Pergamon

Tetrahedron Letters, Vol. 36, No. 46, pp. 8391-8394, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01813-1

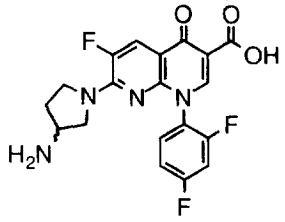
A Practical Stereoselective Synthesis of (*2S, 4S*)-4-*tert*-Butoxycarbonylamino-2-Methylpyrrolidine [1]

Qun Li,* Daniel T. W. Chu, Kathleen Raye, Akiyo Claiborne, Louis Seif, Bryan Macri and Jacob J. Plattner

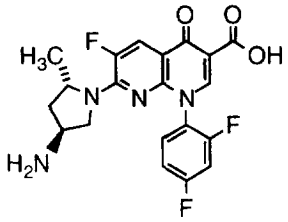
Abbott Laboratories, 100 Abbott Park Road, Abbott Park, Illinois 60064-3500

Abstract: *Two practical syntheses of (2S, 4S)-4-tert-butoxycarbonylamino-2-methylpyrrolidine, an important intermediate for quinolone antibacterial agents, have been developed through the combination of diastereo and enantioselective reactions starting from ethyl crotonate and L-alanine, respectively.*

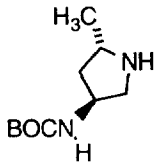
Tosufloxacin (**1**, A-60969) is an exceedingly potent clinically utilized 4-quinolone antibacterial agent with a 3-aminopyrrolidinyl group at the 7-position of the naphthyridine ring.[2] Introduction of a methyl group at the 2-position of the pyrrolidine ring of tosufloxacin produced a compound (A-65485, **2**) with substantial increased water solubility (150 fold) while maintaining excellent antibacterial activity.[1, 3] This enhanced water solubility is anticipated to improve the phamacokinetics of the drug. The superb pharmacological properties of **2**[3] mandated an efficient synthetic route to the construction of **3**. The key challenge of this synthesis is the introduction of two chiral centers to the pyrrolidine ring. Our original 12-step approach to **3** required the prohibitively expensive *cis*-4-hydroxy-*D*-proline as a starting material and was not amenable to a commercial scale synthesis.[4, 5]



1, tosufloxacin



2, A-65485

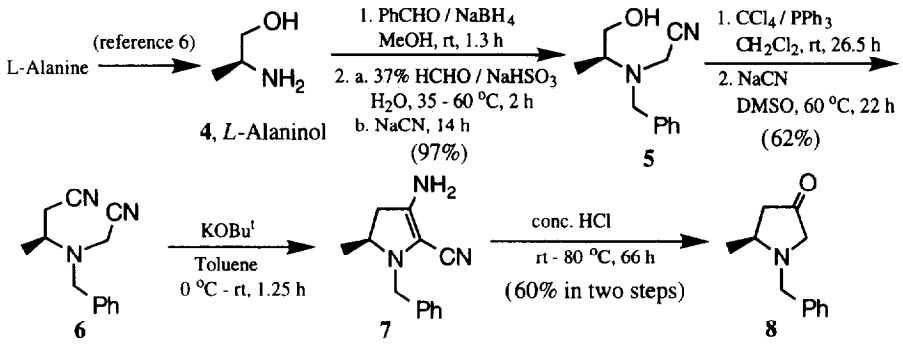


3

Outlined are two practical enantioselective syntheses of **3**.[1] The first route is illustrated in **Scheme 1**. This method utilized *L*-alaninol (**4**), which was obtained by a well established literature method [6] from the reduction of *L*-alanine using the borane-dimethylsulfide complex activated by boron trifluoride-etherate. Reductive condensation of **4** with benzaldehyde using sodium borohydride [7] and consecutive cyanomethylation [8] of the resulting benzylamine produced **5** in 97% yield. Treatment of **5** with carbon tetrachloride and triphenylphosphine, followed by reaction with sodium cyanide in DMSO afforded **6** in 62% yield.[9] Reaction of **6** with potassium *tert*-butoxide in toluene at 0°C resulted in a regioselective cyclization to form **7**. Treatment of **7** with concentrated hydrochloric acid resulted in hydrolysis and decarboxylation to produce pyrrolidinone **8** in 60% yield. The process described above starts with inexpensive *L*-alanine and provides **8** in 36% overall yield.

