Tetrahedron: *Asymmetry* 21 (2010) 2015–2020

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Stereochemistry of terpene derivatives. Part 7: Novel rigidified amino acids from (+)-3-carene designed as chiral GABA analogues ☆

Kamila Gajcy [a], Jolanta Pękala [a], Bożena Frąckowiak-Wojtasek [b], Tadeusz Librowski [c], Stanisław Lochyński [a,d,*]

[a] *Department of Bioorganic Chemistry, Faculty of Chemistry, Wrocław University of Technology, Wybrzeże Wyspiańskiego 27, 50-370 Wrocław, Poland*
[b] *Faculty of Chemistry, Opole University, Oleska 48, 45-052 Opole, Poland*
[c] *Department of Pharmacodynamics, Collegium Medicum, Jagiellonian University, Medyczna 9, 30-688 Kraków, Poland*
[d] *Department of Cosmetology, Wrocław College of Physiotherapy, Kościuszki 4, 50-038 Wrocław, Poland*

ARTICLE INFO

Article history:
Received 12 May 2010
Accepted 22 June 2010
Available online 24 July 2010

ABSTRACT

Several novel cyclopropyl-rigidified γ- and δ-amino acids **3**–**4** have been prepared starting from monoterpene (+)-3-carene **2**. These compounds are proposed as chiral analogues of γ-aminobutyric acid (GABA) **1** and are expected to be of interest as potential inhibitors of GABA receptors.

1. Introduction

Conformationally constrained amino acids containing small rings have been the focus of both synthetic and medicinal chemistry particularly as they apply to the design of novel peptides.[2] The use of modified amino acids in peptide strands allows greater control over the chemical and conformational properties of oligopeptides and offers the promise of an increased metabolic stability and an improved oral bioavailability.[3] The peptide scaffold can be used for probing the structural requirements of receptor-bound ligand conformations.[2] They can also create unusual foldamers and novel helical folds such as nanotubes,[4] peptide segments with novel structural and internal cavity properties.[5]

Rigidified cyclic amino acids play an important role in drug design and development where they exert conformational constraints. They might also be considered as structural analogues of neurotransmitters such as γ-aminobutyric acid (GABA) **1**, which is the main inhibitory neurotransmitter in the mammalian brain.[6] It is well documented that GABA deficiency is associated with several important neurological disorders such as Huntington's chorea, Parkinson's, and Alzheimer's disease in addition to psychiatric disorders, such as anxiety, depression, pain, panic, and mania.[7] When the concentration of GABA diminishes below a threshold level in the brain, convulsions occur; accordingly, raising the brain GABA level terminates the seizures. Although it is known that increasing the brain concentration of GABA prevents convulsions, the high polarity and flexible structure of this compound are probably responsible for its inefficiency as an anticonvulsant when administered orally or intravenously. To resolve this problem, GABA analogues are being designed, as are compounds which have the potential to cross the blood–brain barrier and have an effect on the brain. Numerous compounds having a similar backbone to the GABA structure show an anticonvulsant activity. The most popular GABA analogues are antiepileptic drugs, such as vigabatrin, tiagabine, gabapentin, pregabalin, and felbamate. Recently there has been an increasing interest in the synthesis and pharmacological effects of new GABA derivatives, which can be considered as potent drugs in the treatment of neurodegenerative disorders.

The present aim of our work was the synthesis of new rigid cyclic γ- and δ-amino acids (+)-**3**, (−)-**3**, **4**, considered as GABA analogues. These amino acids are rigidified by a cyclopropyl moiety with a *gem*-dimethyl group. (+)-3-Carene **2**, a major component of turpentine obtained from *Pinus sylvestris* (L.), is the source of a chiral cyclopropyl group for the desired compounds (+)-**3**, (−)-**3,** and **4**, (Fig. 1). The ozonolysis of the unsaturated bond in this monoterpene led to a ketocarboxylic acid **5**, which was a key compound for further transformations. Various organic reactions, such as Schmidt and Curtius rearrangements, enabled the synthesis of desired products in three to six steps with the chirality preserved from (+)-3-carene **2**.

2. Results and discussion

(+)-[(1*S*,3*R*)-3-(Aminomethyl)-2,2-dimethylcyclopropyl]-acetic acid (+)-**3** was synthesized in a four-step procedure (Scheme 1). The ozonolysis of (+)-3-carene **2** followed by the Brown–Garg oxidation[8] gave ketocarboxylic acid **5**, which was the subject of a Curtius rearrangement. Various modifications of the Curtius rearrangement were checked to determine the most appropriate conditions for obtaining the protected ketoamine **6**[9] (Table 1). First,

☆ Part 6. See Ref. 1.

* Corresponding author. Tel.: +48 71 320 24 00; fax: +48 71 328 40 64.
E-mail address: stanislaw.lochynski@pwr.wroc.pl (S. Lochyński).

0957-4166/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2010.06.026

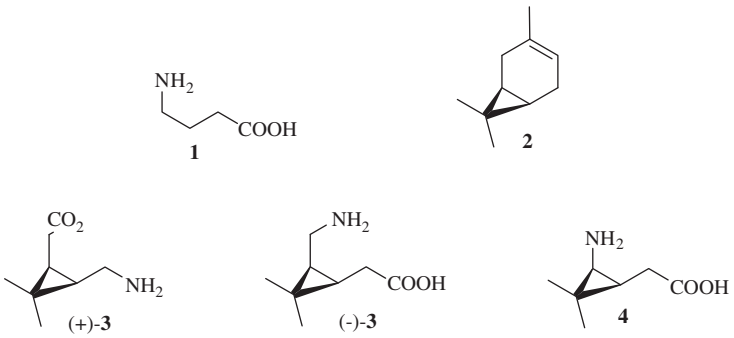
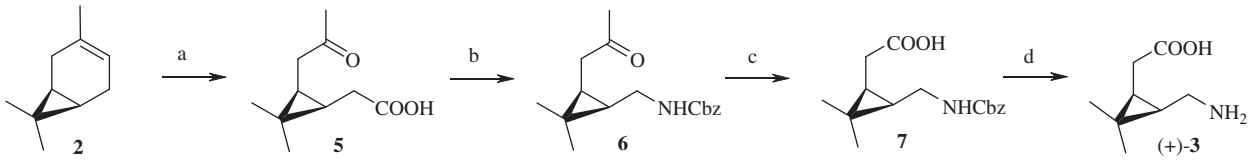


Figure 1. Novel GABA analogues obtained from (+)-3-carene **2**.



