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Novel stereoselective synthesis of all four diastereomers of 3a-methyl-pyrrolo[3,4-*c*]piperidine from glycine ethyl ester

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Abstract—Asymmetric synthesis of all four diastereomers of 3a-methyl-pyrrolo[3,4-*c*]piperidine is described herein. The key steps in this synthesis are the highly diastereoselective hydrogenation of an alkenyl nitrile through a hydroxyl-directed or sterically controlled hydrogenation, and the resolution of enantiomers using a chiral auxiliary.

Chiral piperidine derivatives display a broad range of important biological activities and are versatile precursors of naturally occurring alkaloids.[1] As a consequence, asymmetric synthesis of these piperidines continues to attract considerable attention. [3,4-*c*]Pyrrolopiperidine compounds have recently received great interest due to their antagonist profiles of Substance P (SP),[2] which acts as a neurotransmitter and is the most abundant neurokinin in the mammalian central nervous system (CNS).[3] Additionally, chiral [3,4-*b*]pyrrolopiperidines also serve as useful subunits of quinolones having highly potent antibacterials, especially moxifloxacin (Fig. 1).[4] Certainly, the development of new enantiopure [3,4-*c*]-pyrrolopiperidine compounds is important in view of the above described usefulness in organic synthesis. Herein we wish to report the asymmetric synthesis of four new [3,4-*c*]pyrrolopiperidines starting from glycine ethyl ester.[5] These molecules contain two chiral centres, one of which is a quaternary carbon.[6]

It was expected that the diastereo and enantioselective construction of stereocentres would be enabled the resolution of enantiomer using chiral auxiliary followed by stereoselective hydrogenation. Retrosynthetic analysis towards the synthesis of [3,4-*c*]pyrrolopiperidines is shown in Scheme 1.

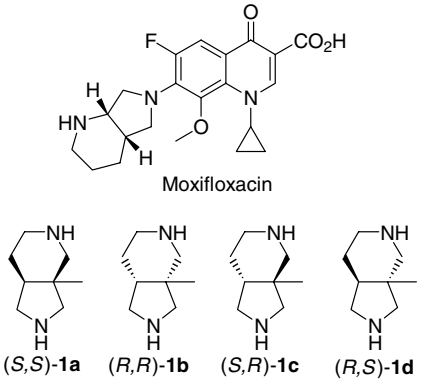

Figure 1.

Our synthesis started with commercially available glycine ethyl ester hydrochloride **2** as illustrated in Scheme 2. Compound **3** was prepared by modification of Rapoport's procedure.[7] Boc-protection of the amino group in glycine ethyl ester followed by Michael addition to ethyl acrylate and cyclization by Dieckmann reaction under basic condition gave 4-ethoxycarbonyl-2-pyrrolidinone **3** in good yield. The treatment of **3** with iodomethane in the presence of K_2CO_3 gave 4-ethoxycarbonyl-4-methyl-2-pyrrolidinone **4** that possesses an all-carbon quaternary stereocentre in 92% yield. The Horner–Wadsworth–Emmons olefination of **4** with diethyl cyanomethylphosphonate provided the corresponding cyanoalkenylpyrrolidine **5** in 98% yield. To resolve the enantiomers of cyanoalkenylpyrrolidine **5**, we examined several chiral auxiliaries (camphorsultams,[8]

