Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 4061–4063

Synthesis of 7-azabicyclo[2.2.1]heptane-1,4-dicarboxylic acid, a rigid non-chiral analogue of 2-aminoadipic acid

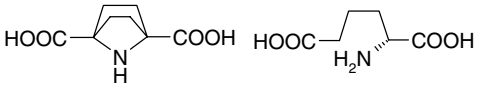
Vladimir S. Kubyshkin, Pavel K. Mikhailiuk and Igor V. Komarov*

Department of Chemistry, Kyiv Taras Shevchenko University, Volodymyrska Street, 64, Kyiv 01033, Ukraine

Received 24 February 2007; revised 27 March 2007; accepted 4 April 2007
Available online 11 April 2007

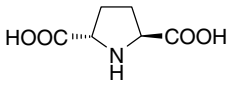
Abstract—A non-chiral, rigid 7-azabicyclo[2.2.1]heptane-1,4-dicarboxylic acid, an analogue of 2-aminoadipic acid, has been synthesized in six steps from dimethyl-*meso*-2,5-dibromohexanedioate in 28% total yield. A key step in the synthesis is double alkylation of a dimethyl pyrrolidine-2,5-dicarboxylate by 1-bromo-2-chloroethane.

In recent years, conformationally restricted molecules have received much attention. One of the reasons for this is the fact that they have been successfully used in medicinal chemistry as building blocks for drug design.[1] As part of our program aimed at the synthesis and application of conformationally restricted amino acids[2] we synthesized and characterized compound **1**, a rigid analogue of (2*R*)-aminoadipic acid **2**, a selective competitive NMDA glutamate receptor antagonist.[3] Compound **1** is also a rigid analogue of naturally occurring *trans*-5-carboxy-L-proline (**3**) isolated from *Schizymenia dubyi*.[4] This fact strengthened our interest in the synthesis, which we report in this Letter.



1

2



3

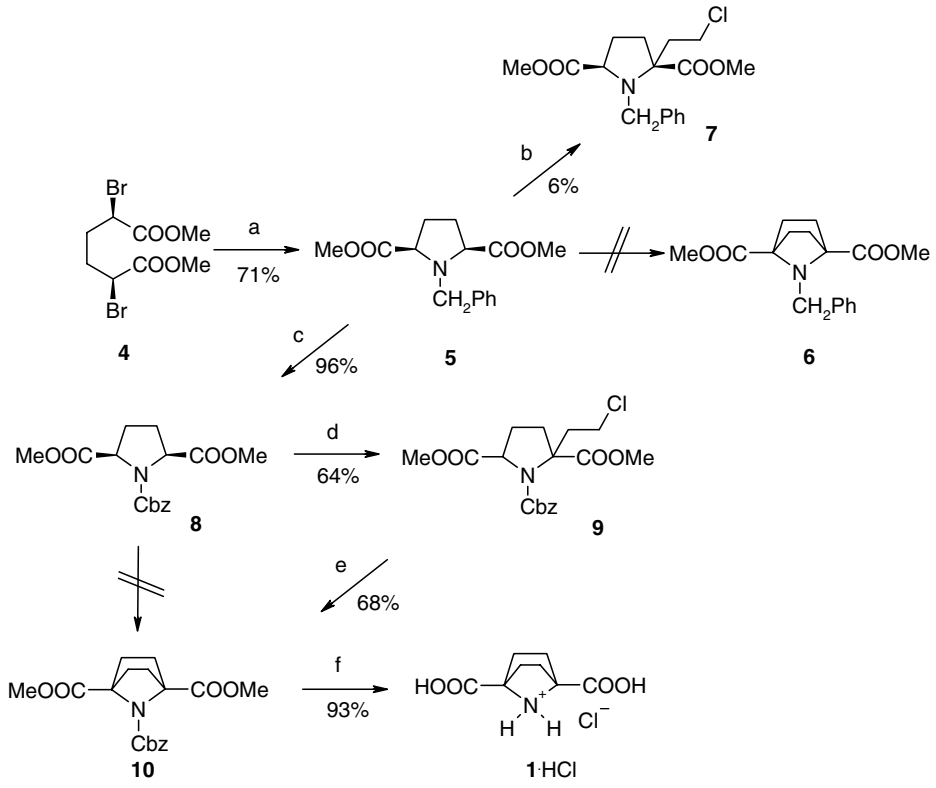
As illustrated in Scheme 1, the synthesis started from easily available dimethyl-*meso*-2,5-dibromohexanedioate **4**.[5] Reaction of **4** with benzylamine in refluxing toluene/water mixture using K_2CO_3 as a base for 30 h proceeded smoothly affording a mixture of corresponding *cis*- and *trans*-pyrrolidines (3/1). The diastereoisomers were separated by flash chromatography; the pure cis-isomer **5** being isolated in 71% yield.[6] It was planned to construct the bicyclic skeleton through an alkylation of the corresponding bis-enolate with 1-bromo-2-chloroethane, as has been described for the synthesis of an analogous carbocyclic skeleton.[7] However, despite much effort, we failed to obtain azabicyclic compound **6** directly from **5** via bis-alkylation. Moreover, all our attempts at the monoalkylation of **5** were only partly successful. A best yield of only 6% of the desired α-(2-chloroethyl)pyrrolidine **7** was achieved. While trying to improve the yield of **7**, it became evident that an N-protecting group other than benzyl had to be used. We thus shifted our attention to the Cbz-protected derivative **8**, which was described recently.[8]