Scheme 1. Reagents: (a) (1) O_3; (2) $Na_2Cr_2O_7$, H_2SO_4; (b) DPPA, TEA, $PhCH_3$, $PhCH_2OH$; (c) NaBrO, H_2O; (d) H_2, Pd/C, MeOH.

Table 1
The modification of the Curtius rearrangement reaction

Run	substrate [equiv]	$PhCH_3$	DPPA [equiv]	TEA [equiv]	$PhCH_2OH$ [equiv]	Ag_2CO_3 [equiv]	Temp [°C]	Time [h]	Yield [%]
1	1.0	–	1.2	1.1	1.2	–	85	25	42
2	1.0	+	1.2	1.1	1.2	–	85	25	61
3	1.0	+	2.0	2.0	1.0	–	85	17	61
4	1.0	+	1.4	3.0	1.7	–	100	17	64
5	1.0	+	1.4	3.0	1.7	–	80	18	49
6	1.0	+	1.4	6.0	1.7	–	80	17	17
7	1.0	+	2.0	2.0	1.0	2.0	90	5	90
8	1.0	+	2.0	2.0	1.0	0.1	85	23	65
9	1.0	+	2.0	2.0	1.0	1.0	90	6	76

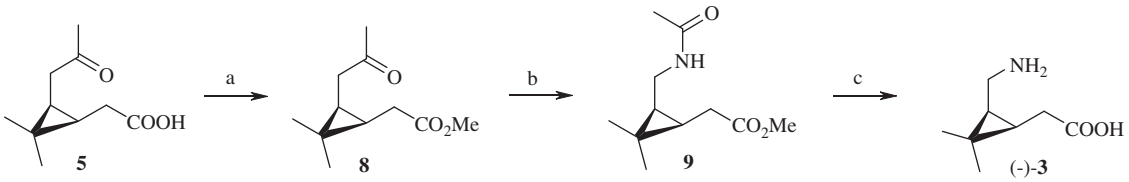
Substrate—ketocarboxylic acid **5**, $PhCH_3$—toluene, solvent of reaction, DPPA—diphenylphosphoryl azide, TEA—triethylamine, $PhCH_2OH$—benzyl alcohol, Ag_2CO_3.

the reaction with DPPA in the presence of triethylamine and benzyl alcohol was used. The yield of this reaction was sufficient when the acyl azide was isolated, and the rearrangement was performed in a separate step. However, the acyl azides are well known as unstable and hazardous compounds, thus we attempted a one-pot method that allowed the direct conversion of carboxylic acid **5** into amine **6**. For a one-pot procedure it turned out that the addition of toluene as a solvent significantly improved the yield from 42% to 61% (runs 1 and 2). An excess of DPPA (2.0 equiv) and TEA (2.0 equiv) did not have any influence on the yield but the time was shortened (run 3). When the Curtius reaction was conducted at a higher temperature (100 °C) and in the presence of an excess of DPPA (1.4 equiv), TEA (3.0 equiv), and $PhCH_2OH$ (1.7 equiv), product **6** was synthesized in a slightly better yield (run 4). For the reaction with the same ingredients as in run 4 but carried out at a lower temperature (80 °C), the conversion of substrate **5** was attempted in the same time but the product **6** was isolated in only 49% yield (run 5). In the presence of an excess of DPPA (1.4 equiv), TEA (6.0 equiv), and $PhCH_2OH$ (1.7 equiv) the reaction was completed in the same time but several by-products occurred and the product was isolated in a very low yield (17%) (run 6). Next, we attempted to investigate silver carbonate as an additional promoter to activate the isocyanate in the Curtius reaction.[10] In fact, in the case of Ag_2CO_3, the reactivity was greatly improved. The best result was obtained in run 7, by using an excess of DPPA (2.0 equiv), TEA (2.0 equiv), and Ag_2CO_3 (2.0 equiv). The time of the completed reaction decreased by about threefold than in the experiment without adding Ag_2CO_3 and product **6** was isolated in 90% yield (run 3).

The *N*-Cbz-protected ketoamine **6** was then, in the haloform reaction, converted into *N*-Cbz-protected amino acid **7**[11] by treatment with hypobromite. The hydrogenation of **7** (H_2, Pd/C) gave the first designed GABA analogues, amino acid (+)-**3**[12] (Scheme 1).

The (−)-enantiomer of σ-amino acid **3** was obtained in a three-step procedure (Scheme 2). The key compound **5** was subjected to the esterification using a 3% solution of hydrogen chloride in methanol. In the Schmidt reaction with hydrazoic acid, prepared from sodium azide and methanesulfonic acid in dimethoxyethane, carried out at −30 °C to room temperature, methyl ester **8** was converted into amido ester **9**.[13] The hydrolysis of the obtained amino derivative **9** gave amino acid (−)-**3**.[14] The values of specific rotations for (+)-**3** and (−)-**3** were $[\alpha]_D^{20} = +34.1$ (*c* 2.0, MeOH) and $[\alpha]_D^{24} = -34.1$ (*c* 2.0, MeOH), respectively.

