Synthesis of a Conformationally Rigid Analogue of 2-Aminoadipic Acid Containing an 8-Azabicyclo[3.2.1]octane Skeleton

Vladimir S. Kubyshkin,[a,c] Pavel K. Mykhailiuk,*[a,c] Anne S. Ulrich,[b,c] Igor Komarov[a]

[a] Department of Chemistry, Kyiv National Taras Shevchenko University, Vul. Volodymyrska 64, 01033 Kyiv, Ukraine

[b] Institut für Biologische Grenzflächen, Karlsruhe Institute of Technology, Forschungszentrum Karlsruhe, POB 3640, 76021 Karlsruhe, Germany

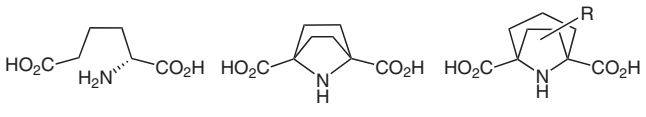
[c] Institut für Organische Chemie, Karlsruhe Institute of Technology, Universität Karlsruhe, Fritz-Haber-Weg 6, 76133 Karlsruhe, Germany
Fax +380(44)2251273; E-mail: pashamk@gmx.de

Received 11 May 2009; revised 19 May 2009

Abstract: A new, conformationally rigid analogue of 2-aminoadipic acid, 8-[(benzyloxy)carbonyl]-3-methylene-8-azabicyclo[3.2.1]octane-1,5-dicarboxylic acid, is synthesized from dimethyl *rac*-2,5-dibromohexanedioate. The key steps involve alkylation–cyclization of 1-benzyl 2,5-dimethyl pyrrolidine-1,2,5-tricarboxylate with 3-chloro-2-(chloromethyl)prop-1-ene to yield the 8-azabicyclo[3.2.1]octane skeleton.

Key words: conformational restriction, bicyclic compounds, pyrrolidines, alkylations, cyclization

The concept of conformational restriction has been widely utilized to modify the physical, chemical and biological characteristics of organic compounds.[1] In particular, application of this concept to α-amino acids is of significant practical interest since conformationally restricted amino acids, upon replacing their natural analogues, have been used to improve the pharmacological properties of peptides and peptidomimetics.[2] (2*R*)-Aminoadipic acid (**1**) is a selective competitive *N*-methyl D-aspartic acid (NMDA) glutamate receptor antagonist.[3] We recently prepared its non-chiral, conformationally rigid analogue **2** which contains a 7-azabicyclo[2.2.1]heptane skeleton.[4] Herein we report our studies on the synthesis of bicyclic compounds of type **3**, analogues of (2*R*)-aminoadipic acid, possessing a conformationally rigid 8-azabicyclo[3.2.1]octane skeleton (Figure 1).



1 2 3

Figure 1 The structures of (2*R*)-Aminoadipic acid and conformationally rigid analogues

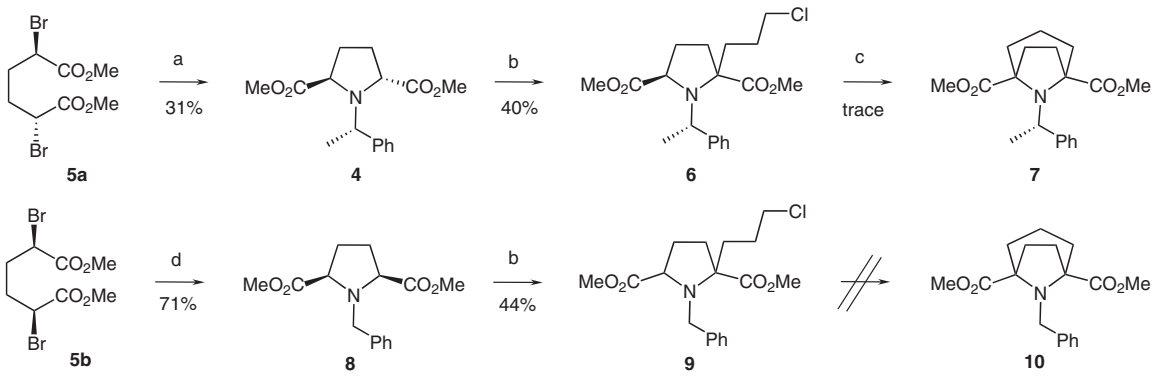
Initially, a strategy involving consecutive bis-alkylation of the corresponding protected 2,5-dicarbomethoxypyrrolidine was investigated to prepare the unsubstituted rigid amino acid **3a** (R = H). The chiral phenylethyl residue was chosen as an N-protecting group in order to enable the possibility of further asymmetric derivatization of **3**. The starting pyrrolidine **4** was obtained from dimethyl *rac*-2,5-dibromohexanedioate **5a**[5] and (*S*)-1-phenylethylamine according to the literature procedure (Scheme 1).[6] Next, treatment of pyrrolidine **4** with lithium diisopropylamide (1.15 equiv) at –78 °C for two hours, followed by subsequent addition of 1-bromo-3-chloropropane (1.5 equiv), afforded compound **6** in 40% yield as a single diastereomer.[7] The addition of hexamethylphosphoramide (HMPA) (4–6 equiv) as a cosolvent[8] was found to be crucial for the success of this step.[9] Despite the fact that preparation of the 8-azabicyclo[3.2.1]octane skeleton via intramolecular alkylation of substituted pyrrolidines has already been described in the literature,[10] all our attempts to cyclize **6** were unsuccessful. Reacting substituted pyrrolidine **6** with various bases (lithium diisopropylamide, sodium hydride, lithium hexamethyldisilazide or potassium hexamethyldisilazide) in the presence of hexamethylphosphoramide did not produce **7** even at room temperature. Upon increasing the temperature, a complex mixture was formed from which the target compound **7** was isolated, albeit in a very poor yield (less than 1%).

