Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 6733–6736
Tetrahedron Letters

Access to novel substituted diazaadamantanes via semi-natural tetrahydrocytisine

Alexandre V. Ivachtchenko,* Alexandre Khvat, Sergey E. Tkachenko, Yuri B. Sandulenko and Vladimir Y. Vvedensky

Chemical Diversity Labs Inc., 11558 Sorrento Valley Rd., Suite 5, San Diego, CA 92121, USA

Received 27 May 2004; revised 10 July 2004; accepted 13 July 2004
Available online 30 July 2004

Abstract—Novel 1,3-diazaadamantane structures **3** and **6** were prepared from tetrahydro(−)-cytisine **1** using intermolecular conversions within the bispidine moiety. 2-Oxo derivative **6** was synthesized using a microwave-assisted procedure, which reduces the reaction time and increases the purity of the crude reaction mixture. Alternative possibilities of intermolecular cyclizations were also explored. Though less successful, they provided interesting insights into the chemistry of bispidine systems.

1. Introduction

Synthetic and natural compounds containing 3,7-diazabicyclo[3.3.1]nonane (also known as bispidine) moiety have been described as cardiovascular drugs,[1] antipsychotic,[2] and analgesic[3] agents. Due to interesting physiological activities, chemistry of bispidines attracted serious attention of researchers in the past years. Several synthetic approaches[4] and studies about crystal structures, stereochemistry, and conformational analysis[5] of bispidines have been reported. Recently, we developed an efficient synthetic approach to novel 3,4,7-trisubstituted bispidine core building blocks and bispidine combinatorial libraries,[6] which are of great interest in the discovery of potent and selective nAChR ligands.

In this work, we explore the possible use of the obtained bispidines for construction of novel molecular scaffolds, such as 1,3-diazaadamantane, which have been the subject of considerable interest. Three biologically active alkaloids acosmine, acosmine acetate, and panacosmine with diazaadamantane skeleton have been recently isolated from the seeds of *Acosmium panamense*[7] (Fig. 1). Several synthetic 1,3-diazaadamantane derivatives were described as potent blockers of sodium channels,[8] ligands of κ-opiate and σ-receptors,[9] and oncolytics.[10] It can be concluded that 1,3-diazaadamantane systems are of pharmacological interest and are interesting synthetic targets.[11]

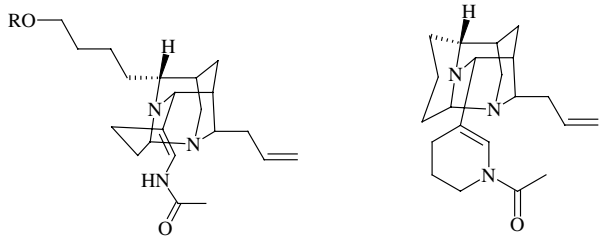
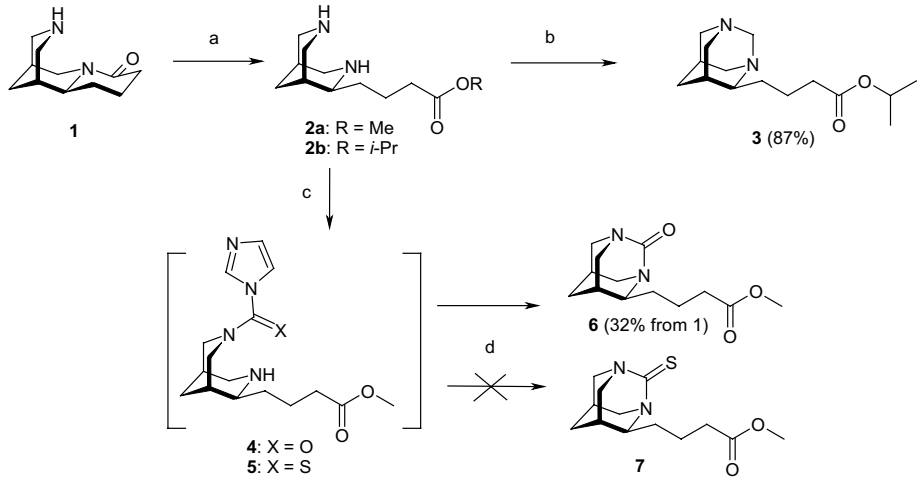


Figure 1. Structures of natural biologically active 1,3-diazaadamantane derivatives.

