PREPARATION OF (6*R*)- AND (6*S*)-(1*R*,4*R*)-6-METHYL-2-(*p*-TOLUENESULFONYL)-5-PHENYLMETHYL-2,5-DIAZABICYCLO[2.2.1]HEPTANES, INTERMEDIATES IN A SYNTHESIS OF NEW QUINOLONES

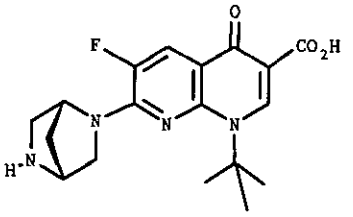
Philippe Remuzon,* Daniel Bouzard, Christian Dussy, Jean-Pierre Jacquet, and Massoud Massoudi

Bristol-Myers Squibb Pharmaceutical Research Institute, B.P.62, Lognes, 77422 Marne-la-Vallee Cedex 2, France

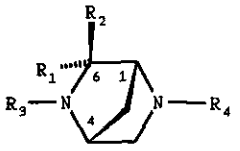
Abstract-An efficient chiral synthesis of both diastereoisomers (**2a**) and (**2b**) was performed using *trans*-4-hydroxy-L-proline as starting material. These bridged piperazines were used in the preparation of quinolones.

In the course of our investigations on the synthesis of new quinolones, BMY 40062[1] (**1**) (Figure 1) was found to be a potent antibacterial agent. The chiral (1*R*,4*R*)- or (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptane groups have already been used as the C_7-substituent of other antimicrobial quinolones.[2,3] To extend our work in this area, we were interested in modifying the naphthyridine (**1**) by adding a methyl group on the chiral bridged piperazine (**2**).

We started from the *trans*-4-hydroxy-L-proline (**3**) (Scheme 1), which after inversion at C_2, *N*,*O*-ditosylation and inversion at C_4, provided the 4-acetoxy-*N*-tosyl-D-proline ethyl ester (**5**) in 29% yield (from **3**) as previously



1



2

a: R_1= Me, R_2= H, R_3= Bn, R_4= Ts

b: R_1= H, R_2= Me, R_3= Bn, R_4= Ts

c: R_1= Me, R_2= R_3= R_4= H

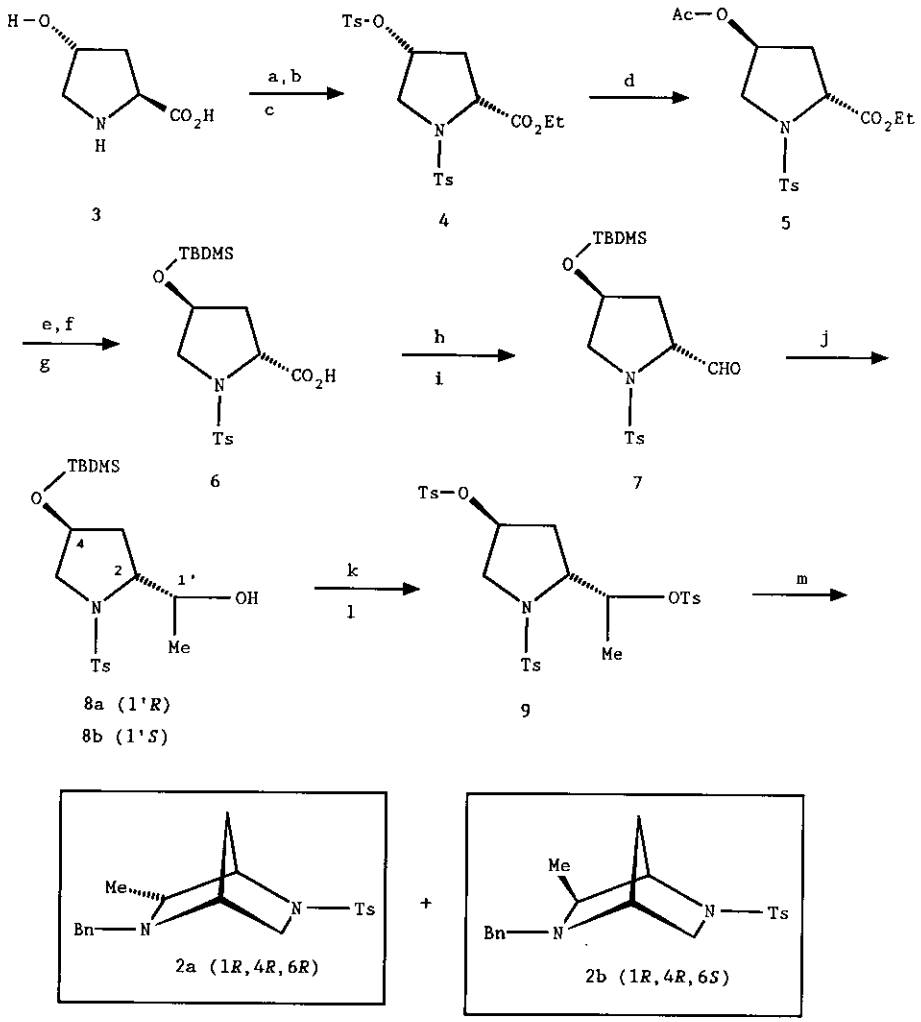
d: R_2= Me, R_1= R_3= R_4= H

Figure 1

described.[1]