To reduce steric hindrance at the reaction center in **6**, which may be preventing the alkylation, we replaced the chiral phenylethylamine auxiliary with the less bulky benzylamine moiety.[11] The corresponding analogue **9** was obtained in 44% yield from pyrrolidine **8**[4] using the same strategy as that applied for the synthesis of **6**. However, cyclization of **9** into bicyclic compound **10** did not occur.

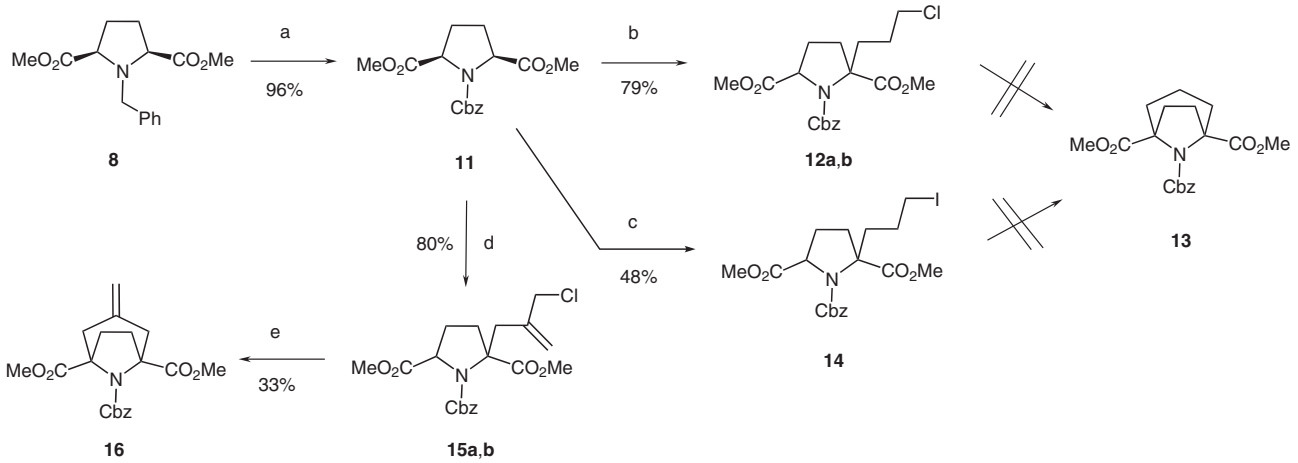
Next, the suitability of the benzyloxycarbonyl (Cbz) N-protecting group was investigated. Mono-alkylation of **11** (itself prepared via removal of the benzyl group in **8** and N-protection of the resulting product using benzyl chloroformate) on reaction with 1-bromo-3-chloropropane gave a mixture of diastereomers **12a**,**b** (3:1) in an improved 79% yield. However, all attempts to prepare the desired 8-azabicyclo[3.2.1]octane skeleton **13** failed. Exchanging the chloride leaving group for the more labile iodide (compound **14**) did not improve the situation (Scheme 2).

Recently, Stevens et al. reported that 3-chloro-2-(chloromethyl)prop-1-ene was an efficient reagent for the alkylation of pyroglutamic acid derivatives in their synthesis of a 6-azabicyclo[3.2.1]octane cage system.[12] In fact, mono-alkylation of **11** with 3-chloro-2-(chlorometh-

SYNTHESIS 2009, No. 19, pp 3327–3331
Advanced online publication: 21.08.2009
DOI: 10.1055/s-0029-1216963; Art ID: Z09309SS