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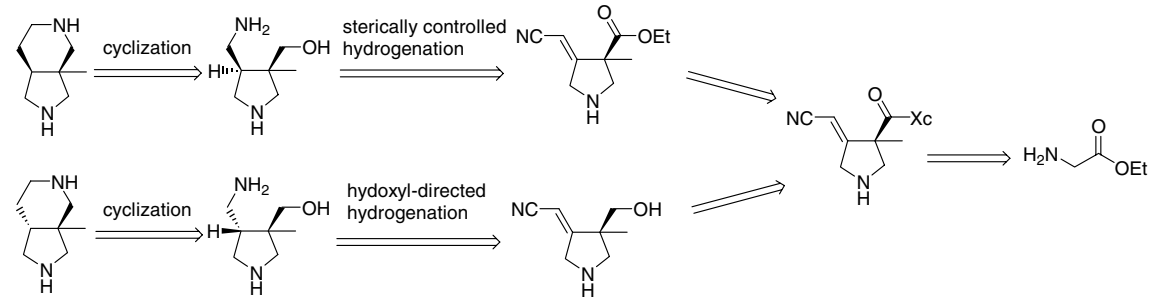
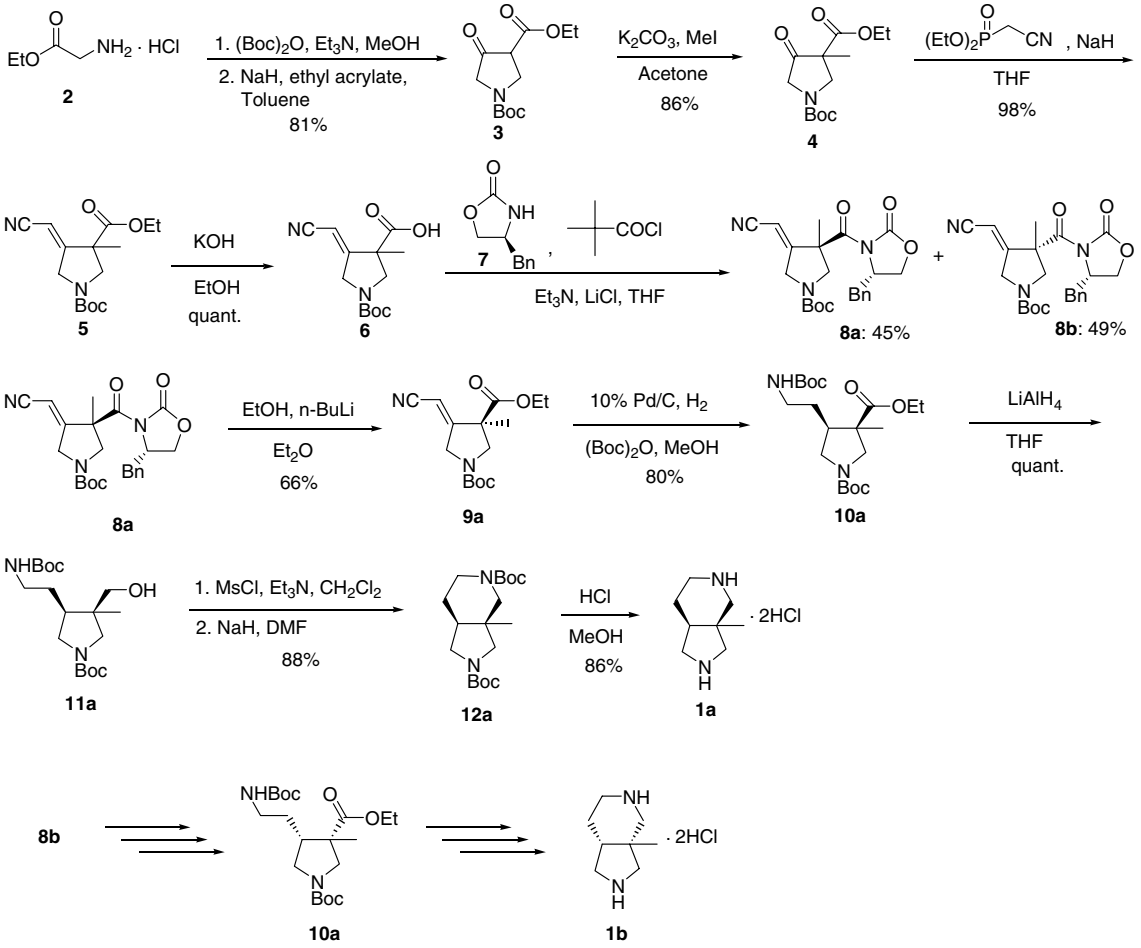


Scheme 1.



Scheme 2.

benzosultams[9] and 2-oxazolidinones[10]) and found that readily commercially available (*S*)-4-benzyl-2-oxazolidinone **7** was the best for the separation of diastereoisomers by column chromatography.[11] Saponification of the ethyl ester of **6** with NaOH followed by coupling with (*S*)-4-benzyl-2-oxazolidinone **7** using a mixed anhydride method (*t*-BuCOCl, LiCl, Et_3N)[12] afforded a 1:1.1 mixture of acyloxazolidinones **8a** and **8b** in 94% yield. This diastereomeric mixture was readily separated by column chromatography on up to 25 g scale.[13] Next, treatment of acyloxazolidinone **8a** with lithium ethoxide cleaved the auxiliary and afforded the enantiopure ethyl ester **9a** in 66% yield.