The last designed amino acid **4** was prepared starting from the previously obtained methyl ester **8**, in six steps. At first, the Baeyer–Villiger (B–V) reaction was investigated. The reaction was conducted via two methods: with and without a solvent. Under standard B–V reaction conditions, with chloroform as the solvent, the reaction took a couple of days. In the second method, we decided to use solvent-free conditions, which significantly shortened the reaction time; thus the reaction was nearly complete after 1 h. In this method, the B–V reaction was carried out with methyl ester **8** using *m*-chloroperbenzoic acid without a solvent and after 1 h CH_2Cl_2 was added for easier stirring of the mixture, which allowed the completion of the reaction leading to acetoxy ester **10**.[15] Next, the acetoxy ester was hydrolyzed in the presence of K_2CO_3 and methanol gave hydroxy ester **11**, which after oxidation with the Brown–Garg reagent, giving carboxy ester **12.**[16] Using



Scheme 2. Reagents: (a) 3% HCl in CH_3OH; (b) NaN_3, $MeSO_3H$, DME; (c) NaOH, H_2O, EtOH.

DPPA (2.0 equiv) in the presence of triethylamine (2.0 equiv) and benzyl alcohol (1.0 equiv), with the additive of Ag_2CO_3 (2.0 equiv) the *N*-Cbz-protected amino ester **13**[17] was obtained, which was then hydrolyzed in the presence of KOH to the *N*-Cbz-protected amino acid **14**.[18] Finally, deprotection of compound **14** by means of H_2 (Pd/C) led to the third designed GABA analogue **4**[19] (Scheme 3).

3. Conclusion

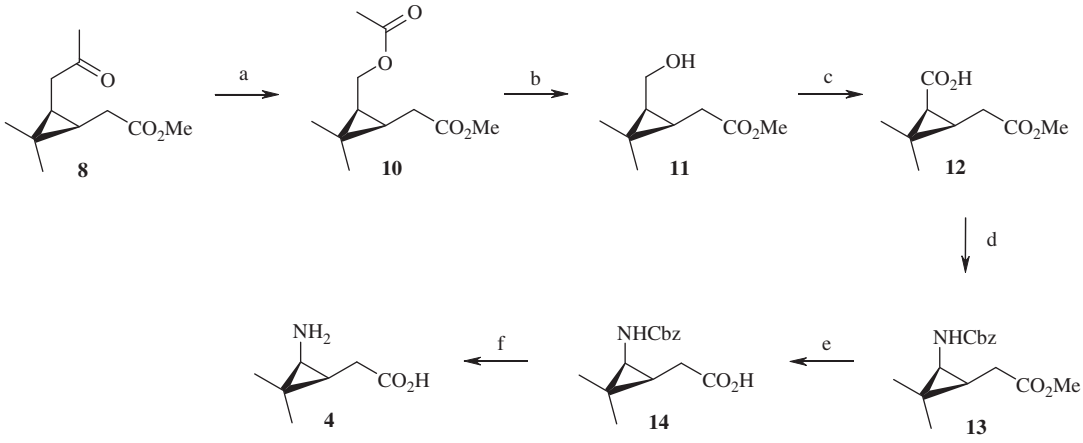
The preliminary results of pharmacological in vivo tests of amido ester **9** showed that it had an influence on the central nervous system. The compound investigated increased the spontaneous locomotor activity in mice. It favorably prolonged the latency time. Furthermore, the amido ester protected animals from death and showed anticonvulsant activity. It was also indicated to be non-toxic, which is a very important point for the design of potential drugs. Further pharmacological tests of all the obtained amino derivatives are currently in progress.

4. Experimental

(+)-3-Carene was purchased from Acros Organics ($[\alpha]_D^{20} = +15.2$ (neat); ($n_D^{20} = 1.4697$, d = 0.864 g/cm^3, bp = 171–172 °C, ee = 100%). All materials were obtained from commercial suppliers: Sigma, Aldrich, and POCh and were used without purification. The course of all the reactions and the composition of products were checked by thin-layer chromatography (TLC). TLC was carried out on precoated TLC plates with silica gel 60 F_{254} 0.2 mm (Merck) with visualization by irradiation with a short-wavelength UV light. Plates were developed in a mixture of hexane and acetone and methanol applied in various ratios and visualized with 20% ethanolic H_2SO_4, containing 0.1% of anisaldehyde or solution of ninhydrin (for amino acids). Preparative column chromatography was carried out on silica gel (230–400 mesh, Merck) with a mixture of hexane, ethyl acetate, and acetone (various ratios) as an eluent. IR spectra were taken from liquid films or in KBr on Perkin Elmer 621 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ with TMS as an internal standard on a Bruker Avance™ DRX 300 instrument. Chemical shifts (δ) are reported in ppm and coupling constants (J) are given in Hertz. ^{13}C–^{1}H substitution was determined with HMQC correlation and DEPT-135 experiments. The names of compounds are compatible with IUPAC nomenclature. Numbering of carbon atoms in all compounds was changed to simplify interpretation of ^{1}H , ^{13}C NMR spectra. Optical rotation measurements were obtained on a PolAAr-31 automatic polarimeter (Optical Activity Ltd). Ozone was generated by the IMPOZ-4 ozonator.

4.1. (−)-[(1*R*,3*S*)-2,2-Dimethyl-3-(2-oxopropyl)cyclopropyl]-acetic acid 5

Ozone was bubbled through a cooled (0 °C) solution of (+)-3-carene **2** (68.12 g, 0.50 mol) in a concentrated acetic acid (200 ml) for 5 h. The cooled reaction mixture was then allowed to warm up to room temperature and treated with water (50 ml). The Brown–Garg reagent[8] (312 ml) was added dropwise to a magnetically stirred solution of ozonolysis product kept at 25–30 °C temperature. The solution was stirred at room temperature until no starting material was detected by TLC (3.5 h). Water (500 ml) was added to the mixture and the aqueous phase was extracted with diethyl ether. The combined extracts were dried over $MgSO_4$ and evaporated to give a crude product. Saturated aqueous $NaHCO_3$ was added to a solution of crude ketocarboxylic acid **5** in diethyl ether and biphasic mixture was stirred at room temperature until the evolution of CO_2 ceased. The layers were separated and the aqueous phase was acidified with 5% H_2SO_4 and extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The resulting product (48.81 g, 53% yield) was purified by column chromatogra-