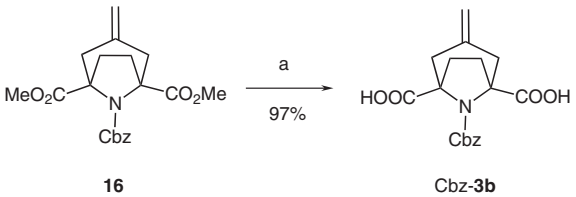


Scheme 1 *Reagents and conditions*: (a) (i) (*S*)-1-phenylethylamine (1 equiv), K_2CO_3 (3 equiv), toluene–H_2O, reflux, 30 h, (ii) NaOMe–MeOH, H_2O, r.t., 36 h; (b) (i) LDA (1.15 equiv), HMPA (5 equiv), THF, –78 °C, 2 h, (ii) 1-bromo-3-chloropropane (1.5 equiv), –78 °C to r.t., 12 h; (c) LDA (1.5 equiv), HMPA (5 equiv), THF, (i) –78 °C to r.t., 12 h, or (ii) reflux, 10 h; (d) 1-phenylmethanamine (1 equiv), K_2CO_3 (3 equiv), toluene–H_2O, reflux, 30 h.



Scheme 2 *Reagents and conditions*: (a) (i) H_2, 5% Pd/C, 40 °C, 48 h, (ii) CbzCl (1.1 equiv), K_2CO_3, H_2O, r.t., 12 h; (b) (i) LDA (1.05 equiv), HMPA (5 equiv), THF, –78 °C, 2 h, (ii) 1-bromo-3-chloropropane (1.5 equiv), –78 °C to r.t., 12 h; (c) (i) LDA (1.15 equiv), HMPA (5 equiv), THF, –78 °C, 2 h, (ii) 1,3-diiodopropane (1.5 equiv), –78 °C to r.t., 12 h; (d) (i) LDA (1.15 equiv), HMPA (5 equiv), THF, –78 °C, 2 h, (ii) 3-chloro-2-(chloromethyl)prop-1-ene (1.5 equiv), –78 °C to r.t., 12 h; (e) LDA (1.5 equiv), HMPA (5 equiv), THF, (i) –78 °C, 2 h, (ii) –78 °C to r.t., 12 h.

yl)prop-1-ene smoothly afforded a mixture of the two diastereomeric alkenes **15a**,**b** (3:4) in a good yield of 80%. Subsequent cyclization of the mixture of **15a**,**b** with lithium diisopropylamide in the presence of hexamethylphosphoramide produced the target 8-azabicyclo[3.2.1]octane **16** in 33% yield. Attempts to transform **11** into **16** via a one-step bis-alkylation were only partially successful resulting in a mixture of the target compound **16**, starting material **11**, and the mono-alkylated diastereomeric products **15a**,**b**. Finally, basic hydrolysis of **16** afforded the target compound, Cbz-**3b** (Scheme 3).



Scheme 3 *Reagents and conditions*: (a) NaOH (10 equiv), MeOH–H_2O–THF (5:8:5), r.t., 96 h.

In summary, we have shown that intramolecular alkylation of pyrrolidine derivatives to form the corresponding 8-azabicyclo[3.2.1]octane skeleton is highly dependent on both the alkylating agent and the N-protecting group. The benzyloxycarbonyl group was found to be superior than benzyl and phenylethyl groups in the above-mentioned reactions. 3-Chloro-2-(chloromethyl)prop-1-ene was shown to be an efficient electrophilic agent for constructing this cage system. The conformationally rigid analogue of 2-aminoadipic acid, Cbz-**3b** was obtained in good yield and the preparation of other representative examples is ongoing.

Starting materials and reagents were purchased from Acros, Merck, Fluka and Enamine. Solvents were purified according to standard procedures. Melting points were recorded using a Büchi 510 melting point apparatus and are uncorrected. Analytical TLC was conducted using Polychrom SIF_{254} plates. Column chromatography was performed using Kieselgel Merck 60 silica gel (230–400 mesh) as the stationary phase. ^1H and ^{13}C NMR spectra were recorded either on a Varian Unity Plus 400 spectrometer (at 400.4 and 100.7 MHz, respectively) or on a Bruker Avance 500 spectrometer (at

499.9 or 124.9 MHz) using $CDCl_3$ or CD_3OD as solvent. Chemical shifts are reported in ppm downfield from TMS as the internal standard. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument by chemical ionization (CI). Elemental analyses were obtained using a Elementar Vario MICRO cube instrument.

Mono-alkylated Pyrrolidines 6, 9, 12a,b, 14 and 15a,b; General Procedure

To a soln of the N-protected 2,5-dicarbomethoxypyrrolidine (1 equiv) and HMPA (4–6 equiv) in THF at –78 °C was added dropwise a soln of LDA (1.15 equiv) in THF. The resulting black mixture was stirred for 2 h at –78 °C followed by slow addition of the alkylating agent (1.5 equiv). The reaction mixture was left to stir overnight (12 h) whilst gradually warming to r.t. The reaction mixture was quenched with saturated NH_4Cl (50 mL), THF was removed under vacuum. Extraction with EtOAc (3 × 100 mL), drying over $MgSO_4$, filtration, and evaporation followed by flash column chromatography (silica gel, hexane–EtOAc mixtures) afforded the products as colorless oils. Typical reaction scale was 1–3 g of starting material.