Here we communicate our success in developing convenient approaches toward the synthesis of novel 1,3-diazaadamantanes starting from the recently described bispidine-containing structures. Recently, we have demonstrated that the amide bond of the N-alkylated tetrahydrocytisine derivatives can be efficiently cleaved using acidic hydrolysis, and the resulting products can be easily isolated as methyl or isopropyl esters.[6] In this work, methyl and isopropyl esters **2a**,**b** were efficiently synthesized from tetrahydro(−)-cytisine **1** using a similar method (Scheme 1). After pH adjustment by sodium bicarbonate and acetic acid, the reaction mixture

Keywords: 1,3-Diazaadamantane; Tetrahydro(−)-cytisine; Microwave-assisted; Intermolecular cyclizations; (1*S*,5*S*)-1,3-Diaza-tricyclo-[3.3.1.1*3,7*]decanes.
* Corresponding author. Tel.: +1-858-7944860; fax: +1-858-7944931; e-mail: av@chemdiv.com

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.07.056



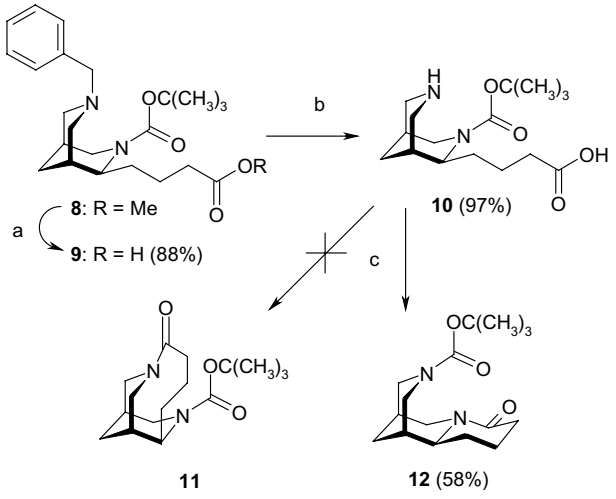
Scheme 1. Reagents and conditions: (a) HCl/ROH, reflux, 12–24 h; (b) paraform, THF, rt, 12 h; (c) CDI (for **4**) or TCDI (for **5**), MeOH, rt, 30 min; (d) MW irradiation, 20 min.

containing esters **2a** or **2b** could be used in the next step without further purification.

Treatment of **2b** with paraform in THF at room temperature smoothly provided compound **3**[12] in a high yield (87%). Treatment of **2a** with 1,1′-carbonyldiimidazole (CDI) in a water–methanol solution yielded the reactive intermediate **4**, which could be carried on directly into the next step without separation. Irradiation of the reaction mixture in the microwave reactor at 130 °C led to ester **6**.[13] The reaction performed under microwaves was completed after 15–20 min. There is a clear advantage in using this mode as compared to the more common thermal conditions. Based on LC–MS data, the yield under microwaves was higher, than under thermal conditions. This reflects a cleaner reaction with fewer side-products, as observed on analysis of the crude reaction mixtures, and thus easier purification. Interestingly, our attempts to obtain the corresponding 2-thioxo derivative **7** using the same experimental protocols failed. Based on LC–MS analysis of the reaction mixture, interaction of **2** with 1,1′-thiocarbonyldiimidazole (TCDI) instead of CDI led to 7-(imidazole-1-carbothioyl) derivative **5**. However, even after prolonged microwave or standard thermal activation of **5**, TLC or LC–MS analysis could not detect any traces of **7** in the reaction mixture.