Scheme 3. Reagents: (a) *m*CPBA, then CH_2Cl_2; (b) K_2CO_3, MeOH; (c) $Na_2Cr_2O_7$, H_2SO_4; (d) DPPA, Et_3N, $PhCH_3$, $PhCH_2OH$; (e) NaOH, H_2O, EtOH; (f) H_2, Pd/C, MeOH.

phy eluting with hexane–acetone to give ketocarboxylic acid **5** as a yellow oil. $[\alpha]_D^{20} = -14.6$ (*c* 5.0, $CHCl_3$); $n_D^{20} = 1.4578$; IR (film, cm^{-1}): 2951 (s), 2735 (w), 1713 (vs), 1452 (m), 1376 (m), 1229 (m), 1168 (s); ^1H NMR ($CDCl_3$, 300 MHz): 0.94 and 1.14 (2s, 6H at C-9 and C-10); 0.96–1.02 (m, 2H at C-3 and C-5); 2.19 (s, 3H at C-8); 2.30 (dd, *J* = 8.6, 7.30 Hz, 2H at C-6); 2.38–2.43 (m, 2H at C-2); ^{13}C NMR ($CDCl_3$, 75 MHz): 14.82 (C-9), 17.15 (C-4), 21.00 (C-5), 21.41 (C-3), 28.29 (C-10), 29.50 (C-8), 29.95 (C-6), 39.19 (C-2), 179.15 (C-7), 208.98 (C-1).

4.2. (−)-Benzyl {[(1*R*,3*S*)-2,2-dimethyl-3-(2-oxopropyl)cyclopropyl]methyl}carbamate 6

A solution of ketocarboxylic acid **5** (0.42 g, 2.23 mmol), DPPA (0.97 ml, 4.48 mmol), and triethylamine (0.62 ml, 4.47 mmol) in dry toluene (10 ml) was stirred at room temperature for 30 min, and then warmed to 85 °C. After 30 min stirring the reaction mixture was cooled to the room temperature. Next, benzoic alcohol (0.24 ml, 2.27 mmol) and Ag_2CO_3 (1.24 g, 4.50 mmol) were added and the reaction was carried out at 85 °C for 5 h. The reaction progress was monitored by TLC (3:1 hexane/acetone). The Ag_2CO_3 was filtered and the toluene was removed at a reduced pressure to afford carbamate **6**. The residue was chromatographed on silica gel (30:1 hexane/acetone). $[\alpha]_D^{24} = -25.25$ (*c* 2.0, $CHCl_3$); $n_D^{24} = 1.5114$; IR (film, cm^{-1}): 3341 (m), 2948 (ms), 2889 (m), 1717 (vs), 1528 (s), 1376 (m), 1167 (m), 698 (ms), 616 (w); ^1H NMR ($CDCl_3$, 300 MHz): 0.72–0.85 (m, 2H at C-2 and C-4); 0.88 and 1.00 (2s, 6H at C-8 and C-9); 2.08 (s, 3H at C-7); 2.26 (dd, *J* = 17.8, 7.7 Hz, 1H at C-1); 2.49 (dd, *J* = 17.6, 5.3 Hz, 1H at C-5); 2.88–2.97 (m, 1H at C-1); 3.23–3.28 (m, 1H at C-5); 4.9 (s, 1H at N); 5.01 (s, 2H at C-11); 7.21–7.30 (m, 5H at C-13, C-14, C-15, C-16, C-17); ^{13}C NMR ($CDCl_3$, 75 MHz): 14.96 (C-4), 17.39 (C-3), 21.47 (C-9), 25.65 (C-2), 28.55 (C-8), 29.85 (C-7), 37.72 (C-5), 38.86 (C-1), 66.47 (C-11), 127.98 (C-15), 128.25 (C-13, C-17), 128.43 (C-14, C-16), 136.66 (C-12), 156.26 (C-10), 209.12 (C-6). Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.42; H, 8.23; N, 4.96.

4.3. (+)-[(1*S*,3*R*)-3-({[(Benzyloxy)carbonyl]amino}methyl)-2,2-dimethylcyclopropyl]acetic acid 7

To an ice-cooled solution of sodium hypobromite [prepared from bromine (0.85 cm^3, 16.50 mmol) and sodium hydroxide (2.20 g, 55.00 mmol) in water (22.00 ml)], carbamate **6** was added dropwise and the reaction mixture was stirred at room temperature for about 4 h. Then, the mixture was washed with diethyl ether, treated with sodium sulfite and, finally, 10% H_2SO_4 was added to reach pH 2–3. The acid solution was extracted with diethyl ether and the combined organic extracts were dried over magnesium sulfate. The solvent was removed to obtain protected amino acid **7** (0.95 g, 84%) which was purified by column chromatography (10:1 hexane/acetone). $[\alpha]_D^{24} = +15.9$ (*c* 0.5, $CHCl_3$); $n_D^{25} = 1.4695$; IR (film, cm^{-1}): 3334 (m), 3091 (s), 3034 (s), 2952 (s), 1714 (vs), 1531 (m), 1456 (s), 1349 (s), 1250 (vs), 1131 (s), 1047 (s), 754 (ms), 738 (ms), 698 (s), 600 (w); ^1H NMR ($CDCl_3$, 300 MHz): 0.70–0.86 (m, 2H at C-3 and C-5); 0.92 and 1.01; (2s, 6H at C-7 and C-8); 2.20 (dd, *J* = 16.6, 8.3 Hz, 1H at C-2); 2.39 (dd, *J* = 16.7, 6.2 Hz, 1H at C-6); 2.98 (dd, *J* = 16.3, 8.9 Hz, 1H at C-2); 3.30 (dd, *J* = 16.8, 6.4 Hz, 1H at C-6), 5.03 (s, 1H at N); 5.07 (s, 2H at C-10); 7.23–7.27 (m, 5H at C-12, C-13, C-14, C-15, C-16); ^{13}C NMR ($CDCl_3$, 75 MHz): 14.85 (C-7 or C-8), 17.74 (C-4), 22.20 (C-3), 25.72 (C-5), 28.56 (C-7 or C-8), 29.64 (C-2), 37.79 (C-10), 66.71 (C-6), 128.09 and 128.54 (C-12, C-13, C-14, C-15, C-16), 136.62 (C-11), 156.45 (C-9), 179.08 (C-1). Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.63; H, 7.48; N, 4.96.

