Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 1481–1483
Tetrahedron Letters

Synthesis of orthogonally protected 3,8-diazabicyclo[3.2.1]octane-2-carboxylic acid—a versatile building block for the synthesis of cocaine analogues

Stefan Pichlmair,* Kurt Mereiter and Ulrich Jordis*

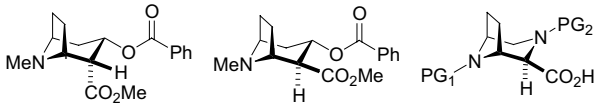
Department of Chemistry, Vienna University of Technology, Getreidemarkt 9, A-1060 Vienna, Austria

Received 13 October 2003; revised 3 December 2003; accepted 8 December 2003

Abstract—An eight-step synthesis of an orthogonally protected 3,8-diazabicyclo[3.2.1]octane from commercially available pyroglutamic acid was developed. The target compound can be used as a versatile building block for combinatorial synthesis of pharmacologically useful compounds and features a hidden α-, β-, δ- and ε-amino acid, which can also be seen as an example of a new class of cocaine analogues.

The demand for multi-functionalized building blocks with pharmaceutical applications is growing. Many drugs in modern medicinal chemistry have been developed, which contain piperazine as subunits.[1a–e] 2-Carboxyl-piperazine subunits have been incorporated into a number of medicinally useful compounds: for example, *N*-methyl-D-aspartate (NMDA) antagonists,[2a] HIV protease inhibitors and metalloproteinase inhibitors.[2b–f] Bridged piperazine analogues have been studied extensively for treating immune disorders, as constrained bicyclic peptidomimetic synthons,[3a,b] as dopamine uptake inhibitors for the treatment of cocaine abuse and as analogues of the potent natural analgesic epibatidine.[3c,d]

Several syntheses of the 3,8-diazabicyclo[3.2.1]octane skeleton have been reported.[3a,b,4] The synthesis of an orthogonally protected 3,8-diazabicyclo[3.2.1]octane-2-carboxylic acid, featuring an α-, β-, δ- and ε-amino acid has, to date, not been reported. This structure can also be envisioned as an aza analogue of pseudococaine. Herein we report the synthesis of the orthogonally protected and functionalized 3,8-diazabicyclo-[3.2.1]octane **1**.



Cocaine Pseudococaine **1**

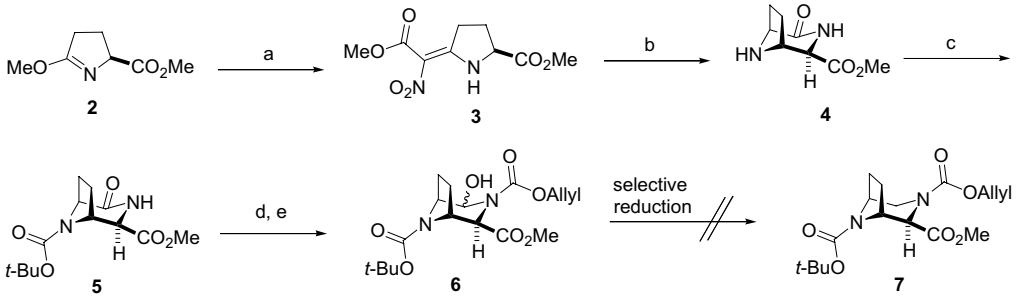
Starting from 5-methoxy-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid methyl ester **2** prepared by esterification and *O*-methylation of commercially available pyroglutamic acid,[4g,5] heating with stoichiometric amounts of methyl nitroacetate afforded **3** as a mixture of *E*/*Z* isomers in 44% yield. Hydrogenation of **3** resulted in cyclization of the intermediate to the methyl 3,8-diazabicyclo[3.2.1]octane-2-carboxylate **4** as a mixture of the axial and equatorial products. Isolation of the equatorial product was achieved by crystallization of the fumarate in 57% yield.[6]