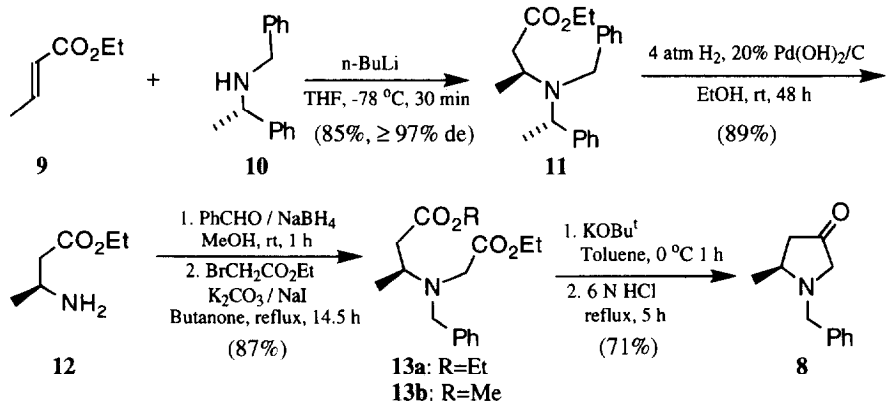
The second route employed recent discoveries in diastereoselective Michael addition of chiral lithium amides to α, β-unsaturated esters pioneered by Davies and Ichihara (**Scheme 2**).[10, 11] This method utilized the

Scheme 1



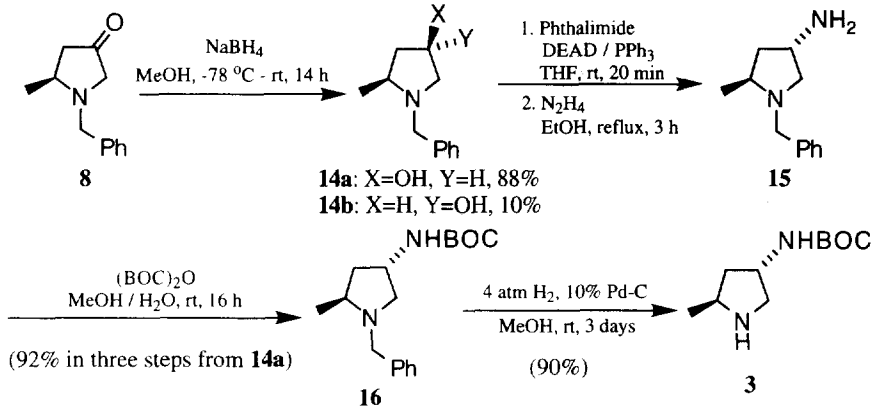
easily available[12] *S*-N-(1-methylbenzyl)benzylamine[13, 10f] as a chiral auxiliary. Addition of *trans*-ethyl crotonate (**9**) at -78°C to a THF solution of the lithium salt of *S*-N-(1-methylbenzyl)benzylamine (**10**), which was generated *in situ* from reaction of the corresponding amine with *n*-butyllithium at 0°C, gave **11** in 97% d.e.[14] and 85% yield. Complete debenzylation of **11** with 20% $Pd(OH)_2$ on carbon under 4 atmospheres of hydrogen in ethanol gave *S*-β-aminobutyrate **12** in 89% yield. In contrast to previous reports,[16] a facile removal of the less hindered benzyl group could be achieved selectively under acidic condition in 94% yield.[15] Reductive benzylation in methanol, followed by alkylation with ethyl bromoacetate in the presence of K_2CO_3 and NaI in refluxing 2-butanone provided a mixture of diethyl ester **13a** and monomethyl ester **13b** (ratio: 78 : 28) in 87% yield. The latter was apparently introduced in the benzylation step through an ester exchange reaction. The mixture of **13a** and **13b** underwent a Dieckmann cyclization using $KOBu^t$ in toluene and subsequent decarboxylation in refluxing 6N HCl furnished **8** in 71% yield. The reactions involved in this process are technically simple and the starting materials are inexpensive. The overall yield of **8** from **9** is 47%.