Catalytic hydrogenation of both alkenyl and nitrile functions in **9a** (50 psi H_2, 10% Pd–C) and in situ Boc-protection of amine provided cis isomer **10a** as the major product, which is obviously obtained by steric control. This stereoselective hydrogenation can be performed in a variety of solvents,[14] more efficiently in high dielectric media in general. The preparative scale of stereoselective hydrogenation in MeOH afforded cis isomer **10a** in 80% yield with 91:9 dr. Reduction of the ester group with $LiAlH_4$ followed by the mesylation of the hydroxyl group and cyclization under NaH in DMF afforded a bis-Boc-protected [3,4-*c*]pyrrolopiperidine **12a** in 88% yield. Finally, treatment of **12a** with

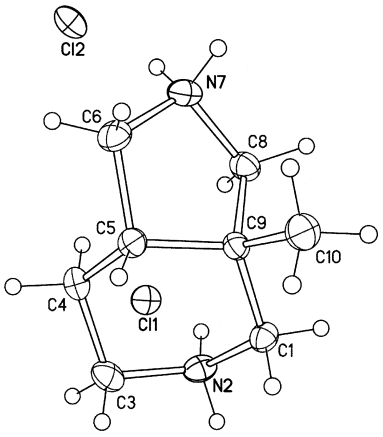


Figure 2. X-ray structure of (*S*,*S*)-**1a**.

MeOH/HCl gave the desired [*S*,*S*]-3a-methyl-pyrrolo-[3,4-*c*]piperidine **1a** in 86% yield. For identification of the absolute stereochemistry, [3,4-*c*]pyrrolopiperidine **1a** was recrystallized from MeOH and subjected to X-ray crystallographic analysis (Fig. 2).[15]

Likewise, acyloxazolidinone **8b** was transformed into [*R*,*R*]-3a-methyl-pyrrolo[3,4-*c*]piperidine **1b** using an analogous sequence of reactions (Scheme 2). The analytical and spectroscopic data for all of the compounds in this sequence are provided in Supplementary data.

To obtain the *trans*-pyrrolo[3,4-*c*]piperidine, we employed a hydroxyl-directed hydrogenation,[16] wherein the substrate is bound to the catalyst surface on the same side as the hydroxyl group, resulting in the addition of hydrogen *syn* to the coordinating moiety. Treatment of acyloxazolidinone **8a** with sodium borohydride afforded the enantiopure alcohol **13a** in 80% yield. The hydrogenation of **13a** (50 psi H_2, 10% Pd–C, $(Boc)_2O$, EtOAc) provided trans isomer **11c** as the major product (dr 13:1) in 82% yield (Scheme 3).[14] Mesylation of the hydroxyl group followed by cyclization using NaH in DMF and deprotection of Boc under MeOH/HCl afforded the desired [*S*,*R*]-3a-methyl-pyrrolo[3,4-*c*]piperidine **1c** in good yield. Acyloxazolidinone **8b** was also transformed into [*R*,*S*]-3a-methyl-pyrrolo[3,4-*c*]piperidine **1d** using an analogous sequence of reactions.

In conclusion, we have established a new strategy for the synthesis of chiral pyrrolo[3,4-*c*]piperidine compounds possessing an all-carbon quaternary stereocentre at the 3a position. This asymmetric route would be potentially useful for the synthesis of numerous 3a-substituted-pyrrolo[3,4-*c*]piperidines,[2b] which is now in progress and will be reported in due course.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.05.100.

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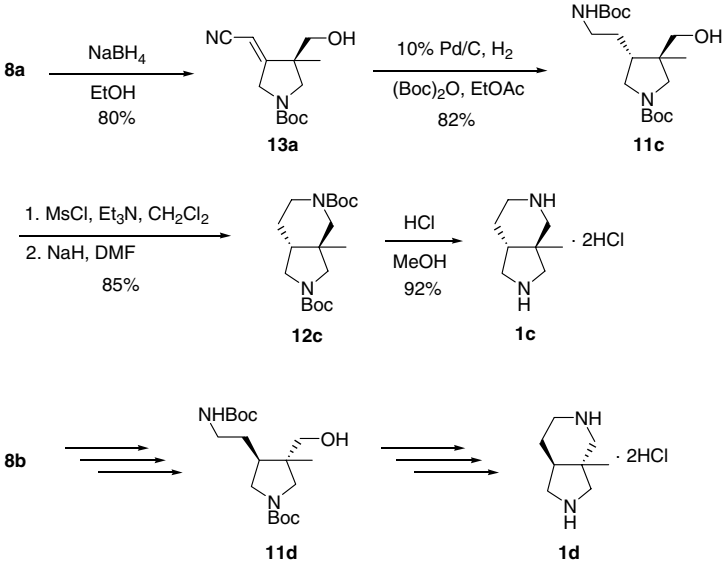

Scheme 3.