8-Azabicyclo[3.2.1]octanes 7 and 16; General Procedure

To a soln of the mono-alkylated N-protected 2,5-dicarbomethoxypyrrolidine (1 equiv) and HMPA (4–6 equiv) in THF at –78 °C was slowly added LDA (1.5 equiv) in THF. The reaction mixture was left to stir overnight (12 h) whilst gradually warming to r.t.; in the case of **6**, the reaction mixture was additionally heated under reflux for 10 h. The reaction mixture was quenched with saturated NH_4Cl (50 mL), THF was removed under vacuum. Extraction with EtOAc (3 × 100 mL), drying over $MgSO_4$, filtration, and evaporation and purification by flash column chromatography (silica gel, hexane–EtOAc mixtures) gave the cyclized products **7** and **16** as colorless oils. Typical reaction scale was 1–3 g of starting material.

Dimethyl (5*R*)-2-(3-Chloropropyl)-1-[(1*S*)-1-phenylethyl]pyrrolidine-2,5-dicarboxylate (6)

Colorless oil; yield: 40%; R_f = 0.70 (hexane–EtOAc, 2:1).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.24–7.14 (m, 5 H, Ph), 4.24 (q, *J* = 7.2 Hz, 1 H, NC*H*CH_3), 3.81 (d, *J* = 8.8 Hz, 1 H, C*H*CO_2Me), 3.60 (m, 2 H, CH_2Cl), 3.51 (s, 3 H, OCH_3), 3.36 (s, 3 H, OCH_3), 2.35 (m, 1 H), 2.21–1.96 (m, 5 H), 1.90 (m, 1 H), 1.67 (dd, *J* = 6.8, 3.2 Hz, 1 H), 1.30 (d, *J* = 7.2 Hz, 3 H, NCHCH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 175.39 (s, *C*O_2Me), 174.14 (s, *C*O_2Me), 143.93 (s, *C*, Ph), 128.64 (s, *C*H, Ph), 128.16 (s, *C*H, Ph), 127.63 (s, *C*H, Ph), 70.65 (s, N*C*CO), 63.73 (s, N*C*HCO), 60.71 (s, N*C*HCH_3), 51.55 (s, O*C*H_3), 51.26 (s, O*C*H_3), 45.77 (s, *C*H_2Cl), 33.45 (s, *C*H_2), 32.31 (s, *C*H_2), 29.38 (s, *C*H_2), 28.68 (s, *C*H_2), 22.45 (s, NCH*C*H_3).

MS (CI): *m*/*z* (%) = 370.4 [(M^+ + H), ^{37}Cl], 368.4 [(M^+ + H), ^{35}Cl].

Dimethyl 8-[(1*S*)-1-Phenylethyl]-8-azabicyclo[3.2.1]octane-1,5-dicarboxylate (7)

Colorless oil; yield: <1%; R_f = 0.45 (hexane–EtOAc, 4:1).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.42 (d, *J* = 7.6 Hz, 2 H, Ph), 7.25 (t, *J* = 7.6 Hz, 2 H, Ph), 7.15 (t, *J* = 7.6 Hz, 1 H, Ph), 4.18 (q, *J* = 6.8 Hz, 1 H, NC*H*CH_3), 3.78 (s, 3 H, OCH_3), 2.79 (s, 3 H, OCH_3), 2.46 (ddd, *J* = 13.2, 4.4, 1.6 Hz, 1 H), 2.42 (ddd, *J* = 11.6, 4.4, 1.6 Hz, 1 H), 2.30 (tdd, *J* = 12.0, 4.0, 1.6 Hz, 1 H), 2.01 (dd, *J* = 12.8, 5.6 Hz, 1 H), 1.93–1.72 (m, 6 H), 1.21 (d, *J* = 6.8 Hz, 3 H, NCHCH_3).

MS (CI): *m*/*z* (%) = 332.4 [(M^+ + H)].

Dimethyl 1-Benzyl-2-(3-chloropropyl)pyrrolidine-2,5-dicarboxylate (9)

Colorless oil; yield: 44%; R_f = 0.60 (hexane–EtOAc, 4:1).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.30–7.21 (m, 5 H, Ph), 3.91 (d, $^2J_{H–H}$ = 13.6 Hz, 1 H, CH_2Ph), 3.74 (s, 3 H, OCH_3), 3.66 (d, $^2J_{H–H}$ = 13.6 Hz, 1 H, CH_2Ph), 3.61 (dd, *J* = 12.8, 3.2 Hz, 1 H, C*H*CO_2Me), 3.49 (t, *J* = 6.0 Hz, 2 H, CH_2Cl), 3.45 (s, 3 H, OCH_3), 2.30 (m, 1 H), 2.20–1.91 (m, 4 H), 1.89–1.77 (m, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 174.11 (s, *C*O_2Me), 173.87 (s, *C*O_2Me), 139.06 (s, *C*, Ph), 128.99 (s, *C*H, Ph), 128.63 (s, *C*H, Ph), 128.01 (s, *C*H, Ph), 71.87 (s, N*C*CO), 65.11 (s, N*C*HCO), 52.93 (s, N*C*H_2), 51.34 (s, O*C*H_3), 51.02 (s, O*C*H_3), 45.82 (s, *C*H_2Cl), 33.51 (s, *C*H_2), 32.24 (s, *C*H_2), 28.12 (s, *C*H_2), 27.68 (s, *C*H_2).

