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

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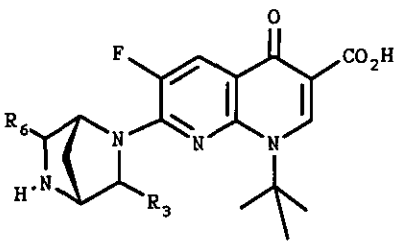
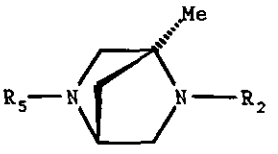
Abstract-An efficient chiral synthesis of the (1*R*,4*R*)-1-methyl-2-(*p*-toluenesulfonyl)-5-phenylmethyl-2,5-diazabicyclo[2.2.1]-heptane (**2b**) was performed using *trans*-4-hydroxy-L-proline as starting material. This bridged piperazine was used in the preparation of new naphthyridones (**16**) and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

In the course of our investigations on the synthesis of new quinolones, BMY 40062[1] (**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 C_3 and C_6 on the chiral bridged piperazine of **1a**, we were interested in the addition of a methyl group at other positions like C_1 and C_4.



1

a: R_3= R_6= H (BMY 40062)
b: R_3= H, R_6= Me (6*R* and 6*S*)
c: R_6= H, R_3= Me (3*R* and 3*S*)



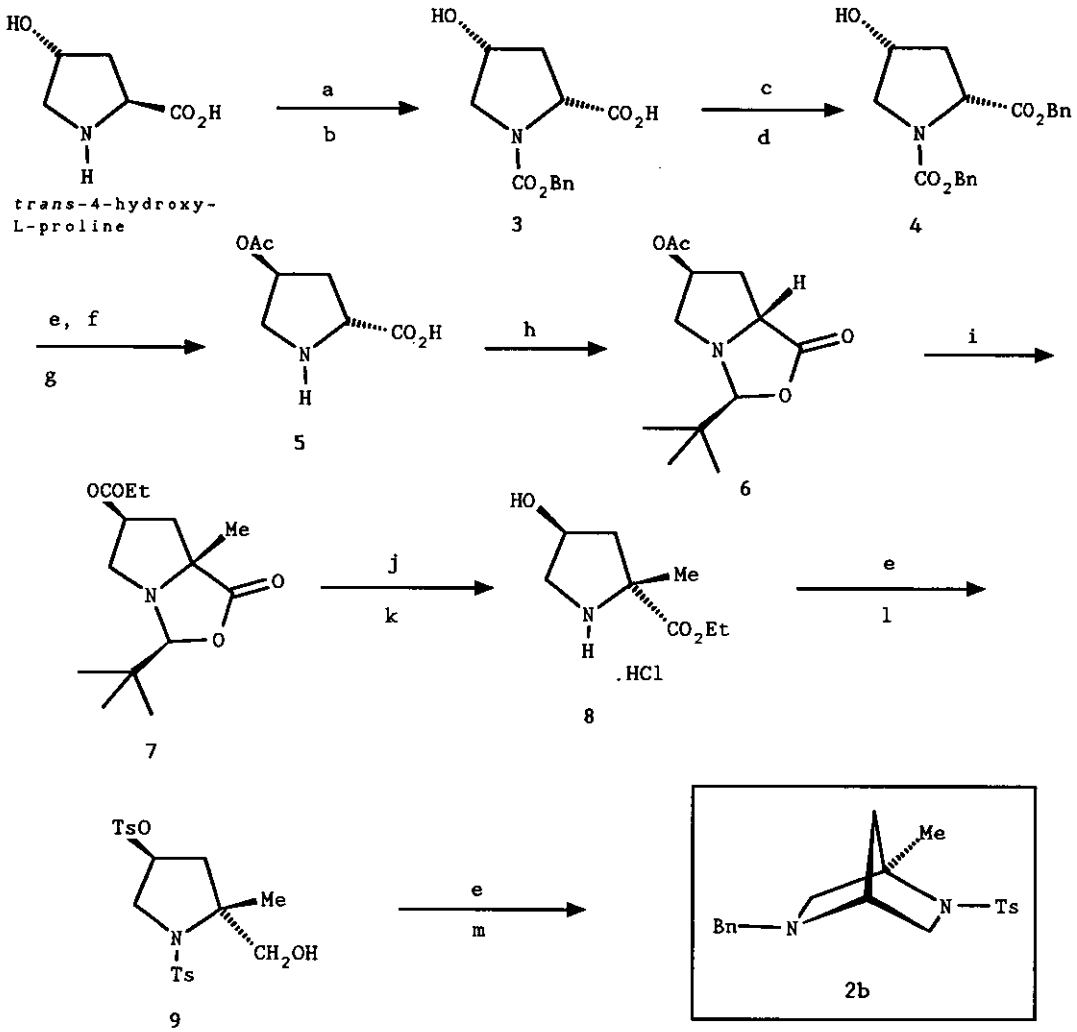
2

a: R_2= R_5= H
b: R_2= Ts, R_5= Bn

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**.