Protection of **4** with di-*tert*-butyl dicarbonate (Boc_2O), followed by protection of the *sec*-amide with allyl chloroformate (AllocCl) using *n*-BuLi as base followed by reduction with Super Hydride ($LiBHEt_3$) gave hemiaminal **6**. Neither the reaction with Et_3SiH/BF_3–OEt_2 nor *O*-acetylation followed by $NaBH_4$ reduction led to the desired compound (Scheme 1) **7**.[7]

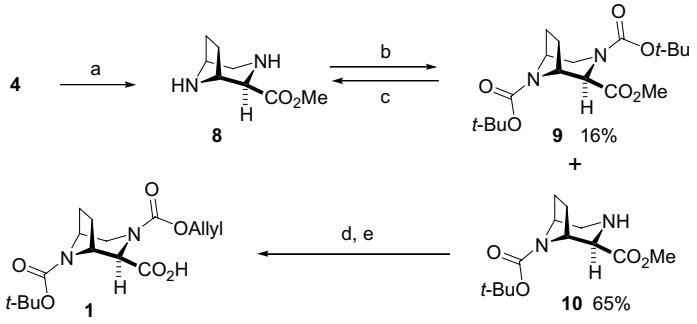
Selective reduction of the amide **4** to the diamine **8** and protection with di-*tert*-butyl dicarbonate yielded 65% of monoprotected product **10** and 16% of diprotected product **9**. Compound **9** was deprotected with

Keywords: Orthogonal amine protection groups; 3,8-Diazabicyclo[3.2.1]octane; Building block; Cocaine analogue.
* Corresponding authors. Tel.: +43-1-58801-15401; fax: +43-1-58801-15499; e-mail addresses: stefan.pichlmair@univie.ac.at; ujordis@pop.tuwien.ac.at

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.12.031



Scheme 1. Reagents and conditions: (a) $O_2NCH_2CO_2Me$, 60 °C, 30 h, neat, 44%; (b) H_2, 10%-Pd/C, MeOH, 4 d, rt, 57% of the equatorial diastereomer; (c) Boc_2O, Et_3N, CH_2Cl_2, −5 °C then warm up to rt, 92%; (d) *n*-BuLi, dry THF, −78 °C then AllocCl, rt, 1 h, 83%; (e) $LiBHEt_3$, dry THF, −78 °C, 30 min, 100%; (Boc_2O = di-*tert*-butyl dicarbonate, AllocCl = allyloxycarbonyl chloride).



Scheme 2. Reagents and conditions: (a) BH_3–SMe_2, dry THF, rt, 3 h, 76%; (b) Boc_2O, Et_3N, CH_2Cl_2, 1 h, 0 °C, 65%; (c) CF_3CO_2H, CH_2Cl_2, 3 h, rt, 95%; (d) AllocCl, Et_3N, CH_2Cl_2, 4 h, 0 °C, 99%; (e) LiOH, Dioxane:H_2O = 1:1, 3 h, rt, 95%.

trifluoroacetic acid in order to recover diamine **8**. By repeating the protection deprotection sequence a second time, the overall yield of **10** could be raised to 75%. Protection of compound **10** with allyl chloroformate and hydrolysis of the methyl ester gave target compound **1** in 94% yield (Scheme 2).[8]