Scheme 2



Conversion of **8** to the final target compound **3** is illustrated in **Scheme 3**. Reduction of the ketone **8** yielded *cis* and *trans* alcohols **14**. Among the reagents tried,[17] sodium borohydride in methanol at -78°C provided the best selectivity with a *cis* and *trans* ratio of about 9 to 1. The two isomers **14a** and **14b** were separated by column chromatography.[18] The amine **15** was obtained through a Mitsunobu [19] reaction of **14a** with phthalimide and followed by removal of the imide with hydrazine. Reaction of amine **15** with $(BOC)_2O$ provided **16** in 92% yield from **14a**. Hydrolysis of the benzyl group furnished the title compound **3** (90%).

Scheme 3



In conclusion, two efficient and stereoselective processes for the preparation of (*2S, 4S*)-4-butoxycarbonylamino-2-methylpyrrolidine, an important intermediate for quinolone antibacterial agents have been developed. These processes enable the rapid and large-scale preparation of the pyrrolidine intermediate.[20]

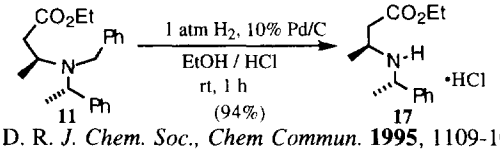
Acknowledgment: We wish to thank Drs. Fariborz Mohamadi and Zhenkun Ma for helpful discussions. We also acknowledge the support from the Structure Chemistry Department for analysis of the compounds.