Hydrogenation of the disubstituted pyrrolidine **5** using 10% palladium on charcoal as the catalyst followed by reaction with Cbz-Cl furnished the corresponding urethane **8** in 96% overall yield. In contrast to **5**, treating **8** with 1.15 equiv of LDA at −78 °C for 2 h and subsequent addition of 1.5 equiv of 1-bromo-2-chloroethane generated **9** as a single stereoisomer in 64% yield. The presence of HMPA (5 equiv) in the reaction mixture was found to be crucial, otherwise the yield was only 5–10%. The relative configuration of the stereogenic centers in **9** was not determined as these were lost in the next step of the synthesis.

Intramolecular alkylation of **9** to produce the key intermediate **10** was next explored. Although the construction

Keywords: Non-natural amino acids; Conformational restriction; Ester enolate alkylation.
* Corresponding author. Tel.: +380 67 500 11 51; fax: +380 44 225 12 73; e-mail: ik214@yahoo.com

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.04.019



Scheme 1. Reagents and conditions: (a) $PhCH_2NH_2$, K_2CO_3, toluene/water, reflux, 30 h; (b) (i) 1.15 equiv LDA, 5 equiv HMPA, THF, −78 °C, 2 h; (ii) 1.5 equiv $BrCH_2CH_2Cl$, −78 °C→rt, overnight; (c) (i) H_2, Pd/C, 40 °C, 48 h; (ii) 1.1 Cbz-Cl, K_2CO_3, water, rt, overnight; (d) (i) 1.15 equiv LDA, 5 equiv HMPA, THF, −78 °C, 2 h; (ii) 1.5 equiv $BrCH_2CH_2Cl$, −78 °C→rt, overnight; (e) 1.3 equiv LDA, 5 equiv HMPA, THF (i) −78 °C, 2 h; (ii) −78 °C→rt, overnight; (f) 3 N HCl, reflux, 12 h.

of a 7-azabicyclo[2.2.1]heptane skeleton by an analogous reaction has been documented in the literature,[9] careful experimentation was required to find the optimal conditions in our particular case. The best result was obtained while treating **9** with 1.3 equiv LDA/5 equiv of HMPA at −78 °C for 2 h. Under the above conditions, compound **10** was obtained in 68% yield as a colorless liquid. It should be noted, that although procedures for the synthesis of both **9** and **10** are almost identical, in our hands, all attempts to carry out the direct conversion of **8** to **10** were not productive. Finally, hydrolysis of **10** afforded the amino acid **1**·HCl in 93% yield.[10]