4.4. (+)-[(1*S*,3*R*)-3-(Aminomethyl)-2,2-dimethylcyclopropyl]-acetic acid (+)-3

A mixture of **7** (0.10 g, 0.34 mmol) and 5% Pd/C (35.00 mg) in MeOH (10 ml) was vigorously stirred under an H_2 atmosphere for 3 h. The Pd-catalyst was filtered off, and the filtrate was evaporated to gain (+)-**3** $[\alpha]_D^{20} = +34.1$ (*c* 2.0, MeOH); mp = 154–160 °C; IR (KBr, cm^{-1}): 3424 (s), 2943 (m), 1563 (vs), 1396 (s), 741 (w); ^1H NMR (D_2O, 300 MHz): 0.71–0.80 (m, 2H at C-3 and C-5); 0.82 and 0.91 (2s, 6H at C-7 and C-8); 1.96 (dd, *J* = 15.6, 10.0 Hz, 1H at C-2); 2.22 (dd, *J* = 15.4, 5.3 Hz, 1H at C-2); 2.83 (dd, *J* = 13.4, 9.5 Hz, 1H at C-6); 3.02 (dd, *J* = 13.4, 6.2 Hz, 1H at C-6); ^{13}C NMR (D_2O, 75 MHz): 14.00 and 27.70 (C-7 and C-8), 18.00 (C-4), 22.33 (C-3), 24.59 (C-5), 32.70 (C-2), 37.87 (C-6), 182.09 (C-1). Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 60.93; H, 9.88; N, 9.06.

4.5. (−)-Methyl [(1*R*,3*S*)-2,2-dimethyl-3-(2-oxopropyl)cyclopropyl]acetate 8

The ketocarboxylic acid **5** (10.00 g, 54.29 mmol) was taken up in 3% methanolic HCl (40.00 g) and after being left at room temperature and magnetic stirring for 4 h worked up to the required keto ester **9**, which was detected by TLC (5:1 hexane/acetone). The mixture was then washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with diethyl ether and the combined organic layers were dried over $MgSO_4$. After solvent evaporation under reduced pressure, the crude product (86% yield) was purified by vacuum fractional distillation, which gave 8.50 g of appropriate keto ester **8** as a pale amber oil. $[\alpha]_D^{24} = -23.0$ (*c* 5.0 $CHCl_3$); $n_D^{25} = 1.4519$; IR (film, cm^{-1}): 3621 (w), 2952 (s), 2868 (m), 1740 (vs), 1717 (vs), 1376 (m), 1167 (s); ^1H NMR ($CDCl_3$, 300 MHz): 0.79 and 1.00 (2s, 6H at C-9 and C-10); 0.82–0.91 (m, 2H at C-3 and C-5); 2.05 (s, 3H at C-8); 2.12 (dd, *J* = 11.5, 6.9 Hz, 2H at C-2); 2.23–2.27 (m, 2H at C-6); 3.56 (s, 3H at C-11) ; ^{13}C NMR ($CDCl_3$, 75 MHz): 14.83 (C-9), 17.11 (C-4), 21.05 (C-5), 21.68 (C-3), 28.34 (C-10), 29.49 (C-8), 29.88 (C-6), 39.21 (C-2), 51.58 (C-11), 173.61 (C-7), 208.31 (C-1).

4.6. (+)-Methyl {(1*R*,3*S*)-3-[(acetamino)methyl)-2,2-dimethyl-cyclpropyl}acetate 9

Methanesulfonic acid (26 ml) was added dropwise to a stirred mixture of keto ester **8** (5.00 g, 25.21 mmol) and dimethoxyethane (17.20 ml) cooled to −30 °C. The sodium azide (4.92 g, 75.36 mmol) was then added portionwise under gentle stirring keeping the temperature at −30 °C (2 h). The solution was allowed to slowly reach room temperature until the evolution of nitrogen ceased (4 h). More dimethoxyethane (52 ml) and 25% ammonium hydroxide were added till pH 9 was reached. The resulting solution was extracted with diethyl ether. The organic layer was dried over $MgSO_4$ and the solvent was evaporated giving amido ester **9** (3.67 g, 68%) as a yellow oil. The residue was purified by chromatography on silica gel eluting with hexane/acetone mixture (4.5:1). $[\alpha]_D^{24} = +20.2$ (*c* 1.0 $CHCl_3$); $n_D^{25} = 1.4629$; IR (film, cm^{-1}): 3293 (ms), 3083 (w), 2952 (ms), 1740 (vs), 1652 (vs), 1437 (s), 1375 (ms), 1173 (s), 712 (w); ^1H NMR ($CDCl_3$, 300 MHz): 0.81–0.93 (m, 2H at C-3 and C-5); 0.98 and 1.08 (2s, 6H at C-9 and C-10); 1.98 (s, 3H at C-11); 2.16 (dd, *J* = 16.5, 9.3 Hz, 1H at C-6); 2.55 (dd, *J* = 16.6, 9.2 Hz, 1H at C-6); 2.84 (ddd, *J* = 13.7, 9.6, 4.0 Hz, 1H at C-2); 3.70 (ddd, *J* = 13.7, 6.2, 4.2 Hz, 1H at C-2); 3.71 (s, 3H at C-8); 6.31 (s, 1H at N); ^{13}C NMR ($CDCl_3$, 75 MHz): 14.90 (C-10), 17.57 (C-4), 22.42 (C-3), 23.18 (C-9), 25.41 (C-5), 28.50 (C-11), 29.45 (C-2), 35.91 (C-6), 51.86 (C-8), 170.07 (C-1), 174.84 (C-7). Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 61.76; H, 9.09; N, 6.74.

