Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 46 (2005) 323–324

Stereoselective synthesis of (3*R*,4*S*)-3-methoxy-4-methylaminopyrrolidine☆

A. Madhan and B. Venkateswara Rao*

Organic Division III, Indian Institute of Chemical Technology, Hyderabad 500 007, India

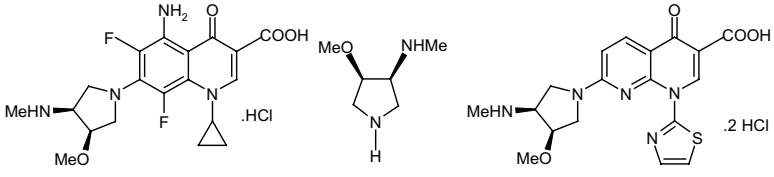
Received 17 September 2004; revised 28 October 2004; accepted 5 November 2004
Available online 25 November 2004

Abstract—An efficient stereoselective approach for the synthesis of (3*R*,4*S*)-3-methoxy-4-methylaminopyrrolidine, a part of the structure of quinoline antibacterial compound (**1a**) and the naphthyridine antitumour agent (**1b**) has been described.

Chiral and nonracemic pyrrolidines are found as subunits in many biologically active natural and unnatural products.[1] Okada et al.[2,3] showed that a new series of quinoline compounds, for example, (**1a**), bearing a (3*R*,4*S*)-3-methoxy-4-methylaminopyrrolidine, had the highest in vivo and excellent in vitro antibacterial activity against pathogens such as Gram+ve and Gram−ve bacteria and were chosen for further evaluation of their biological activities. Tsuzki et al.[4] also reported that (3*R*,4*S*)-3-methoxy-4-methylaminopyrrolidine attached to the naphthyridine ring at C-7 of (**1b**) led to potent cytotoxic activity against murine P388 leukemia cells.

In continuation of our interest in the synthesis of biologically active compounds having vicinal amino and hydroxyl units,[5] we developed recently an approach for the synthesis of chiral pyrrolidines[5g] (*S*,*S*)-**3** and (*S*,*R*)-**4** in optically pure form. Prior to our work there was only one reported approach for the synthesis of **2**, whereby the chiral compound was obtained after resolution.[3] Herein we present a short stereoselective approach for the synthesis of **2** starting from commercially available (*R*)-2,3-*O*-isopropylidene glyceraldehyde.[5e]

Our approach to the synthesis of pyrrolidine **2** is outlined in Scheme 1. (*R*)-2,3-*O*-Isopropylidene glyceraldehyde **5** was converted into **6** by the imine addition reaction reported by Cativiela and co-workers[6] This approach was utilised by us earlier for the synthesis of (−)-cytoxazone and azasugars.[5a,e] Compound **6** on treatment with 60% AcOH at rt gave diol **7**, $[\alpha]_D^{25}$ −25.2 (*c*



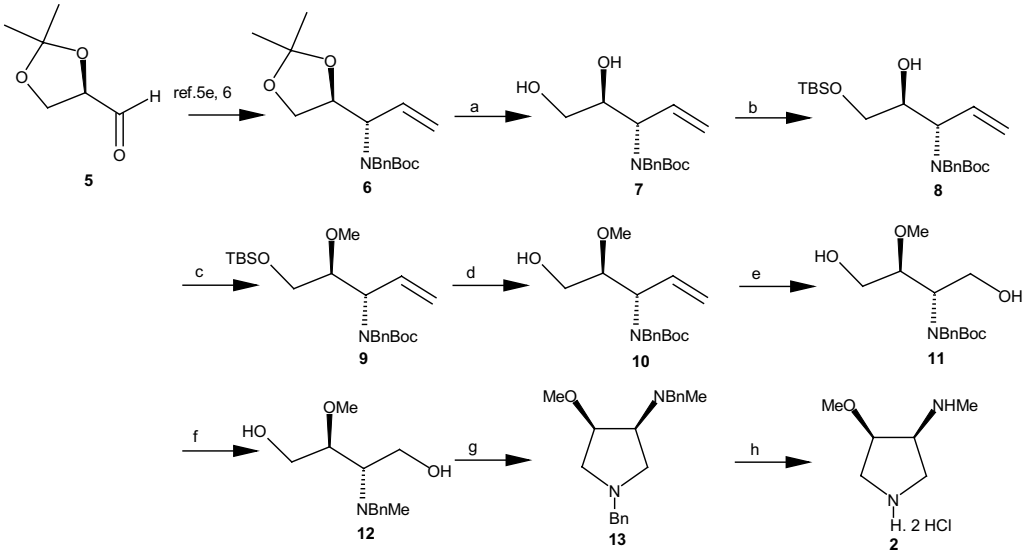
(**1a**) (***R,S***) - **2** (**1b**)

(***S,S***) - **3** (***S,R***) - **4**

☆ IICT Communication No.: 040927.

* Corresponding author. Tel.: +91 040 27160123x2614; fax: +91 040 27160512; e-mail: venky@iict.res.in

0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2004.11.033



Scheme 1. Reagents and conditions: (a) 60% AcOH, rt, 12 h, 84%; (b) TBS-Cl, imidazole, DCM, 0 °C to rt, 8 h, 75%; (c) MeI, AG_2O, DMF, 0 °C to rt, 12 h, 82%, (d) TBAF, THF, 0 °C to rt, 8 h, 84%; (e) O_3, DCM, $NABH_4$, MeOH; −78 °C to rt, 12 h, 75%; (f) $LiAlH_4$, THF, reflux, 6 h, 75%; (g) Tf_2O, 2,6-lutidine, DCM, −78 °C, 30 min, $BnNH_2$, DCM, −78 °C to rt, 24 h, 77%; (h) H_2, Pd/C, MeOH, HCl, rt, 12 h, 85%.