References and Notes

1. Chu, D. T. W; Li, Q; Tanaka, K; Alder, J; Claiborne, A; Lico, I; Raye, K; Rosen, T; Plattner, J. J. Presented in part at the *32nd ICAAC* **1992**, Abstract 652.
2. (a) Chu, D. T. W; Fernandes, P. B; Claiborne, A; Gracey, E. H; Pernet, A. G. *J. Med. Chem.* **1986**, *29*, 2363-2369. (b) Sojima, R; Shimada, K. *Drugs Fut.* **1989**, *14*, 536-538.
3. (a) Marsh, K; Eiden, E; Hernandez, L; Chu, D. T. W. *32nd ICAAC* **1992**, Abstract 654. (b) Clement, J.J; Tanaka, S. K; Alder, J; Vojtko, C; Beyer, J; Hensey, D; Ramer, N; McDaniel, D; Chu, D. T. W. *Antimicrob. Agents Chemother.* **1994**, *38*, 1071-1078.
4. Rosen, T; Chu, D. T. W; Lico, I. M; Fernandes, P. B; Marsh, K; Shen, L; Cepa, V. G; Pernet, A. G. *J. Med. Chem.* **1988**, *31*, 1598-1611.
5. For other synthesis of **3** starting from 4-hydroxy-*L*-proline see: Cesare, P. D; Bouzard, D. B; Essiz, M; Jacquet, J. P; Ledoussal, B; Kiechel J. R; Remuzon, P; Kessler, R. E; Fung-Tomc, J; Desiderio, J. *J. Med. Chem.* **1992**, *35*, 4205-4213.
6. Gage, J. R; Evans, D. A. *Org. Synth.* **1989**, *68*, 77-82.
7. Schwan, T, J; Lougheed, G. S; Burrous, S. E. *J. Heterocyclic Chem.* **1974**, *11*, 807-810.
8. Allen, C. F; VanAllan, J. A. *Org. Synth. Coll. Vol. 3*, **1955**, 275.
9. Only the chloride was obtained when **5** was treated with MsCl. It apparently proceeded via aziridinium intermediate by neighboring group participation.
10. (a) Davies, S. G; Ichihara, O. *Tetrahedron: Asymmetry* **1991**, *2*, 183-186. (b) Davies, S. G; Ichihara, O; Walters, I. A. S. *Synlett* **1994**, 117-118. (c) Davies, S. G; Walters, I. A. S. *J. Chem. Soc. Perkin Trans. 1* **1994**, 1129-1139. (d) Davies, S. G; Ichihara, O; Walters, I. A. S. *J. Chem. Soc. Perkin Trans. 1* **1994**, 1141-1147. (e) Davis, S. G; Hedgecock, C. J. R; McKenna, J. M. *Tetrahedron: Asymmetry* **1995**, *6*, 827-830. (f) Tsukada, N; Shimada, T; Gyoung, Y. S; Asao, N; Yamamoto, Y. *J. Org. Chem.* **1995**, *60*, 143-148.
11. For a review see: Cole, D. C. *Tetrahedron* **1994**, *50*, 9517-9582.
12. A modified procedure of Cain et al [13b] was used to make *S*-N-benzyl-1-phenylethylamine conveniently (it is now also available from Aldrich and Fluka): The mixture of *S*-methylbenzylamine (91.25 g, 0.753 mol) and benzaldehyde (79.93g, 0.750 mol) in 400 mL of methanol was stirred at room temperature for 2 h before being added $NaBH_4$ (21.20 g, 0.560 mol) in portions over 1 h period, while maintaining the reaction temperature at 20 to 28°C. The mixture was stirred at room temperature for an additional 16 h. The solvent was then removed under vacuum. The residue was dissolved in CH_2Cl_2, and the solution was washed with water (3X), dried over $MgSO_4$ and concentrated to give a colorless liquid, which was distilled (b.p. 109-110°C / 0.25 mmHg) to afford the title compound (151.20 g, 95%).

13. (a) Yamaguchi, S; Yasuhara, F; Kabuto, K. *J. Org. Chem.* **1977**, *42*, 1578-1581. (b) Cain, C. M; Cousins, R. P. C; Coumbarides, G; Simpkins, N. S. *Tetrahedron*, **1990**, *46*, 523-544. (c) Juaristi, E; Murer, P; Seebach, D. *Synthesis* **1993**, 1243-1246.
14. The diastereomeric excess was determined by ^{1}HNMR.
15. We found that the benzyl group of **11** can be selectively cleaved under acidic condition using 10% Pd/C to give **17**, which may be an important intermediate [16, 10e-f] useful for further derivatizations.

Procedure: The mixture of **8** (24.1 g. 74.05 mmol), 10% Pd/C (3.00 g) and concentrated HCl (12.0 mL) in methanol (240 mL) was stirred under 1 atomosphere of H_2 for 1h at room temparature. Reaction was then filtered through Celite. The filtrate was concentrated under vacuum to give pure **17** as a white solid (18.9 g, 94%):