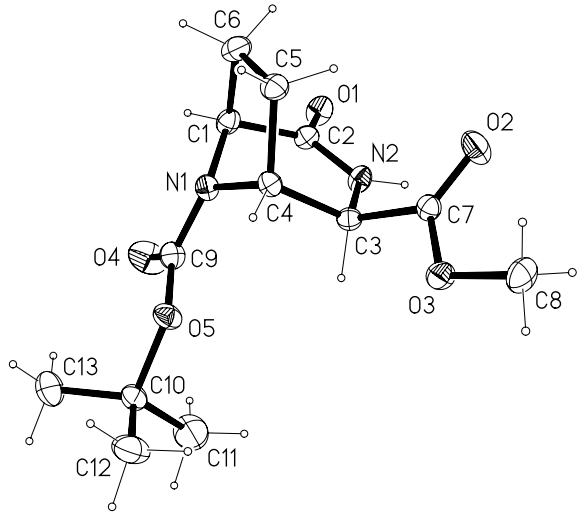


Figure 1. Structural view of **5** in the solid state.[9] Selected bond lengths and angles (Å, °): N(1)–C(1) 1.458(2), N(1)–C(4) 1.468(2), N(1)–C(9) 1.361(2), N(2)–C(2) 1.338(2), N(2)–C(3) 1.458(2), C(1)–C(2) 1.519(2), C(1)–C(6) 1.527(2), C(3)–C(4) 1.543(2), C(3)–C(7) 1.516(2), C(4)–C(5) 1.538(2), C(5)–C(6) 1.539(2), C(1)–N(1)–C(4) 104.2(1), C(2)–N(2)–C(3) 126.1(1), N(2)–C(2)–C(1) 116.0(1).

The stereochemistry of the carboxyl group in **4** (axial or equatorial) could not be determined from the NMR spectra. However X-ray crystallography of **5** established the expected equatorial position for the carboxylate group (Fig. 1).[9]

In summary, we have achieved a diastereoselective synthesis of the 3,8-diazabicyclo[3.2.1]octane-2-carboxylic acid framework, readily available from cheap pyroglutamic acid. Additionally, we have shown a way to protect both amino groups orthogonally.

Acknowledgements

The scientific input of Dr. C. Kuehn for the planning of this synthesis and the discussion of NMR spectra is gratefully acknowledged.

References and notes

1. (a) Bhatt, V.; Trivedi, A. C.; Narula, R. C. *Chem. Eng. World* **1990**, *25*, 75–82; (b) Robarge, M. J.; Husbands, S. M.; Kieltyka, A.; Brodbeck, R.; Thurkauf, A.; Newman, A. H. *J. Med. Chem.* **2001**, *44*, 3175–3186; (c) Lober, S.;

Hubner, H.; Utz, W.; Gmeiner, P. *J. Med. Chem.* **2001**, *44*, 2691–2694; (d) Hsin, L.-W.; Dersch, C. M.; Baumann, M. H.; Stafford, D.; Glowa, J. R.; Rothman, R. B.; Jacobson, A. E.; Rice, K. C. *J. Med. Chem.* **2002**, *45*, 1321–1329; (e) Tagat, J. R.; Steensma, R. W.; McCombie, S. W.; Nazareno, D. V.; Lin, S.-I.; Neustadt, B. R.; Cox, K.; Xu, S.; Wojcik, L.; Murray, M. G.; Vantuno, N.; Baroudy, B. M.; Strizki, J. M. *J. Med. Chem.* **2001**, *44*, 3343–3346.

2. (a) Lehmann, J.; Schneider, J.; McPherson, S.; Murphy, D. E.; Bernhard, P.; Tsai, C.; Bennett, D. A.; Pastor, G.; Steel, D. J.; Boehm, C.; Cheney, D. L.; Liebman, J. M.; Williams, M.; Wood, P. L. *J. Pharmacol. Exp. Ther.* **1987**, *240*, 737–746; (b) Dorsey, B. D.; Levin, R. B.; McDaniel, S. L.; Vacca, J. P.; Guare, J. P.; Darke, P. L.; Zungay, J. A.; Emini, E. A.; Schleif, W. A.; Quintero, J. C.; Lin, J. H.; Chen, I. W.; Holloway, M. K.; Fitzgerald, P. M. D.; Axel, M. G.; Ostovic, D.; Anderson, P. S.; Huff, J. R. *J. Med. Chem.* **1994**, *37*, 3443–3451; (c) Bender, S. L.; Melnick, M. J.; US 5753653, 1998; *Chem. Abstr.* **1998**, *129*, 16140; (d) De, B.; Natchus, M. G.; Pikul, S.; Almstead, N. G.; Matthews, R. S.; Taiwo, Y. O.; Cheng, M. WO 9808825, 1998; *Chem. Abstr.* **1998**, *128*, 217385; (e) Broka, C. A.; Campbell, J. A.; Castelhano, A. L.; Chen, J. J.; Hendricks, R. T.; Melnick, M. J.; Walker, K. A. M.; DE 19802350, 1998; *Chem. Abstr.* **1998**, *129*, 148991; (f) Zook, S. E.; Dagnino, R.; Deason, M. E.; Bender, S. L.; Melnick, M. J.; WO 9720824, 1997; *Chem. Abstr.* **1997**, *127*, 108945.