In this work, we also attempted to obtain 8-oxo-3,9-diaza-tricyclo[7.3.1.0*4,11*]tridecane-3-carboxylic acid *tert*-butyl ester **11** belonging to a new, earlier unknown, type of tricyclic bispidine derivatives (Scheme 2). Ester **8**, described in our recent paper,[6] was hydrolyzed with aqueous sodium hydroxide to give acid **9**.[14] Mild palladium-catalyzed hydrogenation of **9** in methanol (H_2/Pd, rt, 12 h) resulted in selective 3-N-debenzylation, which afforded **10** in a high yield.[15]

Treatment of acid **10** with 1,1′-carbonyldiimidazole in dichloromethane at room temperature yielded a product, which could be erroneously characterized as **11** based on interpretation of LC–MS, ^{1}H NMR, and ^{13}C



Scheme 2. Reagents and conditions: (a) 3 N NaOH, H_2O/1,4-dioxane, reflux, 24 h; (b) H_2/Pd, MeOH, atm press., 12 h; (c) CDI, CH_2Cl_2, reflux, 24 h.

NMR spectra. However, after the pure crystals of this compound were obtained, X-ray crystallographic analysis conclusively established its true constitution and revealed the intact bispidine structure annulated with a 2-piperidone moiety (Fig. 2). Apparently, under the described reaction conditions, unusual $N^3 \rightarrow N^7$ migration of Boc protecting group prevents formation of the original eight-membered ring of compound **11** and results in restoration of an initial tetrahydro(−)-cytisine scaffold of compound **12**.

All new compounds were characterized by ^{1}H NMR, ^{13}C NMR, LC–MS, and HRMS.

In summary, we have developed an original synthetic approach to new (1*S*,*S*)-1,3-diaza-tricyclo[3.3.1.1*3,7*]-decanes representing interesting tetrahedral bispidine adducts. Access to various related derivatives is now possible. Compounds **3** and **6** represent useful intermediates for discovery of novel physiologically active

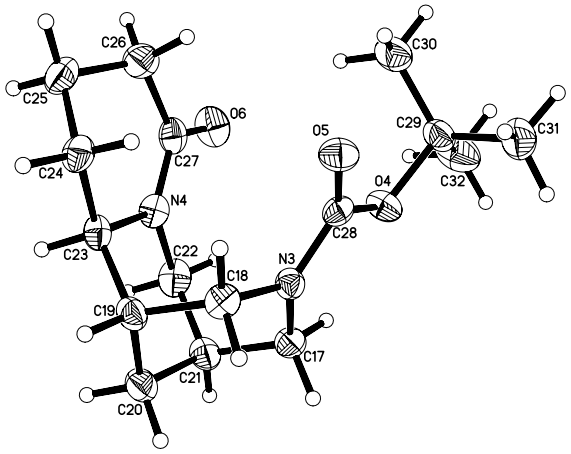


Figure 2. ORTEP plot for X-ray crystal structure of **12**.

compounds. Biological testing of the obtained compounds and their further exploration as initial synthons for synthesis of novel polycyclic structures are currently under way.

Acknowledgements

The authors would like thank Dr. Scott R. Wilson from University of Illinois for solving the X-ray structure.