References and notes

1. Komarov, I. V.; Grygorenko, A. O.; Turov, A. V.; Khilya, V. P. *Russ. Chem. Rev.* **2004**, *73*, 785–810.
2. (a) Gorichko, M. V.; Grygorenko, O. O.; Komarov, I. V. *Tetrahedron Lett.* **2002**, *43*, 9411–9412; (b) Mikhailiuk, P. K.; Afonin, S.; Chernega, A. N.; Rusanov, E. B.; Platonov, M. O.; Dubinina, G. G.; Berditsch, M.; Ulrich, A. S.; Komarov, I. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 5659–5661; (c) Grygorenko, O. O.; Artamonov, O. S.; Palamarchuk, G. V.; Zubatyuk, R. I.; Shishkin, O. V.; Komarov, I. V. *Tetrahedron: Asymmetry* **2006**, *17*, 252–258.
3. (a) Biscoe, T. J.; Evans, R. H.; Francis, A. A.; Martin, M. R.; Watkins, J. C.; Davies, J.; Dray, A. *Nature* **1977**, *270*, 743; (b) McLennan, H.; Hall, J. G. *Brain Res.* **1978**, *149*, 541; (c) Lodge, D.; Headley, P. M.; Hall, J. G. *Brain Res.* **1978**, *152*, 603.
4. Mauger, A. B. *J. Nat. Prod.* **1996**, *59*, 1205–1211.
5. Dimethyl-*meso*-2,5-dibromohexanedioate **4** was prepared following the original procedure for diethyl-*meso*-2,5-dibromohexanedioate (Guha, P. C.; Sankaran, D. K. *Org. Synth. Coll.* **1955**, *3*, 623).
6. The synthesis of **5** has been described in the literature ((a) Kemp, D. S.; Curran, T. P. *J. Org. Chem.* **1988**, *53*, 5729–5731; (b) Cignarella, G.; Nathansohn, G. *J. Org. Chem.* **1961**, *26*, 1500–1504); however we utilized the modified procedure (water/toluene; K_2CO_3 as a base) as was originally used for the preparation of *N*-phenylethyl pyrrolidine-2,5-dicarboxylates (Yamamoto, Y.; Hoshino, J.; Fujimoto, Y.; Ohmoto, J.; Sawada, S. *Synthesis* **1993**, *3*, 298–302).
7. Della, E. W.; Tsanaktsidis, J. *Aust. J. Chem.* **1985**, *38*, 1705–1718.
8. (a) Kemp, D. S.; Curran, T. P. *J. Org. Chem.* **1986**, *51*, 2377–2378; (b) Chan, M. F.; Raju, B. G.; Kois, A.; Varughese, J. I.; Varughese, K. I.; Balaji, V. N. *Heterocycles* **1999**, *51*, 5–8.
9. (a) Campbell, J. A.; Rapoport, H. *J. Org. Chem.* **1996**, *61*, 6313–6325; (b) Hart, B. P.; Rapoport, H. *J. Org. Chem.* **1999**, *64*, 2050–2056; (c) Xu, Y.; Choi, J.; Calaza, I.; Turnert, S.; Rapoport, H. *J. Org. Chem.* **1999**, *64*, 4069–4078.
10. Spectral data of key compounds:
Compound **9**: ^{1}H NMR (500 MHz, $CDCl_3$, rotamers), δ: 7.32 (m, 5H), 5.23 and 5.02 (AB system, $J = 12$ Hz, 0.8H; O–CH_2–Ph), 5.14 and 5.08 (AB system, $J = 12.5$ Hz, 1.2H; O–CH_2–Ph), 4.65 (dd, $J = 3.5$; 9 Hz, 0.4H; CH–CH_2), 4.58 (dd, $J = 4$; 8.5 Hz, 0.6H; CH–CH_2), 3.77 (s, 1.2H, OCH_3), 3.72 (s, 1.8H, OCH_3), 3.63 (s, 1.8H, OCH_3), 3.44