3. (a) Blumberg, L. C.; Brown, M. F.; Glaude, R. P.; Poss, C. S. WO 0232901, 2002; *Chem. Abstr.* **2002**, *136*, 340711; (b) Dinsmore, C. J.; Bergman, J. M.; Bogusky, M. J.; Culberson, J. C.; Hamilton, K. A.; Graham, S. L. *Org. Lett.* **2001**, *3*, 865–868; (c) Zhang, Y.; Rothman, R. B.; Dersch, C. M.; de Costa, B. R.; Jacobson, A. E.; Rice, K. C. *J. Med. Chem.* **2000**, *43*, 4840–4849; (d) Barlocco, D.; Cignarella, G.; Tondi, D.; Vianello, P.; Villa, S.; Bartolini, A.; Ghelardini, C.; Galeotti, N.; Anderson, D. J.; Kuntzweiler, T. A.; Colombo, D.; Toma, L. *J. Med. Chem.* **1998**, *41*, 674–681.

4. For a racemic synthesis of the 3,8-diazabicyclo-[3.2.1]octane skeleton, see: (a) Schipper, E.; Boehme, W. R. *J. Org. Chem.* **1961**, *26*, 3599–3602; (b) Testa, E.; Cignarella, G.; Fontanella, L.; Occelli, E. *Farmaco, Ed. Sci.* **1969**, *24*, 418–434; (c) Sturm, P. A.; Henry, D. W.; Thomson, P. W.; Zeilinger, J. B.; McCall, J. W. *J. Med. Chem.* **1974**, *17*, 481–487; (d) Blackman, S. W.; Baltzly, R. *J. Org. Chem.* **1961**, *26*, 2750–2755; (e) Cignarella, G.; Nathansohn, G.; Occelli, E. *J. Org. Chem.* **1961**, *26*, 2747–2750; (f) Cignarella, G.; Nathansohn, G. *J. Org. Chem.* **1961**, *26*, 1500–1504, For an asymmetric synthesis of a corresponding 3,8-diazabicyclo[3.2.1]octan-2-one, see: (g) Jain, S.; Sujatha, K.; Krishna, K. V. R.; Roy, R.; Singh, J.; Anand, N. *Tetrahedron* **1992**, *23*, 4985–4998; (h) Bergman, J. M.; Dinsmore, C.; Graham, S. L. WO20609, 1998; *Chem. Abstr.* **1999**, *130*, 311810; (i) Campanini, L.; Dureault, A.; Depezay, J.-C. *Tetrahedron Lett.* **1995**, *36*, 8015–8018; (j) Lessen, T. A.; Demko, D. M.; Weinreb, S. M. *Tetrahedron Lett.* **1990**, *31*, 2105–2108; (k) Garner, P.; Sunitha, K.; Ho, W.-B.; Youngs, W. J.; Kennedy, V. O.; Djebli, A. *J. Org. Chem.* **1989**, *54*, 2041–2042; (l) Allway, P.; Sutherland, J. K.; Joule, J. A. *Tetrahedron Lett.* **1990**, *31*, 4781–4782.