Methanolysis of the 4-acetoxy group of **5**, protection of the free hydroxy function with a *tert*-butyldimethylsilyl group and finally alkaline hydrolysis of the ethyl ester, gave the acid (**6**)[4] in 82% yield from **5**. Amidation of **6** with 3,5-dimethylpyrazole and DCCI, performed in 98% yield, was followed by reduction with $LiAlH_4$[5] at -40°C leading to the aldehyde (**7**)[6](71%). Reaction of **7** with MeMgBr gave a mixture of the diols (**8a**)[7]and (**8b**)[8] in 91% yield (these two diastereoisomers could be separated by chromatography on silica gel at this step). The mixture of diols was deprotected with 3.3 % conc. HCl in EtOH (87%), ditosylated with p-toluenesulfonyl chloride (96.4%) and finally cyclized with benzylamine in refluxing toluene for 48 h to yield a mixture (~50/50 ratio) of the expected bridged piperazines (**2a**)[9] and (**2b**)[10] which were easily separated by column chromatography on silica gel (62% total yield for both isomers).

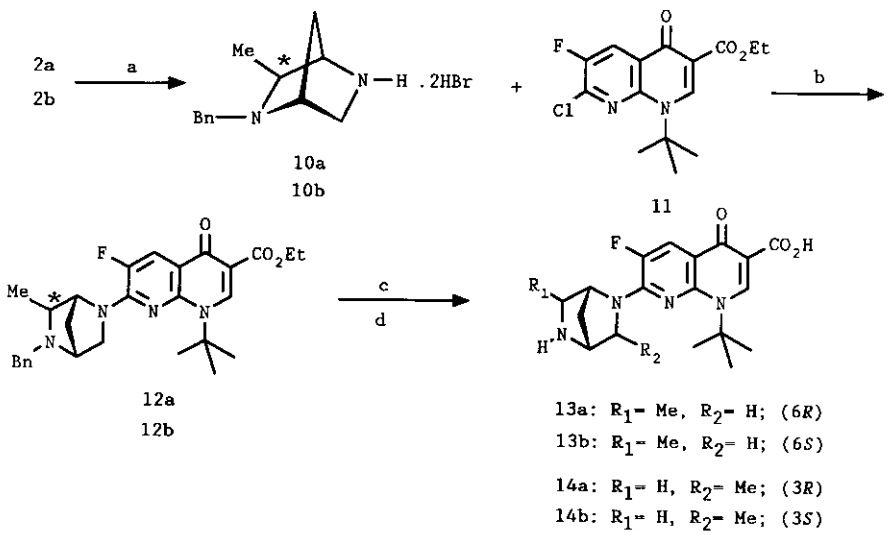
Each bridged piperazine (**2a**) or (**2b**) was detosylated with 33% HBr in AcOH at 80°C and the resulting dihydrobromide salts (**10a**) or (**10b**)[11] were condensed with ethyl 7-chloro-1,8-naphthyridine-3-carboxylate (**11**) to provide **12a** or **12b** (Scheme 2). Debenzylation followed by hydrolysis of the ethyl



a) Ac_2O,AcOH; b) EtOH,HCl; c) TsCl,NEt_3,pyridine; d) NEt_4^+ AcO^-; e) Na_2CO_3, MeOH,,87%; f) ImH,ClTBDMS,DMF,98%; g) KOH,EtOH,96%; h) 3,5-Dimethylpyrazole,DCCI, $CHCl_3$,98%; i) $LiAlH_4$,THF,71%; j) MeMgBr,Et_2O,91%; k) 3.3% conc.HCl,EtOH,87%; l) TsCl,pyridine,97%; m) $BnNH_2$,toluene,62%.

Scheme 1

esters (**12**) led to **13a** or **13b**.[12] The isomer (**13b**) showed a two-fold better *in vitro* antibacterial activity than **13a**.



a) 33% HBr,AcOH,70-90%,b) DBU,MeCN,62-85%; c) H_2,10% Pd/C,1N HCl,MeOH,80-99%; d) 1N NaOH or 1N HCl, EtOH, 63-75%.