(s, 1.2H, OCH_3), 3.7 (m, 2H, CH_2Cl), 2.83 (m, 0.6H; CH_2–CH_2Cl), 2.65 (m, 0.4H; CH_2–CH_2Cl), 2.55 (m, 1H; CH_2–CH_2Cl), 2.29 (m, 2H), 2.13 (m, 1H), 2.00 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, rotamers), δ: 173.52 (*C*O_2Me), 173.26 (*C*O_2Me), 173.07 (*C*O_2Me), 172.93 (*C*O_2Me), 154.68 (N—*C*(=O)—O), 154.27 (N—*C*(=O)—O), 136.36 (*C*, Ph), 135.86 (*C*, Ph), 128.81 (*C*H, Ph), 128.73 (*C*H, Ph), 128.67 (*C*H, Ph), 128.64 (*C*H, Ph), 128.28 (*C*H, Ph), 127.77 (*C*H, Ph), 69.48 (O–*C*H_2–Ph), 68.63 (O–*C*H_2–Ph), 68.09 (N–*C*–CO_2Me), 67.59 (N–*C*–CO_2Me), 61.95 (N*C*H–CO_2Me), 61.08 (N–*C*H–CO_2Me), 53.00 (CO_2*Me*), 52.74 (CO_2*Me*), 52.68 (CO_2*Me*), 52.51 (CO_2*Me*), 40.43 (*C*H_2Cl), 40.14 (*C*H_2Cl), 38.50 (*C*H_2), 37.99 (*C*H_2), 36.16 (*C*H_2), 35.06 (*C*H_2), 27.76 (*C*$H_2$$CH_2$Cl), 27.03 (*C*$H_2$$CH_2$Cl); IR (KBr), cm^{-1}: 1745 (C=O)$^+$, 1710 (C=O, N—C(=O)—O); MS (*m*/*z*): 386 (^{37}Cl M+1), 384 (^{35}Cl M+1)$^+$. Anal. Calcd for $C_{18}H_{22}ClNO_6$: C, 56.33; H, 5.78; N, 3.65. Found: C, 55.90; H, 5.35; N, 3.51.

Compound **10**: ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.20 (m, 5H; Ph), 4.90 (s, 2H; O–CH_2–Ph), 3.45 (s, 6H; OCH_3), 2.16 (d, $J = 6.5$ Hz, 4H), 1.66 (d, $J = 6.5$ Hz, 4H); ^{13}C NMR (101 MHz, $CDCl_3$), δ: 168.99 (*C*O_2Me), 155.63 (N—*C*(=O)—O), 135.33 (*C*, Ph), 128.49 (*C*H, Ph), 128.12 (*C*H, Ph), 127.98 (*C*H, Ph), 70.48 (O–*C*H_2–Ph), 67.70 (N–*C*–COOMe), 51.45 (COO*Me*), 32.64 (*C*H_2); IR (KBr), cm^{-1}: 1745 (C=O), 1714 (C=O, N—C(=O)—O); MS (*m*/*z*): 348 (M+1)$^+$. Anal. Calcd for $C_{18}H_{21}NO_6$: C, 62.24; H, 6.09; N, 4.03. Found: C, 61.92; H, 5.86; N, 4.00.

Compound **1**·HCl: ^{1}H NMR (400 MHz, CD_3OD), δ: 2.30 (s, 4H); ^{13}C NMR (101 MHz, CD_3OD), δ: 170.52 (*C*O_2H), 72.49 (N–*C*–CO_2H), 32.28 (*C*H_2); MS (*m*/*z*): 186 (M−Cl)$^+$. Anal. Calcd for $C_8H_{12}ClNO_4$: C, 43.35; H, 5.46; N, 6.32. Found: C, 43.10; H, 5.14; N, 5.95. mp >300 °C (decomp.). IR (KBr), cm^{-1}: 3030, 1741 (C=O), 1405, 1228.