References and notes

1. (a) Wick, E.; Bell, U.; Dengler, H. J. *Med. Welt* **1971**, *22*, 303–304; (b) Bosch, R. F.; Milek, I. V.; Popovic, K.; Mermi, J.; Mewis, C.; Khlkamp, V.; Seipel, L. J. *Cardiovasc. Pharmacol.* **1999**, *33*, 762–771; (c) Hahn, K.-J.; Kirchengast, M. EP 0701442, 1996; *Chem. Abstr.* 121(15)170560S; (d) Schon, U.; Heitmann, W.; Matzel, U. EP 0550383, 1995; *Chem. Abstr.* 119(19)203392C; (e) Pugsley, M. K.; Goldin, A. L. *Eur. J. Pharmacol.* **1998**, *342*, 93–104.
2. Krahling, H.; Fuchs, A.; Ruhland, M.; Schön, U.; Mol, F.; Tulp, M. *Pharmacopsychiatry* **1988**, *21*, 399–401.
3. Siener, T.; Cambareri, A.; Kuhl, U.; Englberger, W.; Haurand, M.; Kogel, B.; Holzgrabe, U. *J. Med. Chem.* **2000**, *43*, 3746–3751.
4. (a) Mannich, C.; Veit, F. *Chem. Ber.* **1935**, *68B*, 506–512; (b) Miyahara, Y.; Goto, K.; Inazu, T. *Synthesis* **2001**, *3*, 364–366; (c) Bohlmann, F.; Ottawa, N.; Keller, R. *Annalen* **1954**, *587*, 162–176; (d) Schön, U.; Antel, J.; Brückner, R.; Messinger, J. *J. Med. Chem.* **1998**, *41*, 318–331.
5. (a) Zefirov, N. S.; Palyulin, V. A. *Top. Stereochem.* **1991**, *20*, 171–230; (b) Jeyaraman, R.; Avila, S. *Chem. Rev.* **1981**, *81*, 149–174.
6. Ivachtchenko, A. V.; Tkachenko, S. E.; Sandulenko, Y. B.; Vvedensky, V. Y.; Khvat, A. A. *J. Comb. Chem.*, in press.
7. Nuzillard, J.-M.; Connolly, J.; Delaude, C.; Richard, B.; Zeches-Hanrot, M.; Le Men-Olivier, L. *Tetrahedron* **1999**, *55*, 11511–11518.
8. Yamawaki, I.; Bukovac, S.; Sunami, A. *Chem. Pharm. Bull.* **1994**, *42*, 2365–2369.
9. Brandt, W.; Drosihn, S.; Haurand, M.; Holzgrabe, U.; Nachtsheim, C. *Arch. Pharm. (Weinheim, Ger.)* **1996**, *329*, 311–324.
10. Arutyunyan, G.; Chachoyan, A.; Agadzhanyan, Ts.; Garibdzhanyan, B. *Pharm. Chem. J. (Engl. Transl.)* **1996**, *30*, 739–741.
11. For an example of synthetic and crystallographic studies of 1,3-diazaadamantanes, see: Aghajanian, T. Y.; Arutyunian, G. L.; Shahkhatuni, R. K. *Chem. Heterocycl. Comp.* **2003**, *39*, 767–770.
12. A solution of diamine **2b** (0.10 g, 0.39 mmol) and paraform (30 mg, 1 mmol) in THF (5 mL) was stirred at 20 °C for 12 h. The reaction mixture was filtered through a silica gel pad (THF). The filtrate was concentrated in vacuo to afford **3** (0.091 g, 87%) as an oil. ^{1}H NMR ($CDCl_3$) δ 4.93 (d, J = 6.2 Hz, 1H), 4.58–4.72 (m, 1H), 4.54 (d, J = 12.0 Hz, 1H), 4.35 (d, J = 12.0 Hz, 1H), 3.05–4.80 (m, 6H), 1.40–2.30 (m, 10H), 1.16 (d, J = 6.2 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 172.5, 67.6, 66.8, 62.0, 57.4, 55.9, 50.2, 34.4, 33.7, 29.2, 27.3, 24.3, 21.7, 21.4; LC–MS *m/z* 267 (M^++1). HRMS: MH^+ 266.3921 (expected 266.3925).
