3.87 (m, 1H, H-3'); 7.12-7.35 (m, 7H, Ar, tosyl and benzyl); 7.80 (d, $J = 8$ Hz, 2H, Ar, tosyl).
10. The bridged piperazine (**2a**) was obtained from **2b**, after debenylation

and detosylation, in 40% yield as its dihydrobromide salt; mp > 260 °C; $[\alpha]_D -12.5^\circ$ (c= 0.25, H₂O); nmr (DMSO-d₆) δ : 1.65 (s, 3H, Me-1); 2.11 (s, 2H, H-7 and H-7'); 3.27 (d, J = 12.4 Hz, 1H, H-3); 3.43 (dd, J = 2.6 Hz and J = 12.4 Hz, 1H, H-3'); 3.62 (m, 2H, H-6 and H-6'); 4.48 (broad s., 1H, H-4).

11. **14**: amorphous solid; nmr (CDCl₃) δ : 1.40 (t, J = 7 Hz, 3H, Me, ester); 1.75 (m, 1H, H-7, pip.); 1.83 (m, 12H, t-butyl and Me-1, pip.); 2.08 (m, 1H, H-7', pip.); 2.90 (d, J = 10 Hz, H-6, pip.); 3.35-3.50 (m, 2H, H-4 and H-6', pip.); 3.60-3.80 (m, 3H, CH₂Ph and H-3, pip.); 4.06 (m, 1H, H-3', pip.); 4.38 (q, J = 7 Hz, 2H, CH₂, ester); 7.24-7.33 (m, 5H, CH₂Ph), 8.18 (d, J = 12.4 Hz, H-5); 8.82 (s, 1H, H-2).
12. **15**: mp 155 °C; nmr (CDCl₃) δ : 1.40 (t, J = 7 Hz, 3H, Me, ester); 1.84 (s, 9H, t-butyl); 1.91 (s, 3H, Me-4, pip.); 2.08 (m, 2H, H-7 and H-7', pip.); 3.75-3.77 (m, 1H, H-3, pip.); 3.88 (m, 2H, H-6 and H-6', pip.); 3.97-3.98 (m, 1H, H-3', pip.); 4.38 (q, J = 7 Hz, 2H, CH₂, ester); 5.04 (m, 1H, H-1, pip.); 8.19 (d, J = 12 Hz, 1H, H-5); 8.80 (s, 1H, H-2).
13. **16** (hydrochloride salt): mp > 260 °C; $[\alpha]_D +20.2^\circ$ (c= 0.5, MeOH); nmr (DMSO-d₆) δ : 1.89 (s, 3H, Me-1, pip.); 1.89 (s, 9H, t-butyl); 2.12 (d, J = 11 Hz, 1H, H-7, pip.); 2.38 (d, J = 11 Hz, 1H, H-7', pip.); 3.29 (d, J = 11 Hz, 1H, H-6, pip.); 3.76-3.81 (m, 2H, H-6' and H-3, pip.); 4.15 (m, 1H, H-3', pip.); 8.29 (d, J = 12.2 Hz, H-5); 8.97 (s, 1H, H-2).
14. **17** (hydrochloride salt): mp > 260 °C; $[\alpha]_D +17.4^\circ$ (c= 0.5, MeOH); nmr (DMSO-d₆) δ : 1.73 (s, 3H, Me-4, pip.); 1.90 (s, 9H, t-butyl); 2.07 (d, J = 11 Hz, 1H, H-7, pip.); 2.26 (d, J = 11 Hz, 1H, H-7', pip.); 3.48 (m, 2H, H-6 and H-6', pip.); 3.87 (d, J = 11 Hz, 1H, H-3, pip.); 4.25 (d, J = 11 Hz, 1H, H-3', pip.); 5.12 (m, 1H, H-1, pip.); 8.16 (d, J = 12.6 Hz, 1H, H-5); 8.90 (s, 1H, H-2).

Received, 16th January, 1992