16. Davies, S. G; Fenwick, D. R. *J. Chem. Soc., Chem Commun.* **1995**, 1109-10 & references cited therein.
17. Reduction of **8** have been tried using the following reagents and conditions (*cis*: *trans*): $NaBH_4$ / MeOH / -50°C (6.0 : 1), $NaBH_4$ / MeOH / -10°C (5.8 : 1), $NaBH_4$ / MeOH / 23°C (4.1 : 1), $LiAlH_4$ / THF / -78°C (7.8 : 1), $NaBH_4$ / THF / -10°C (5.8 : 1), L-Selectride® / THF / -78°C (6.8 : 1), L-Selectride® / toluene / -78°C (6.8 : 1), L-Selectride® / CH_2Cl_2 / -78°C (4.9 : 1), K-Selectride® / THF / -78°C (3.1 : 1), LS-Selectride® / THF / -78°C (2.0 : 1), $LiBH(OBu\text{-}t)_3$ / CH_2Cl_2 / -78 to 23°C (1.8 : 1), DIBAL / THF / -78°C (1.2 : 1), DIBAL / toluene / -78°C (1.9 : 1), DIBAL / CH_2Cl_2 / -78°C (2.2 : 1), H_2 / Pt / MeOH / 23°C(1 : 1).
18. The mixture of **14a** and **14b** could also be used without separation for the next steps and the isomeric pure **16** was obtained in this case by a simple recrystalization in ethyl acetate / hexane
19. Hegedus, L. S; Holden, M. S; McKearin, J. M. *Org. Synth.* **1984**, *62*, 48-57.
20. Physical and spectroscopic data for selected new compounds. **5**: MS (DCI / NH_3) 205 (M+H), ^{1}HNMR ($CDCl_3$) δ 1.21 (d, *J*=7.5 Hz, 3H), 2.47 (dd, *J*=3, 8 Hz, 1H), 3.30 (m, 1H), 3.45 (d, *J*=10.5 Hz, 1H), 3.46 (d, *J*=10.5 Hz, 1H), 3.54 (m, 2H), 3.70 (d, *J*=13.5 Hz, 1H), 3.90 (d, *J*=13.5 Hz, 1H), 7.34 (m, 5H); **6**: MS (DCI / NH_3) 231, 233 ($M+NH_4$), ^{1}HNMR ($CDCl_3$) δ 1.41 (d, *J*=6.5 Hz, 3H), 2.57 (dd, *J*=6.5, 16.5 Hz, 1H), 2.66 (dd, *J*=6.5, 16.5 Hz, 1H), 3.34 (sextet, *J*=6.5 Hz, 1H), 3.48 (s, 2H), 3.81 (s, 2H), 7.36 (m, 5H); **7**: MS (DCI / NH_3) 214 (M+H), ^{1}HNMR ($CDCl_3$) δ 1.31 (d, *J*=6 Hz, 3H), 3.28 (dd, *J*=4, 15 Hz, 1H), 3.44 (d, *J*=13 Hz, 1H), 3.52 (dd, *J*=3, 15 Hz, 1H), 3.74 (m, 1H), 4.04 (d, *J*=13 Hz, 1H), 4.38 (br, 2H), 7.38 (m, 5H); **8**: MS (DCI / NH_3) 190 (M+H), $[\alpha]_D^{22}$=+212.4° (C=1.90, $CHCl_3$) (from **Scheme 1**), $[\alpha]_D^{26}$=+208.9° (C=1.92, $CHCl_3$) (from **Scheme 2**); ^{1}HNMR ($CDCl_3$) δ 1.35(d, *J*=6 Hz, 3H), 2.14 (dd, *J*=10, 18 Hz, 1H), 2.50 (dd, *J*=6, 18 Hz, 1H), 2.64 (d, *J*=17 Hz, 1H), 2.98 (m, 1H), 3.24 (d, *J*=17 Hz, 1H), 3.28 (d, *J*=13 Hz, 1H), 4.20 (d, *J*=13 Hz, 1H), 7.31 (m, 5H). IR (neat): 1755 cm^{-1}; **11**: MS (DCI / NH_3) 326 (M+H), ^{1}HNMR ($CDCl_3$) δ 1.13 (d, *J*=7 Hz, 3H), 1.16 (t, *J*=7 Hz, 3H), 1.35 (d, *J*=7 Hz, 3H), 2.10 (dd, *J*=6, 14 Hz, 1H), 2.36 (dd, *J*=6, 14 Hz, 1H), 3.44 (m, 1H), 3.67 (d, *J*=14 Hz, 1H), 3.74 (d, *J*=14 Hz, 1H), 3.88-4.07 (m, 3H), 7.19-7.42 (m, 10H); **13a**: MS (DCI / NH_3) 308 (M+H), ^{1}HNMR ($CDCl_3$) δ 1.12 (d, *J*=6 Hz, 3H), 1.24 (t, *J*=7 Hz, 6H), 2.29 (dd, *J*=6, 16 Hz, 1H), 2.64 (dd, *J*=6, 16 Hz, 1H), 3.28 (s, 2H), 3.41 (m, 1H), 3.66 (s, 3H), 3.69 (d, *J*=14 Hz, 1H), 3.82 (d, *J*=14 Hz, 1H), 4.10 (q. *J*=7 Hz, 4H), 7.31 (m, 1H); **13b**: MS (DCI / NH_3) 294 (M+H), ^{1}HNMR ($CDCl_3$) δ 1.13 (d, *J*=6 Hz, 3H), 1.24 (t, *J*=7 Hz, 6H), 2.30 (dd, *J*=6, 16 Hz, 1H), 2.64 (dd, *J*=6, 16 Hz, 1H), 3.28 (s, 2H), 3.41 (m, 1H), 3.69 (d, *J*=14 Hz, 1H), 3.78 (d, *J*=14 Hz, 1H), 4.10 (q. *J*=7 Hz, 2H), 7.31 (m, 1H); **14a**: MS (DCI / NH_3) 192 (M+H), ^{1}HNMR ($CDCl_3$) δ 1.23 (d, *J*=6 Hz, 3H), 1.46 (m, 1H), 2.70 (br, 1H), 2.19 (dd, *J*=4.5, J=10 Hz, 1H), 2.40 (m, 2H), 2.84 (d, J=10 Hz, 1H), 3.14 (d, J=13 Hz, 1H), 4.05 (d. J=13 Hz, 1H), 4.12 (m 1H,), 7.31 (m, 5H); **14b**: MS (DCI / NH_3) 192 (M+H), ^{1}HNMR ($CDCl_3$) δ 1.16 (d, *J*=6 Hz, 1H), 1.82 (m, 2H), 2.18 (dd, 1H, *J*=5, 10 Hz, 1H), 2.82 (m, 1H), 3.26 (d, *J*=10 Hz, 1H), 3.29 (d, *J*=13 Hz, 1H), 4.02 (d, *J*=13 Hz, 1H), 4.36 (m, 1H), 7.31 (m, 5H); **16**: m.p. 82-83°C, $[\alpha]_D^{24}$= +99.4° (C=1.08, $CHCl_3$), MS (DCI / NH_3) 291 (M+H), ^{1}HNMR ($CDCl_3$) δ 1.15 (d, *J*=6 Hz, 3H), 1.41 (s, 9H), 1.72 (m, 1H), 1.93 (m, 2H), 2.63 (m, 1H), 3.21 (d, *J*=13 Hz, 1H), 3.26 (m, 1H), 3.98 (d, *J*=13 Hz, 1H), 4.07 (m, 1H), 4.48 (br, 1H); **3**: m.p. 67-68°C, $[\alpha]_D^{24}$=+1.23° (C=0.57, $CHCl_3$), MS (DCI / NH_3) 201 (M+H), ^{1}HNMR ($CDCl_3$) δ 1.15(d, *J*=6 Hz, 3H), 1.44 (s, (1H), 1.54-1.63 (m, 2H), 1.75 (m, 1H), 2.64 (dd, *J*=5, 12 Hz, 1H), 3.26 (m, 1H), 3.38 (dd, *J*=7, 12 Hz, 1H), 4.12 (br, 1H), 4.63 (br, 1H). IR (KBr): 1685 cm^{-1}.

(*Received in USA* 23 *August* 1995; *revised* 19 *September* 1995; *accepted* 21 *September* 1995)