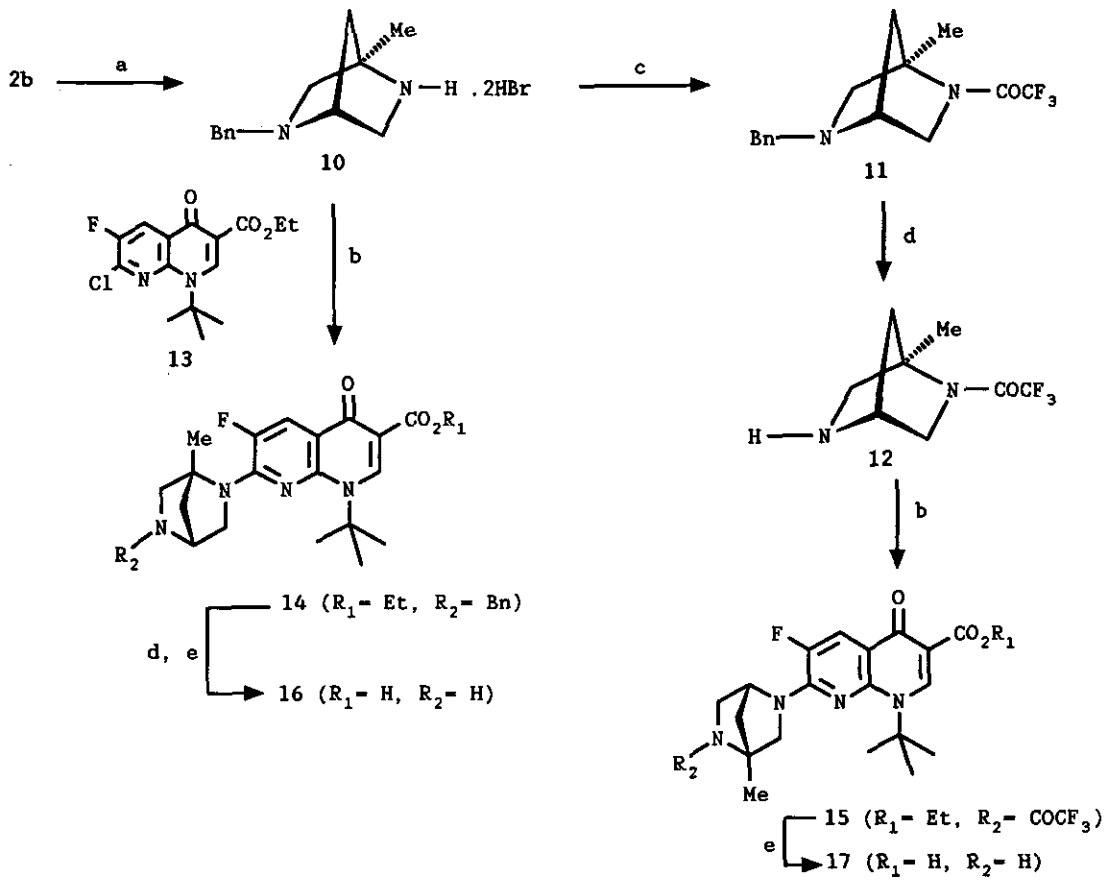
The chiral acid (**5**)[4] was converted to the instable adduct (**6**)[5] according to literature procedures[6] with trimethylacetaldehyde in presence of a catalytic amount of trifluoroacetic acid in 90% yield. Deprotonation of **6** with lithium diisopropylamide, followed by alkylation with methyl 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) $Et_4N^+AcO^-$; g) H_2, 10% Pd/C; h) $(CH_3)_3CHO$, 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) $(CF_3CO)_2O$, CH_2Cl_2; d) H_2, 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° (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° (c= 0.86, 0.5 N HCl); lit.,[6]: mp 171-173 °C, $[\alpha]_D$ -26.6° (c= 0.865, 0.5 N HCl) for the (2*S*,4*R*) isomer.
5. **6**: mp 100 °C; $[\alpha]_D$ +11° (c= 0.5, $CHCl_3$); lit.,[6]: mp 95.5-96.5 °C, $[\alpha]_D$= -18.4° (c= 0.5, $CHCl_3$) 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° (c= 0.5, MeOH); nmr ($CDCl_3$) δ: 1.28 (t, *J* = 7 Hz, 3H, **CH_3** 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, **CH_2** ester); 4.34 (m, 1H, **H-4**).
8. **9**: oil; nmr ($CDCl_3$) 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, **CH_2**OH 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° (c= 0.5, MeOH); nmr ($CDCl_3$) 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, **CH_2**Ph); 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 debenzylation

and detosylation, in 40% yield as its dihydrobromide salt; mp > 260 °C; $[\alpha]_D$ -12.5° (c= 0.25, H_2O); nmr (DMSO-d_6) 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 ($CDCl_3$) 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, CH_2Ph and **H-3**, pip.); 4.06 (m, 1H, **H-3'**, pip.); 4.38 (q, *J* = 7 Hz, 2H, CH_2, ester); 7.24-7.33 (m, 5H, CH_2**Ph**), 8.18 (d, *J* = 12.4 Hz, **H-5**); 8.82 (s, 1H, **H-2**).
12. **15:** mp 155 °C; nmr ($CDCl_3$) 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, CH_2, 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° (c= 0.5, MeOH); nmr (DMSO-d_6) 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° (c= 0.5, MeOH); nmr (DMSO-d_6) 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**).

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