MS (CI): *m*/*z* (%) = 356.4 [(M^+ + H), ^{37}Cl], 354.4 [(M^+ + H), ^{35}Cl].

1-Benzyl 2,5-Dimethyl 2-(3-Chloropropyl)pyrrolidine-1,2,5-tricarboxylate (12a, 12b)

LDA (1.05 equiv) was used in this experiment; the use of LDA (1.15 equiv) led to formation of a substantial amount (ca. 10% yield) of bis-alkylated product **12c**.

Data for **12a**: Colorless oil; yield: 59%; R_f = 0.35 (hexane–EtOAc, 5:1).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (mixture of rotamers) = 7.39–7.18 (m, 5 H, Ph), 5.11–4.91 (m, 2 H, OCH_2), 4.50 (2 × dd, *J* = 9.2, 3.2 Hz, 1 H, NC*H*), 3.64, 3.59, 3.51, 3.35 (4 × s, 6 H, OCH_3), 3.42 (m, 2 H, CH_2Cl), 2.36–2.27 (m, 1 H), 2.26–1.92 (m, 4 H), 1.92–1.70 (m, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (mixture of rotamers) = 174.18, 173.95, 173.04, 172.86 (4 × s, *C*O_2Me), 154.82, 154.14 (2 × s, N*C*O), 136.43, 136.14 (2 × s, *C*, Ph), 128.62, 128.55, 128.50, 128.41, 128.04, 127.57 (6 × s, *C*H, Ph), 70.05, 69.15 (2 × s, N*C*CO), 67.75, 67.25 (2 × s, O*C*H_2), 61.92, 61.03 (2 × s, N*C*HCO), 52.73, 52.49, 52.42, 52.24 (4 × s, O*C*H_3), 45.54, 45.43 (2 × s, *C*H_2Cl), 35.79, 34.43, 32.57, 31.73 (4 × s, *C*H_2*C*H_2), 27.45, 27.33, 27.11, 26.81 (4 × s, *C*H_2*C*H_2).

MS (CI): *m*/*z* (%) = 400.0 [(M^+ + H), ^{37}Cl], 398.0 [(M^+ + H), ^{35}Cl].

Data for **12b**: Colorless oil; yield: 20%; R_f = 0.20 (hexane–EtOAc, 5:1).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (mixture of rotamers) = 7.41–7.17 (m, 5 H, Ph), 5.25–4.93 (m, 2 H, OCH_2), 4.48 (dd, *J* = 12.0, 8.8 Hz, 0.3 H, NC*H*), 4.37 (dd, *J* = 8.0, 4.4 Hz, 0.7 H, NC*H*), 3.75, 3.54, 3.53, 3.47 (4 × s, 6 H, OCH_3), 3.50 (m, 2 H, CH_2Cl), 2.43–1.51 (m, 8 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (mixture of rotamers) = 172.84, 172.77, 171.84, 171.18 (4 × s, *C*O_2Me), 153.26, 152.76 (2 × s, N*C*O), 136.86, 136.69 (2 × s, *C*, Ph), 128.73, 128.56, 128.40, 128.26, 127.95, 127.88 (6 × s, *C*H, Ph), 69.26, 68.31 (2 × s, N*C*CO), 67.30, 67.10 (2 × s, O*C*H_2), 61.35, 60.60 (2 × s, N*C*HCO), 52.25, 52.13, 52.08, 51.88 (4 × s, O*C*H_3), 44.54, 44.50 (2 × s, *C*H_2Cl), 35.82, 34.66, 33.54, 32.67 (4 × s, *C*H_2*C*H_2), 29.97, 29.25, 28.29, 28.18 (4 × s, *C*H_2*C*H_2).

MS (CI): *m*/*z* (%) = 400.0 [(M^+ + H), ^{37}Cl], 398.0 [(M^+ + H), ^{35}Cl].

1-Benzyl 2,5-Dimethyl 2,5-Bis(3-chloropropyl)pyrrolidine-1,2,5-tricarboxylate (12c)

LDA (1.15 equiv) was used in this experiment.