4.7. (−)-[(1*R*,3*S*)-3-(Aminomethyl)-2,2-dimethylcyclopropyl]-acetic acid (−)-3

A mixture of amido ester **9** (3.00 g, 14.07 mmol) and NaOH (1.2 g, 30.00 mmol) in H_2O (7.05 ml) and ethanol (17.60 ml) was heated to reflux for 4.5 h until no starting material was detected by TLC (1:1 hexane/acetone). The presence of amino acid (−)-**3** in the reaction mixture was detected by ninhydrin eluting with methanol. The mixture was then evaporated to dryness under reduced pressure. The residue was taken up in water (5 ml) and after neutralizing with HCl was triturated with ethanol to afford (−)-**3** (0.75 g, 34%) as a white solid. $[\alpha]_D^{24} = -34.1$ (*c* 2.00, MeOH); mp = 154–160 °C; IR (KBr, cm^{-1}): 3424 (s), 2947 (m), 1643 (s), 1610 (s), 1253 (s), 741 (w); ^1H NMR (D_2O, 300 MHz): 0.62–0.75 (m, 2H at C-3 and C-5); 0.80 and 0.89 (2s, 6H at C-7 and C-8); 1.93 (dd, *J* = 15.5, 9.6 Hz, 1H at C-2); 2.15 (dd, *J* = 15.5, 5.8 Hz, 1H at C-6); 2.66 (dd, *J* = 13.3, 9.0 Hz, 1H at C-2); 2.87 (dd, *J* = 17.3, 4.0 Hz, 1H at C-6); ^{13}C NMR (D_2O, 75 MHz): 13.80 and 22.90 (C-7 and C-8), 18.22 (C-4), 24.21 (C-3), 27.56 (C-5), 32.64 (C-2), 37.44 (C-6), 182.96 (C-1). Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.01; H, 9.78; N, 9.02.

4.8. (+)-Methyl {(1*R*,3*S*)-3-[(acetyloxy)methyl]-2,2-dimethylcyclopropyl}acetate 10

Method 1: To a stirred solution of keto ester **8** (0.79 g, 3.98 mmol) in 100 ml $CHCl_3$, cooled to 0 °C, 4.91 g (28.5 mmol) of 70–75% *m*CPBA and 4.91 g $MgSO_4$ were added. After stirring for 90 h at room temperature, the reaction mixture was diluted with 25 ml of water and 25 ml of CH_2Cl_2. The two-phase system was separated and the water layer was extracted with three portions of CH_2Cl_2. The combined organic layers were washed three times with saturated aqueous $NaHCO_3$, three times with 10% aqueous $Na_2S_2O_3$ and twice with brine, dried over $MgSO_4$ and evaporated under reduced pressure to obtain acetoxyl ester in 80% yield, **10**. The residue was then chromatographed (acetone/hexane 13.6:1).

Method 2: Compound **8** (14.57 g, 73.53 mmol) was placed in a 500 ml round-bottomed flask and then 33.00 g of 70–75% *m*CPBA was added portionwise. The reaction mixture was stirred at room temperature by means of a stirring rod after every added portion. After 1 h the reaction mixture was diluted with 100 ml of CH_2Cl_2 and warmed at 40 °C and stirring was continued for a few hours until no substrate was detected by TLC (2:1 hexane/acetone). After the work-up, as mentioned above, acetoxy ester **10** was isolated (13.32 g, 84%) and then chromatographed on silica gel (80:1 hexane/acetone). $[\alpha]_D^{24} = +28.7$ (*c* 2.0, $CHCl_3$); $n_D^{28} = 1.4426$; IR (film, cm^{-1}): 2953 (s), 1740 (vs), 1436 (s), 1369 (ms), 1243 (s), 1027 (s), 840 (w), 607 (w); ^1H NMR ($CDCl_3$, 300 MHz): 0.94–0.99 (m, 2H at C-3 and C-5); 0.92 and 1.03 (2s, 6H at C-9 and C-10); 1.95 (s, 3H at C-8); 2.26 (d, *J* = 7.2 Hz, 2H at C-2); 3.60 (s, 3H at C-11); 3.94 (dd, *J* = 12.0, 7.9 Hz, 1H at C-6); 4.05 (dd, *J* = 11.9, 7.3 Hz, 1H at C-6); ^{13}C NMR ($CDCl_3$, 75 MHz): 14.83 (C-10), 18.54 (C-4), 20.99 (C-3), 22.74 (C-9), 24.20 (C-5), 28.52 (C-8), 29.77 (C-2), 51.64 (C-11), 62.25 (C-6), 171.19 (C-1), 173.54 (C-7). Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.43; H, 8.68.

4.9. (−)-Methyl [(1*R*,3*S*)-3-(hydroxymethyl)-2,2-dimethylcyclopropyl]acetate 11

A solution of **10** (0.50 g, 2.33 mmol) and K_2CO_3 (12.50 mg) in methanol (12.95 ml) was stirred at room temperature. After 6 h, an excess of K_2CO_3 was added (53.70 mg) and stirring was continued for a further 3 h. The reaction was quenched with saturated aqueous NH_4Cl, extracted with ethyl acetate, dried over $MgSO_4$, and concentrated under reduced pressure to yield **11** (80%) $[\alpha]_D^{24} = -28.5$ (*c* 1.52, $CHCl_3$); $n_D^{25} = 1.4899$, IR (film, cm^{-1}): 3337 (s), 2950 (s), 1720 (vs), 1438 (s), 1333 (ms), 1229 (s), 1201 (s), 1172 (s); ^1H NMR ($CDCl_3$, 300 MHz): 0.95–1.14 (m, 2H at C-3 and C-5); 0.92 and 1.03 (2s, 6H at C-7 and C-8); 2.16 (dd, *J* = 16.2, 10.2 Hz, 1H at C-2); 2.51 (dd, *J* = 16.1, 5.0 Hz, 1H at C-2); 3.43 (dd, *J* = 12.0, 9.6 Hz, 1H at C-6); 3.65 (s, 3H at C-9); 3.73 (dd, *J* = 12.0, 5.4 Hz, 1H at C-6); ^{13}C NMR ($CDCl_3$, 75 MHz): 15.23 (C-7 or C-8), 20.55 (C-4), 22.19 (C-3), 22.99 (C-7 or C-8), 23.90 (C-5), 31.14 (C-2), 51.22 (C-9), 66.45 (C-6), 170.33 (C-1). Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.50; H, 9.51.