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5. Several quinolones including these 3a-methyl-[3,4-*c*]pyrrolopiperidines have recently been synthesized in our laboratories, which showed strong antibacterial activity against especially tuberculosis. Details of this work will be published later.
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11. The corresponding diastereoisomers of acylcamphorsultam and acylbenzosultam were prepared following the same procedure as described for **8a** and **8b**, starting from (1*S*)-(−)-2,10-camphorsultam and 3-(*S*)-*tert*-butyl-1,2-benzisothiazoline 1,1-dioxide. Diastereoisomers of acylcamphorsultam could not be separated on TLC, and diastereoisomers of acylbenzosultam were separated slightly ($R_f = 0.29$ (more polar diastereoisomer), 0.34 (less polar diastereoisomer) (EtOAc/hexanes = 1:3, v/v)).
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13. *General procedure for the synthesis of acyloxazolidinones* **8a** *and* **8b**: To a solution of compound **6** (18.9 g, 71.0 mmol) and triethylamine (35.0 mL, 250 mmol) in THF (470 mL) was added pivaloyl chloride (26.0 mL, 213 mmol) at −10 °C. A white solid was formed instantaneously. The mixture was stirred at the same temperature for 2 h, and then it was treated with lithium chloride (4.50 g, 107 mmol), followed by (*S*)-4-benzyl-2-oxazolidinone **7** (12.5 g, 71.0 mmol). The reaction mixture was allowed to warm to room temperature. After being stirred for 3 h, the reaction mixture was quenched with water and THF was removed in vacuo. The residue was extracted with EtOAc, and the combined organic layers were washed with 1 M sodium bicarbonate followed by brine, dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash column chromatography (20–45% EtOAc in hexanes, linear gradient) to afford title compound **8a** (14.6 g, 49%, $R_f = 0.22$ (EtOAc/hexanes = 1:3, v/v)) and the more quickly eluting (*R*,*S*) isomer **8b** (13.4 g, 45%, $R_f = 0.46$ (EtOAc/hexanes = 1:3, v/v)). Compound **8a**: mp 82–83 °C; $[\alpha]_D^{23}$ +50.68 (*c* 1.00, $CHCl_3$); IR(KBr) 2978, 2932, 1784, 1702, 1414, 1390; ^{1}H NMR (300 MHz, $CDCl_3$) 7.16–7.37 (m, 5H), 6.79 (d, J = 43.2 Hz, 1H), 4.66 (br s, 1H), 4.18–4.27 (m, 3H), 3.89–4.05 (m, 1H), 3.62 (d, J = 18.9 Hz, 1H), 3.16–3.28 (m, 2H), 2.77–2.84 (m, 1H), 1.67 (s, 3H), 1.48 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 174.5, 152.2, 151.7, 150.7, 135.0, 129.6, 129.1, 127.8, 118.0, 113.8, 81.5, 66.9, 56.6, 55.8, 55.4, 37.8, 28.6, 21.7, 15.7; HRMS (M+): calcd for $C_{23}H_{27}N_3O_5^+$, 425.1951; found, 425.1957. Compound **8b**: mp 76–78 °C; $[\alpha]_D^{23}$ +3.23 (*c* 1.00, $CHCl_3$); IR(KBr) 2979, 2934, 1786, 1706, 1414, 1292; ^{1}H NMR (300 MHz, $CDCl_3$) 7.19–7.37 (m, 5H), 6.79 (d, J = 42.6 Hz, 1H), 4.66 (br s, 1H), 4.02–4.37 (m, 3H), 3.87 (d, J = 13.2 Hz, 1H), 3.47–3.59 (m, 1H), 3.12–3.24 (m, 2H), 2.84 (dd, J = 9.3, 13.2 Hz, 1H), 1.69 (s, 3H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 174.4, 153.7, 152.2, 150.9, 135.2, 130.1, 129.1, 127.7, 118.0, 113.6, 81.4, 67.0, 56.5, 55.7, 55.5, 38.2, 28.5, 21.9, 15.6; HRMS (M+): calcd for $C_{23}H_{27}N_3O_5^+$, 425.1951; found, 425.1953.
14. Solvent study for hydrogenation of **9a**: MeOH: 80% yield, 91:9 cis/trans, EtOH: 75% yield, 87:13 cis/trans, *i*-PrOH: 82% yield, 88:12 cis/trans, EtOAc: 73% yield, 87:13 cis/trans, Solvent study for hydrogenation of **13a**: MeOH: 86% yield, 12:88 cis/trans, EtOH: 81% yield, 10:90 cis/trans, *i*-PrOH: 80% yield, 9:91 cis/trans, EtOAc: 82% yield, 7:93 cis/trans.
15. Crystallographic data for the structure reported in this Letter have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication Number CCDC 640688. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336 0331, e-mail: deposit@ccdc.cam.ac.uk).
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