Colourless oil; yield: 10%; R_f = 0.50 (hexane–EtOAc, 5:1).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.42–7.25 (m, 5 H, Ph), 5.12 (d, $^2J_{H-H}$ = 12.0 Hz, 1 H, OCH_2), 4.98 (d, $^2J_{H-H}$ = 12.0 Hz, 1 H, OCH_2), 3.72 (s, 3 H, OCH_3), 3.51 (m, 2 H, CH_2Cl), 3.45 (s, 3 H, OCH_3), 3.40 (t, *J* = 6.8 Hz, 2 H, CH_2Cl), 2.25 (t, *J* = 6.4 Hz, 2 H), 2.16 (m, 4 H), 2.10–1.80 (m, 6 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 173.98 (s, *C*O_2Me), 173.78 (s, *C*O_2Me), 153.63 (s, N*C*O), 136.05 (s, *C*, Ph), 128.68 (s, *C*H, Ph), 128.64 (s, *C*H, Ph), 128.50 (s, *C*H, Ph), 71.08 (s, N*C*CO), 70.02 (s,

NCCO), 67.55 (s, OCH$_2$), 52.79 (s, OCH$_3$), 52.44 (s, OCH$_3$), 45.69 (s, CH$_2$Cl), 45.47 (s, CH$_2$Cl), 34.93 (s, CH$_2$), 33.87 (s, CH$_2$), 33.36 (s, CH$_2$), 32.49 (s, CH$_2$), 28.14 (s, CH$_2$), 27.93 (s, CH$_2$).

MS (CI): *m*/*z* (%) = 476.0 [(M$^+$ + H), ^{37}Cl/^{35}Cl], 474.0 [(M$^+$ + H), ^{35}Cl/ ^{35}Cl].

1-Benzyl 2,5-Dimethyl 2-(3-Iodopropyl)pyrrolidine-1,2,5-tricarboxylate (14)

Colorless oil; yield: 48%; R_f = 0.50 (hexane–EtOAc, 3:1).

^{1}H NMR (CDCl$_3$, 400 MHz): δ (mixture of rotamers) = 7.35–7.15 (m, 5 H, Ph), 5.25–4.80 (m, 2 H, OCH$_2$), 4.46 (dd, *J* = 9.2, 3.2 Hz, 1 H, NCH), 3.61, 3.56, 3.48, 3.31 (4 × s, 6 H, OCH$_3$), 3.20–2.81 (m, 2 H, CH$_2$I), 2.25–1.71 (m, 8 H).

^{13}C NMR (CDCl$_3$, 100 MHz): δ = 174.08, 173.88, 172.97, 172.80 (4 × s, CO$_2$Me), 154.76, 154.09 (2 × s, NCO), 136.42, 135.98 (2 × s, C, Ph), 128.62, 128.57, 128.50, 128.40, 128.03, 127.55 (6 × s, CH, Ph), 69.80, 68.92 (2 × s, NCCO), 67.74, 67.23 (2 × s, OCH$_2$), 61.91, 61.03 (2 × s, NCHCO), 52.73, 52.49, 52.45, 52.27 (4 × s, OCH$_3$), 35.98, 35.87, 35.14, 34.41 (4 × s, CH$_2$CH$_2$), 28.32, 27.96, 27.44, 26.81 (4 × s, CH$_2$CH$_2$), 7.34, 7.16 (2 × s, CH$_2$I).

MS (CI): *m*/*z* (%) = 490.0 (M$^+$ + H).

1-Benzyl 2,5-Dimethyl 2-[2-(Chloromethyl)prop-2-en-1-yl]pyrrolidine-1,2,5-tricarboxylate (15a, 15b)

Data for **15a**: Colorless oil; yield: 34%; R_f = 0.45 (hexane–EtOAc, 2:1).

^{1}H NMR (CDCl$_3$, 400 MHz): δ (mixture of rotamers) = 7.39–7.30 (m, 5 H, Ph), 5.41–4.86 (m, 4 H, OCH$_2$, =CH$_2$), 4.57 (2 × dd, *J* = 8.8, 4.8 Hz, 1 H, NCH), 4.29–4.08 (m, 2 H, CH$_2$Cl), 3.77, 3.73, 3.61, 3.43 (4 × s, 6 H, OCH$_3$), 3.38, 3.27 (2 × d, $^2J_{H-H}$ = 14.4 Hz, 1 H, C-CH$_2$-C=CH$_2$), 3.88, 3.75 (2 × d, $^2J_{H-H}$ = 14.4 Hz, 1 H, C-CH$_2$-C=CH$_2$), 2.25 (m, 2 H, CH$_2$), 1.06 (m, 2 H, CH$_2$).

^{13}C NMR (CDCl$_3$, 100 MHz): δ (mixture of rotamers) = 174.11, 173.82, 172.61, 172.44 (4 × s, CO$_2$Me), 155.16, 154.66 (2 × s, NCO), 141.21, 141.17 (2 × s, C=CH$_2$), 136.36, 135.77 (2 × s, C, Ph), 128.79, 128.52, 128.44, 128.40, 128.13, 127.87 (6 × s, CH, Ph), 120.73, 120.05 (2 × s, C=CH$_2$), 70.17, 69.27 (2 × s, NCCO), 67.95, 67.46 (2 × s, OCH$_2$), 62.38, 61.45 (2 × s, NCHCO), 52.76, 52.58, 52.43, 52.29 (4 × s, OCH$_3$), 49.15, 48.88 (2 × s, CH$_2$Cl), 37.39, 37.16 (2 × s, CH$_2$=CCH$_2$), 35.54, 34.26, 27.57, 26.98 (4 × s, CH$_2$CH$_2$).