4.10. (+)-(1*S*,3*R*)-3-(2-Methoxy-2-oxoethyl)-2,2-dimethylcyclopropanecarboxylic acid 12

The Brown–Garg reagent[8] (34.00 ml) was added dropwise to a magnetically stirred solution of hydroxy ester **11** (2.40 g, 13.93 mmol) in diethyl ether (120 ml) kept at 25–30 °C temperature. The solution was stirred at room temperature until no substrate **12** was detected by TLC (2:1 hexane/acetone). After 19 h, the reaction was diluted with water and the aqueous phase was extracted with diethyl ether. The combined extracts were dried over $MgSO_4$ and evaporated to give 2.40 g of crude product which was then purified by column chromatography eluting with hexane/acetone (11.5:1) to give carboxy ester **12** as a yellow oil. $[\alpha]_D^{23} = +49.7$ (*c* 1.31, $CHCl_3$); $n_D^{24} = 1.4566$; IR (film, cm^{-1}): 3008 (m), 2956 (s), 2681 (w), 1740 (vs), 1693 (vs), 1438 (s), 1333 (ms), 1229 (s), 1171 (s), 1014 (s), 840 (w); ^1H NMR ($CDCl_3$, 300 MHz): 1.21 and 1.23 (2s, 6H at C-7 and C-8), 1.48–1.59 (m, 2H at C-3 and C-5), 2.76 (d, *J* = 6.9 Hz, 2H at C-2), 3.68 (s, 3H at C-9); ^{13}C NMR ($CDCl_3$, 75 MHz): 14.14 (C-8), 26.53 (C-4), 27.95 (C-3), 28.54 (C-2), 28.67 (C-7), 29.03 (C-5), 51.70 (C-9), 173.51 (C-1), 177.39 (C-6). Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.93; H, 7.70.

4.11. (−)-Methyl [(1*R*,3*S*)-3-{[(benzyloxy)carbonyl]amino}-2,2-dimethylcyclopropyl]acetate 13

A solution of carboxy ester **12** (2.18 g, 11.71 mmol), DPPA (3.09 ml, 14.35 mmol), and triethylamine (1.83 ml, 13.20 mmol) in dry toluene (10 ml) was stirred at room temperature for 30 min, and then was warmed to 85 °C. After 30 min of stirring, the reaction mixture was cooled to room temperature to add the benzoic alcohol (1.49 ml, 14.36 mmol) and the reaction was carried out at 85 °C for the following 23.5 h. The reaction progress was monitored by TLC (3:1 hexane/acetone). An excess of benzoic acid and toluene was removed under reduced pressure to give 3.90 g of **13**. The residue was chromatographed on silica gel (24:1 hexane/ethyl acetate). $[\alpha]_D^{24} = -42.0$ (*c* 1.45, $CHCl_3$); $n_D^{27} = 1.5109$; IR (film, cm^{-1}): 3352 (m), 2952 (s), 1725 (vs), 1498 (s), 1331 (ms), 1242 (vs), 1056 (s), 740 (s), 696 (s), 595 (w); ^1H NMR ($CDCl_3$, 300 MHz): 0.98 and 1.11 (2s, 6H at C-6 and C-7), 0.90–1.08 (m, 1H at C-3), 2.08–2.31 (m, 1H at C-5), 2.38 (dd, *J* = 7.0, 3.1 Hz, 2H at C-2), 3.68 (s, 3H at C-8), 5.10 (s, 2H, at C-10), 5.16 (s, 1H at N), 7.26–7.39 (m, 5H, at C-12, C-13, C-14, C-15, C-16); ^{13}C NMR ($CDCl_3$, 75 MHz): 14.00 (C-7 or C-6), 19.64 (C-4), 23.33 (C-6 or C-7), 26.38 (C-3), 29.23 (C-2), 36.29 (C-5), 51.89 (C-8), 66.88 (C-10), 128.05 (C-13 and C-15), 128.47 (C-12 and C-16), 128.61 (C-14), 136.50 (C-11), 157.66 (C-9), 173.62 (C-1). Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.69; H, 7.33; N, 4.98.

4.12. (−)-[(1*R*,3*S*)-3-{[(Benzyloxy)carbonyl]amino}-2,2-dimethylcyclopropyl]acetic acid 14

An aqueous NaOH solution (1.06 g, 26.50 mmol NaOH in 6.30 ml of water) was added to a stirred solution of *N*-Cbz-protected amino ester **13** (3.26 g, 11.19 mmol) in ethanol (15.50 ml), after which the solution was warmed to 50 °C and stirring was con-

tinued for next 4 h. The reaction mixture was extracted with diethyl ether, and then the aqueous layer was treated with 10% H_2SO_4 and washed with diethyl ether. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give **14** (2.71 g, 88% yield), which was purified on silica gel (hexane/acetone 10:1). $[\alpha]_D^{25} = -42.4$ (*c* 0.8, $CHCl_3$); $n_D^{25} = 1.5443$; IR (film, cm^{-1}): 3350 (m), 3065 (s), 2940 (s), 1740 (s), 1700 (s), 1533 (ms), 1467 (s), 1351 (s), 1242 (vs), 1108 (s), 744 (s), 696 (s), 595 (w); ^1H NMR ($CDCl_3$, 300 MHz): 0.83 and 0.96 (2s, 6H at C-6 and C-7), 0.90–1.05 (m, 1H at C-5), 2.04–2.34 (m, 1H at C-3), 2.49 (d, $J = 14.6$ Hz, 2H at C-2), 5.04 (s, 2H at C-9), 5.11 (s, 1H at N), 7.20–7.30 (m, 5H at C-11, C-12, C-13, C-14, C-15); ^{13}C NMR ($CDCl_3$, 75 MHz): 14.12 (C-6 or C-7), 19.70 (C-4), 23.20 (C-6 or C-7), 26.29 (C-5), 29.29 (C-2), 36.32 (C-3), 67.32 (C-9), 128.06 (C-12 and C-14), 128.27 (C-11 and C-15), 128.57 (C-13), 136.14 (C-10), 158.90 (C-8), 178.10 (C-1). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.75; H, 6.98; N, 5.15.