13. A suspension of tetrahydrocytisine **1** (0.145 g, 0.75 mmol) in a 4 N solution of HCl in MeOH (2.5 mL) was heated at reflux for 24 h. The reaction mixture was cooled to 20 °C, and sodium bicarbonate was added until pH 8. The mixture was filtered to give a water–methanol solution of **2a** (LC–MS *m/z* 227 (M^++1)), which was used in the next step without purification. The obtained solution of **2a** was acidified with concentrated AcOH (until pH 6), then 1,1′-carbonyldiimidazole (0.19 g, 1 mmol) was added and the reaction mixture was stirred at 20 °C. Conversion of **2a** into the imidazolide **4** was controlled by LC–MS. The reaction was complete after 30 min. The reaction mixture was irradiated in the microwave reactor at 130 °C for 20 min, and then concentrated in vacuo. Flash column chromatography (silica gel, EtOH–THF, 20–100%) of the obtained residue provided **6** (0.061 g, 32% yield from **1**) as a white solid. Mp 103–105 °C; ^{1}H NMR ($CDCl_3$) δ 4.74 (d, J = 13.6 Hz, 1H), 4.57 (d, J = 13.9 Hz, 1H), 4.17 (dd, J = 1.8, 13.5 Hz, 1H), 3.57 (s, 3H), 3.43 (dt, J = 3.0, 11.4 Hz, 1H), 3.05 (dt, J = 2.2, 13.3 Hz, 1H), 2.72–2.88 (m, 2H), 2.25–2.45 (m, 2H), 2.00–2.23 (m, 1H), 1.70–1.95 (m, 5H), 1.40–1.70 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 169.8 (C=O), 156.0 (C=O), 59.4 (CH), 52.5 (CH), 49.0 (CH_2), 45.7 (CH_2), 44.2 (CH_2), 33.3 (CH_2), 33.1 (CH), 32.7 (CH_2), 27.8 (CH_2), 27.7 (CH_3), 20.0 (CH_2); LC–MS *m/z* 253 (M^++1). HRMS: MH^+ 252.3298 (expected 252.329).
14. A solution of ester **8**[4] (0.454 g, 1.09 mmol) and 3 N NaOH (1 mL) in dioxane (5 mL) was stirred at 20 °C for 24 h. The reaction mixture was concentrated in vacuo, acidified with 10% H_2SO_4 (until pH 3) and then extracted with EtOAc (2 × 3 mL). The combined organic layer was washed with water (2 × 2 mL), dried over magnesium sulfate, and filtered. The filtrate was concentrated in vacuo to afford **9** (0.388 g, 88%). ^{1}H NMR ($CDCl_3$) δ 10.05 (br s, 1H), 7.22–7.32 (m, 5H), 4.08–4.20 (m, 2H), 3.44, 3.38 (AB, J = 12.9 Hz, 2H), 3.12 (dd, J = 3.2, 13.2 Hz, 1H), 2.83 (d, J = 11.3 Hz, 1H), 2.57 (d, J = 10.2 Hz, 1H), 1.90–2.30 (m, 7H), 1.68–1.85 (m, 1H), 1.42–1.67 (m, 3H), 1.45 (s, 9H), 1.20–1.32 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 178.7, 156.2, 138.6, 129.3, 128.1, 127.0, 79.3, 67.1, 63.1, 58.7, 54.5, 42.9, 33.8, 29.6, 29.3, 28.5, 27.9, 27.6, 22.1; LC–MS *m/z* 403 (M^++1). HRMS: MH^+ 402.5446 (expected 402.5449).
15. A solution of **9** (0.378 g, 0.94 mmol) in methanol (10 mL) containing 10% palladium on carbon (5 mg) was stirred in an atmosphere of hydrogen at room temperature for 12 h.

The reaction mixture was filtered, and the solvent was removed in vacuo to give **10** (0.284 g, 97%). ^{1}H NMR ($CDCl_3$) δ 10.05 (br s, 1H), 7.25 (br s, 1H), 4.25 (d, J = 13.2 Hz, 1H), 4.08 (d, J = 12.9 Hz, 1H), 3.18–3.66 (m, 3H), 3.04 (d, J = 2.2 Hz, 1H), 2.88 (d, J = 13.2 Hz, 1H), 2.30–2.55 (m, 2H), 1.80–2.20 (m, 5H), 1.60–1.80 (m, 3H), 1.47 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 175.5, 156.4, 81.6, 57.8, 48.6, 48.5, 43.9, 33.4, 30.4, 30.3, 28.4, 28.4, 25.7, 20.6; LC–MS 313 (M^++1). HRMS: MH^+ 312.4125 (expected 312.4122).