MS (CI): *m*/*z* (%) = 409 [(M$^+$), ^{35}Cl], 374 [(M$^+$ – ^{35}Cl)].

Anal. Calcd for $C_{20}H_{24}ClNO_6$: C, 58.61; H, 5.90; N, 3.42. Found: C, 58.61; H, 5.92; N, 3.09.

Data for **15b**: Colorless oil; yield: 46%; R_f = 0.30 (hexane–EtOAc, 2:1).

^{1}H NMR (CDCl$_3$, 400 MHz): δ (mixture of rotamers) = 7.53–7.44 (m, 5 H, Ph), 5.45–5.11 (m, 4 H, OCH$_2$, =CH$_2$), 4.43 (2 × dd, *J* = 8.8, 3.2 Hz, 1 H, NCH), 4.06–3.88 (4 × d, $^2J_{H-H}$ = 12.4 Hz, 2 H, CH$_2$Cl), 3.78, 3.76, 3.58, 3.54 (4 × s, 6 H, OCH$_3$), 3.22, 3.07 (2 × d, $^2J_{H-H}$ = 14.4 Hz, 1 H, C-CH$_2$-C=CH$_2$), 3.73–3.69 (2 × d, $^2J_{H-H}$ = 9.6 Hz, 1 H, C-CH$_2$-C=CH$_2$), 2.38–2.01 (m, 4 H, CH$_2$CH$_2$).

^{13}C NMR (CDCl$_3$, 100 MHz): δ (mixture of rotamers) = 173.31, 173.03, 172.14, 171.84 (4 × s, CO$_2$Me), 153.86, 153.47 (2 × s, NCO), 141.47, 141.16 (2 × s, C=CH$_2$), 136.24, 135.73 (2 × s, C, Ph), 128.52, 128.41, 128.43, 128.36, 128.17, 127.08 (6 × s, CH, Ph), 120.16, 119.68 (2 × s, C=CH$_2$), 69.79, 68.80 (2 × s, NCCO), 67.81, 67.44 (2 × s, OCH$_2$), 61.26, 60.57 (2 × s, NCHCO), 52.74, 52.56, 52.37, 52.18 (4 × s, OCH$_3$), 48.64, 48.55 (2 × s, CH$_2$Cl), 39.07, 37.4 (2 × s, CH$_2$=CCH$_2$), 36.06, 34.83, 28.25, 27.36 (4 × s, CH$_2$CH$_2$).

MS (CI): *m*/*z* (%) = 409 [(M$^+$), ^{35}Cl], 374 [(M$^+$ – ^{35}Cl)].

Anal. Calcd for $C_{20}H_{24}ClNO_6$: C, 58.61; H, 5.90; N, 3.42. Found: C, 58.63; H, 5.88; N, 3.19.

8-Benzyl 1,5-Dimethyl 3-Methylene-8-azabicyclo[3.2.1]octane-1,5,8-tricarboxylate (16)

Colorless oil; yield: 33%; R_f = 0.55 (hexane–EtOAc, 2:1).

^{1}H NMR (CDCl$_3$, 500 MHz): δ = 7.38–7.25 (m, 5 H, Ph), 5.08–5.03 (2 × br s, 4 H, OCH$_2$, =CH$_2$), 3.91–3.25 (br s, 6 H, OCH$_3$), 2.81–2.62 (br s, 2 H, CH$_2$), 2.54–2.50 (2 × s, 2 H, CH$_2$), 2.29 (d, *J* = 6.5 Hz, 2 H, CH$_2$), 1.84 (d, *J* = 6.5 Hz, 2 H, CH$_2$).

^{13}C NMR (CDCl$_3$, 125 MHz): δ = 171.61 (s, CO$_2$Me), 154.45 (s, NCO), 139.91 (s, C=CH$_2$), 135.33 (s, C, Ph), 128.52 (s, CH, Ph), 128.46 (s, CH, Ph), 128.40 (s, CH, Ph), 115.65 (s, C=CH$_2$), 68.10 (s, OCH$_2$), 67.88 (br s, NCCO), 52.30 (s, OCH$_3$), 40.28 (br s, CH$_2$=CCH$_2$), 33.75 (br s, CH$_2$CH$_2$).

MS (CI): *m*/*z* (%) = 374 [(M$^+$ + H)], 330 [(M$^+$ – CO$_2$)], 240 [(M$^+$ – Cbz)].

Anal. Calcd for $C_{20}H_{23}NO_6$: C, 64.33; H, 6.21; N, 3.75. Found: C, 64.29; H, 6.26; N, 3.59.