4.13. (−)-[(1*R*,3*S*)-3-Amino-2,2-dimethylcyclopropyl]acetic acid 4

A mixture of **14** (0.20 g, 0.72 mmol) and 5% Pd/C (0.10 g) in MeOH (45 ml) was vigorously stirred under an H_2 atmosphere for 3 h. The Pd-catalyst was filtered off and the filtrate was evaporated to give **4** (0.10 g). $[\alpha]_D^{25} = -20.1$ (*c* 0.69, MeOH); IR (KBr, cm^{-1}): 3352 (m), 2952 (m), 1528 (s), 1242 (vs), 750 (w); ^1H NMR (D_2O, 300 MHz): 0.90 (s, 3H at C-7) and 0.93 (s, 3H at C-6), 0.96–1.08 (m, 1H at C-3), 2.20 (d, $J = 8.0$ Hz, 2H at C-2); 2.24 (d, $J = 8.0$ Hz, 1H at C-5); ^{13}C NMR (D_2O, 75 MHz): 12.60 (C-7), 17.50 (C-4), 21.83 (C-3), 25.34 (C-6), 30.01 (C-2), 34.95 (C-5), 179.33 (C-1). Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.51; H, 9.23; N, 9.98.

Acknowledgements

This work was supported by a fellowship co-financed by the European Union within the European Social Fund and Grant from the Ministry of Science and Higher Education of Poland (Grant N204 13332/3390).

References

1. For part 6, see: Kuriata, R.; Gajcy, K.; Turowska-Tyrk, I.; Lochyński, S. *Tetrahedron: Asymmetry* **2010**, *21*, 805–809.
2. Park, K. H.; Kurth, M. J. *Tetrahedron* **2002**, *58*, 8629–8659.
3. Wipf, P.; Stephenson, C. R. J. *Org. Lett.* **2005**, *7*, 1137–1140.
4. (a) Amorìn, M.; Castedo, L.; Granja, J. R. *J. Am. Chem. Soc.* **2003**, *125*, 2844–2845; (b) Baldauf, C.; Günther, R.; Hofmann, H. J. *J. Org. Chem.* **2005**, *70*, 5351–5361; (c) Brea, R. J.; Amorìn, M.; Castedo, L.; Granja, J. R. *Angew. Chem., Int. Ed.* **2005**, *44*, 5710–5713.
5. (a) Woll, M. G.; Lai, J. R.; Guzei, I. A.; Taylor, S. J. C.; Smith, M. E. B.; Gellman, S. H. *J. Am. Chem. Soc.* **2001**, *123*, 11077–11078; (b) Baldauf, C.; Günther, R.; Hofmann, H. J. *J. Org. Chem.* **2006**, *71*, 1200–1208; (c) Farrera-Sinfreu, J.; Giralt, E.; Castel, S.; Albericio, F.; Royo, M. *J. Am. Chem. Soc.* **2005**, *127*, 9459–9468; (d) Vasudev, P. G.; Shamala, N.; Ananda, K.; Balaram, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 4972–4975.
6. Owens, D. F.; Kriegstein, A. R. *Rev. Neurosci.* **2002**, *3*, 715–727.
7. (a) Ordóñez, M.; Cativiela, C. *Tetrahedron: Asymmetry* **2007**, *18*, 3–99; (b) Gale, K. *Epilepsia* **1989**, *30*, S1–S11; (c) Dalby, N. O. *Eur. J. Pharmacol.* **2003**, *479*, 127–137; (d) Glass, M.; Dragunow, M.; Faull, R. L. M. *Neuroscience* **2000**, *97*, 505–519; (e) Geffen, Y.; Nudelman, A.; Gil-Ad, I.; Rephaeli, A.; Huang, M.; Savitsky, K.; Klapper, L.; Winkler, I.; Meltzer, H. Y.; Weizman, A. *Eur. Neuropsychopharmacol.* **2009**, *19*, 1–13; (f) Kleppner, S. R.; Tobin, A. J. *Emerg. Ther. Targets* **2001**, *5*, 219–239.
8. Brown, H. C.; Garg, C. P. *J. Am. Chem. Soc.* **1961**, *83*, 2952.
9. Lochynski, S.; Gajcy, K.; Pekala, J. Polish Patent Application P385632, 2008.
10. Sawada, D.; Sasayama, S.; Takahashi, H.; Ikegami, S. *Tetrahedron Lett.* **2006**, *47*, 7219–7233.
11. Lochynski, S.; Gajcy, K.; Frackowiak-Wojtasek, B. Polish Patent Application P389321, 2009.
12. Lochynski, S.; Gajcy, K.; Frackowiak-Wojtasek, B. Polish Patent Application P390968, 2010.
13. Lochynski, S.; Frackowiak, B; Gajcy, K.; Kusiak, A.; Librowski, T.; Kubacka, M. Polish Patent Application P382189, 2007.
14. Lochynski, S.; Gajcy, K.; Frackowiak-Wojtasek, B. Polish Patent Application P390970, 2010.
15. Lochynski, S.; Gajcy, K.; Stawinoga, M. Polish Patent Application P388971, 2009.
16. Lochynski, S.; Gajcy, K. Polish Patent Application P389320, 2009.
17. Lochynski, S.; Gajcy, K. Polish Patent Application P389322, 2009.
18. Lochynski, S.; Gajcy, K. Polish Patent Application P390967, 2010.
19. Lochynski, S.; Gajcy, K. Polish Patent Application P390969, 2010.