1.0, $CHCl_3$), which on further reaction with TBDMS-Cl/imidazole afforded **8**, $[\alpha]_D^{25}$ −27.7 (*c* 1.0, $CHCl_3$). Methylation of **8** using MeI/Ag_2O gave **9**, $[\alpha]_D^{25}$ −15.7 (*c* 1.0, $CHCl_3$). Desilylation of **9** with TBAF (0.1 M soln in THF) resulted in **10**, $[\alpha]_D^{25}$ −16.9 (*c* 1.0, $CHCl_3$), which was subjected to ozonolysis followed by $NaBH_4$ reduction to give **11**, $[\alpha]_D^{25}$ −1.59 (*c* 1.0, $CHCl_3$). Treatment of **11** with $LiAlH_4$ gave the *N*-methylated compound **12**, $[\alpha]_D^{25}$ −11.9 (*c* 1.0, $CHCl_3$). Compound **12** on cyclisation with Tf_2O/$BnNH_2$ afforded **13**[7] in 77% yield. Pyrrolidine **13**, underwent debenzylation with H_2/Pd,C finally to afford the target molecule **2**, as its HCl salt[8] with ^1H NMR spectral and physical data in good agreement with the literature.[3]

In conclusion, a general and highly efficient stereoselective synthesis of (3*R*,4*S*)-3-methoxy-4-methylaminopyrrolidine **2** has been achieved (10% overall yield), which is a useful procedure for making this compound on large scale. This approach is likely to be of value in making other analogues.

Acknowledgements

One of the authors (A.M.) thanks the CSIR, New Delhi for a research fellowship. We also thank Dr. J. S. Yadav and Dr. A. C. Kunwar for their support and encouragement.

References and notes

1. (a) Attygalle, A. B.; Morgan, D. E. *Chem. Soc. Rev.* **1984**, *13*, 245–278; (b) Pichon, M.; Figadere, B. *Tetrahedron: Asymmetry* **1996**, *7*, 927–964; (c) O'Hagan, D. *Nat. Prod. Rep.* **1997**, *14*, 637–651.
2. Okada, T.; Ezumi, K.; Yamakawa, M.; Sato, H.; Tsuji, T.; Tsushima, T.; Motokawa, K.; Komatsu, Y. *Chem. Pharm. Bull.* **1993**, *41*, 126–131.
3. Okada, T.; Sato, H.; Tsuzi, T.; Tsushima, T.; Nakai, H.; Yoshida, T.; Matsuura, S. *Chem. Pharm. Bull.* **1993**, *41*, 132–138.
4. Tsuzuki, Y.; Tomita, K.; Shibamori, K.; Sato, Y.; Kashimoto, S.; Chiba, K. *J. Med. Chem.* **2004**, *47*, 2097–2109.
5. (a) Madhan, A.; Kumar, A. R.; Rao, B. V. *Tetrahedron: Asymmetry* **2001**, *12*, 2009–2011; (b) Bhaskar, G.; Rao, B. V. *Tetrahedron Lett.* **2003**, *44*, 915–917; (c) Kumar, A. R.; Bhaskar, G.; Madhan, A.; Rao, B. V. *Synth. Commun.* **2003**, *33*, 2907–2916; (d) Kumar, A. S.; Haritha, B.; Rao, B. V. *Tetrahedron Lett.* **2003**, *44*, 4261–4263; (e) Madhan, A.; Rao, B. V. *Tetrahedron Lett.* **2003**, *44*, 5641–5643; (f) Ravi Kumar, A.; Rao, B. V. *Tetrahedron Lett.* **2003**, *44*, 5645–5647; (g) Ravi Kumar, A.; Santosh Reddy, J.; Rao, B. V. *Tetrahedron Lett.* **2003**, *44*, 5687–5689; (h) Bhaskar, G.; Kumar, V. S.; Rao, B. V. *Tetrahedron: Asymmetry* **2004**, *15*, 1279–1283.
6. Badorrey, R.; Cativiela, C.; Diaz-de-villegas, M. D.; Galvez, J. A. *Synthesis* **1997**, 747–749.
7. *Spectral data for compound* **13**: $[\alpha]_D^{25}$ −44.5 (*c* 0.6, $CHCl_3$), IR (neat, cm^{-1}): 2922, 2788, 1744, 1435, 1211, 755; ^1H NMR (300 MHz, $CDCl_3$): δ 2.19 (s, 3H), 2.60 (dd, 1H, J = 3.0, 10.5 Hz), 2.65–2.75 (m, 1H), 2.89–2.99 (m, 2H), 3.11 (dd, 1H, J = 4.5, 10.5 Hz), 3.36 (s, 3H), 3.46 (d, 1H, J = 12.8 Hz), 3.62–3.76 (m, 3H), 3.81–3.87 (m, 1H), 7.17–7.31 (m, 10H). FABMS *m*/*z* 311 (M^++1).
8. *Spectral data for compound* **2**: mp 179–181 °C [(lit.[3] 181–182 °C)]; $[\alpha]_D^{25}$ −52.0 (*c* 0.75, MeOH) [lit.[3] $[\alpha]_D^{25}$ −53.1 (*c* 1.03, MeOH)]; IR (neat, cm^{-1}): 3272, 2931, 2363, 1644, 1444, 1022; ^1H NMR (400 MHz, CD_3OD): δ 2.81 (s, 3H), 3.37–3.58 (m, 2H), 3.55 (s, 3H), 3.77–3.95 (m, 2H), 4.15 (1H, m), 4.40 (1H, m); ^{13}C NMR (CD_3OD, 75 MHz): δ 77.3, 59.9, 57.7, 45.2, 33.2.