8-[(Benzyloxy)carbonyl]-3-methylene-8-azabicyclo[3.2.1]octane-1,5-dicarboxylic Acid (Cbz-3b)

To a stirred soln of **16** (300 mg, 0.80 mmol) in MeOH–THF (10 mL, 1:1) was added dropwise a soln of NaOH (322 mg, 8.00 mmol, 10 equiv) in H$_2$O (8 mL), and the resulting suspension was stirred for 96 h. The solvent was evaporated and the residue was dissolved in H$_2$O (ca. 10 mL). The aq phase was extracted with CH$_2$Cl$_2$ (3 × 2 mL), acidified to pH 2 with aq HCl and then extracted with EtOAc (3 × 5 mL). The combined EtOAc extracts were dried over Na$_2$SO$_4$ and evaporated to afford Cbz-**3b** as a white solid; yield: 269 mg (97%); mp 199–201 °C.

^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.38–7.24 (m, 5 H, Ph), 5.12–5.05 (2 × br s, 4 H, OCH$_2$, =CH$_2$), 2.80–2.60 (br s, 2 H, CH$_2$), 2.56–2.52 (2 × s, 2 H, CH$_2$), 2.34 (d, *J* = 7.2 Hz, 2 H, CH$_2$), 1.91 (d, *J* = 7.2 Hz, 2 H, CH$_2$).

^{13}C NMR (CD$_3$OD, 100 MHz): δ = 174.92 (s, COOH), 156.44 (s, NCO), 141.85 (s, C=CH$_2$), 137.16 (s, C, Ph), 129.54 (s, CH, Ph), 129.24 (s, CH, Ph), 129.16 (s, CH, Ph), 116.17 (s, C=CH$_2$), 69.68 (br s, NCCO), 69.06 (s, OCH$_2$), 41.06 (br s, CH$_2$=CCH$_2$), 35.18 (br s, CH$_2$CH$_2$).

MS (CI): *m*/*z* (%) = 345 (M$^+$), 301 (M$^+$ – CO$_2$).

Anal. Calcd for $C_{18}H_{19}NO_6$: C, 62.60; H, 5.55; N, 4.06. Found: C, 62.35; H, 5.78; N, 4.32.

References

(1) Hassian, S.; Auzzas, L. *Acc. Chem. Res.* **2008**, *41*, 1241.

(2) (a) Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789. (b) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645. (c) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517. (d) Park, K.-H.; Kurth, M. J. *Tetrahedron* **2002**, *58*, 8629. (e) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2007**, *18*, 569.

(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.; Curtis, D. R. *Brain Res.* **1978**, *152*, 603.

(4) Kubyshkin, V. S.; Mykhailiuk, P. K.; Komarov, I. V. *Tetrahedron Lett.* **2007**, *48*, 4061.

(5) Dimethyl *meso*-2,5-dibromohexanedioate **5a** was obtained using an identical procedure to that described for diethyl

meso-2,5-dibromohexanedioate, see: Guha, P. C.; Sankaran, D. K. *Org. Synth.* **1955**, *3*, 623.

(6) Three diastereomers of **4**: *meso*-, (2*R*,5*R*)- and (2*S*,5*S*)- are formed during the synthesis, each being suitable for alkylation. We chose the crystalline (2*R*,5*R*)-isomer **4**, which was easily separated from the reaction mixture as it crystallizes upon standing in a fridge; the product was filtered off and was washed with hexane. For the original procedure, see: Yamamoto, Y.; Hoshino, J.; Fujimoto, Y.; Ohmoto, J.; Sawada, S. *Synthesis* **1993**, 298.

(7) The configurations at C-2 and C-5 in compounds **6**, **9**, **12a**,**b**, **14** and **15a**,**b** were not determined since they are lost upon subsequent transformation into the non-chiral 8-azabicyclo[3.2.1]octane skeleton.

(8) (a) Romesberg, F. E.; Collum, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 9198. (b) Ferey, V.; Vedrenne, P.; Toupet, L.; Le Gall, T.; Mioskowski, C. *J. Org. Chem.* **1996**, *61*, 7244.

(9) The conversion without addition of HMPA was only 15% after 12 h at 20 °C. After 160 h, the transformation was complete; however, in the ^{1}H NMR spectrum of the crude mixture, together with **6**, a number of unidentified side products were detected. All subsequent alkylations were performed in the presence of HMPA.

(10) Xu, Y.-z.; Choi, J.; Calaza, M. I.; Turner, S.; Rapoport, H. *J. Org. Chem.* **1999**, *64*, 4069.

(11) Einhorn, J.; Einhorn, C.; Ratajczak, F.; Pierre, J.-L. *Synth. Commun.* **2000**, *30*, 1837.

(12) Masschelein, K. G. R.; Stevens, C. V.; Dieltiens, N.; Claeys, D. D. *Tetrahedron* **2007**, *63*, 4712.