5. Fang, F. G.; Danishefsky, S. *J. Tetrahedron Lett.* **1989**, *30*, 3524–3621.

6. 4-Oxo-3,8-diaza-bicyclo[3.2.1]octane-2-carboxylic acid methyl ester **4**: 8 g 10%-Pd/C was suspended in 300 mL of methanol and prehydrogenated at 70 psi for 0.5 h. To this mixture, the ester **3** (8.00 g, 0.033 mmol) in methanol (300 mL) was added and hydrogenated at 45 psi for four days. The catalyst was removed by filtration and the filtrate was evaporated and dried under high vacuum. Addition of saturated fumaric acid in ethanol (110 mL) resulted in the crystallization of **4** at −20 °C overnight. The salt was filtered and washed with diethyl ether (3×60 mL) to give 5.57 g of the fumarate as yellowish crystals. The amine was obtained by extraction of the aqueous solution (20 mL), basified with ammonia to pH 11 using chloroform (20×20 mL), drying of the organic phase (Na_2SO_4) and evaporation gave 3.13 g (52%) of amine **4**. For analytical purposes a small amount of **4** was crystallized from dry THF to give colorless crystals. mp: 122–123 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.45 (s, 1H), 4.35 (d, $J = 8$ Hz, 1H), 3.97–4.08 (m, 1H), 3.75 (s, 3H), 3.72–3.65 (m, 1H), 2.28 (s, 1H), 2.1–1.75 (m, 3H), 1.7–1.4 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.10 (s), 169.60 (s), 60.50 (d), 59.21 (d), 54.00 (q), 52.44 (d), 30.97 (t), 24.70 (t). Anal. Calcd for $C_8H_{12}N_2O_3$: C, 52.17; H, 6.57; N, 15.21. Found C, 52.10; H, 6.41; N, 15.17.

7. For an example of the reduction of a *N*-Boc-protected hemiaminal to the *N*-Boc-amine, see: Murray, P. J.; Starkey, I. D. *Tetrahedron Lett.* **1996**, *37*, 1875–1878.

8. 3,8-Diaza-bicyclo[3.2.1]octane-2,3,8-tricarboxylic acid 3-allyl ester 8-*tert*-butyl ester **1**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.20 (br s, 1H), 6.00–5.77 (m, 1H), 5.37–5.11 (m, 2H), 4.65–4.15 (m, 5H), 3.55–3.34 (m, 2H), 2.25–1.58 (m, 4H), 1.48 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 174.00 (s), 158.00 (s), 153.13 (s), 132.146 (d), 117.92 (t), 80.81 (s), 66.70 (t), 60.00 (d), 53.50 (d), 51.65 (d), 49.75 (t), 29.63 (t), 28.30 (q), 24.32 (t); *m*/*z*: (APCI, negative ionization): 339.2 (M^-, 100%), 281.1 (14%), 207.1 (17%); *m*/*z* (APCI, positive ionization): 241.9 (15%), 241.0 (M^+-Boc, 100%), 197.1 (M^+-Boc-CO_2, 11%), 116.1 (10%), 99.1 (6%); Anal. calcd for $C_{16}H_{24}N_2O_6$: C, 56.46; H, 7.11; N, 8.23. Found C, 56.39; H, 7.04; N, 8.34.

9. Crystal data for **5**: $C_{13}H_{20}N_2O_5$, FW = 284.31, orthorhombic, space group *P*bca (no 61), $D_c = 1.315\,g\,cm^{-3}$, $Z = 8$, $a = 9.487(2)$, $b = 12.270(3)$, $c = 24.673(6)$ Å, $V = 2872.1(12)$ Å^3, $T = 297(2)$ K, Bruker AXS SMART platform 3-circle diffractometer with CCD area detector, $\lambda(MoK\alpha) = 0.71073$ Å, $\mu = 0.101\,mm^{-1}$. Of 27683 reflections measured, 2530 were unique. Refinement on F^2 concluded with the values $R1 = 0.0342$ and $wR2 = 0.0900$ for 182 parameters and 2005 data with $I > 2\sigma_I$. CCDC-187193 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).