Scheme 2

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. T. F. Braish and D. E. Fox, *J.Org.Chem.*, 1990, **55**, 1684.
3. J. S. Kiely, M. P. Hutt, T. P. Culbertson, R. A. Bucsh, D. F. Worth, L. E. Lesheski, R. D. Gogliotti, J. C. Sesnie, M. Solomon, and T. F. Mich., *J.Med.Chem.*, 1991, **34**, 656.
4. **6**: mp 172°C.
5. German Patent DE 2,914,793 (Squibb) (*Chem. Abstr.*, 1979, **92**, 110842h).
6. **7**: oil; nmr(DMSO-d_6) δ: -0.17 (2s, 6H, 2Me, TBDMS); 0.56 (s, 9H, t-butyl, TBDMS); 1.75 and 2.07 (2m, 2H, **CH_2** pyrrolidine); 2.34 (s, 3H, **CH_3**-Ar); 3.01 (dd, *J* = 2 and 10 Hz, 1H, **H-5**, pyrrol.); 3.61 (d, *J* = 10 Hz, 1H, **H'-5**, pyrrol.); 3.78 (m, 1H, **H-2**); 4.34 (m, 1H, **H-4**); 7.39 and

7.61 (2d, J = 8 Hz, 4H, **Ar**); 9.48 (d, J = 4 Hz, **CHO**).

7. **8a:** mp 62°C.

8. **8b:** mp 102°C.

9. **2a:** mp 127°C; nmr ($CDCl_3$) δ: 0.91 (d, J = 10 Hz, 1H, **H-7**); 1.12 (d, J = 6.5 Hz ,3H, **Me-6**); 1.68 (d, J = 10 Hz, 1H, **H-7'**); 2.42 (s, 3H, **CH_3**Ar); 2.75 (q, J = 6 Hz, 1H, **H-6**); 3.02 (dd, J = 2 and 8 Hz, 1H, **H-3**); 3.18 (br s, 1H, **H-4**); 3.20 (m, 1H, **H-3'**); 3.58 (q, J = 4 Hz, 2H, **CH_2**Ph); 4.07 (br s, 1H, **H-1**); 7.26 (m, 5H, **Ph**); 7.29 and 7.70 (2d, J = 8 Hz, 4H, **Ar**-tosyl); $[\alpha]_D$ -58.5° (c = 0.5, MeOH).

10. **2b:** mp 133°C; nmr ($CDCl_3$) δ: 0.79 (d, J = 6.5 Hz, 3H, **Me-6**); 0.93 (d, J = 10 Hz, 1H, **H-7**); 1.66 (d, J = 10 Hz, 1H, **H-7'**); 2.44 (s, 3H, **CH_3**-Ar); 2.73 (q, J = 6Hz, 1H, **H-6**); 2.88 (d, J = 9.5 Hz, 1H, **H-3**); 3.34 (br s, 1H, **H-4**); 3.66 (s, 2H, **CH_2**Ph); 3.71 (d, J = 9.5 Hz, 1H, **H-3'**); 3.93 (br s, 1H, **H-1**); 7.26 (m, 5H, **Ph**); 7.28 and 7.73 (2d, J = 8Hz, 4H, **Ar**-tosyl); $[\alpha]_D$ -18° (c = 0.5, MeOH).

11. The dihydrobromides (**10a**) and (**10b**) were debenzylated to give the piperazines (**2c**) (**2**; R_1= Me; R_2= R_3= R_4= H): mp> 260 °C; $[\alpha]_D$ -23.2° (c = 0.5, MeOH) and (**2d**) (**2**; R_2=Me; R_1=R_3=R_4=H): mp> 260°C; $[\alpha]_D$ -29.4°(c = 0.5, MeOH); **2c**, nmr (DMSO-d_6) δ: 1.49(d, J = 7.2 Hz, 3H, **Me-6**); 2.11 (d, J = 12 Hz, 1H, **H-7**); 2.24 (d, J = 12 Hz, 1H, **H-7'**); 3.40 (d, J = 12 Hz, 1H, **H-3**); 3.46 (d, J = 12 Hz, 1H, **H-3'**); 3.91 (q, J = 7.2 Hz, **H-6**); 4.41 (s, 2H, **H-1** and **H-4**) and **2d** δ: 1.27 (d, J = 6.8 Hz, 3H, **Me-6**); 2.01 (d, J = 12 Hz, 1H, **H-7**); 2.10 (d, J = 12 Hz, 1H, **H-7'**); 3.33 (d, J = 12 Hz, 1H, **H-3**); 3.45 (d, J = 12 Hz, 1H, **H-3'**); 3.93 (q, J = 6.8 Hz, 1H, **H-6**); 4.30 (s, 1H, **H-1**); 4.41 (s, 1H, **H-4**).

12. The 7-[(3*R*)-and (3*S*)-(1*R*,4*R*)-2,5-diazabicyclo[2.2.1]heptan-2-yl] analogs of **13** (**14a,14b**) were also obtained *via* selective protection and deprotection of the bridged piperazine (**10a**) or (**10b**), following a similar procedure as described in an earlier paper: J. P. Jacquet, D. Bouzard, J. R. Kiechel, and P. Remuzon, *Tetrahedron Lett.*, 1991, **32**, 1565.

Received, 8th November, 1991