Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 1035–1042

TETRAHEDRON: *ASYMMETRY*

Novel enantioselective synthesis of *trans*-α-(2-carboxycycloprop-1-yl)glycines: conformationally constrained L-glutamate analogues

Ayhan S. Demir,[a,*] Cihangir Tanyeli,[a] Ali Cagir,[a] M. Nawaz Tahir[b] and Dincer Ulku[b]

[a]*Department of Chemistry, Middle East Technical University 06531 Ankara, Turkey*

[b]*Department of Engineering Physics, Hacettepe University, Beytepe, 06532 Ankara, Turkey*

Received 27 January 1998; accepted 9 February 1998

Abstract

D- and L-α-(2-carboxycycloprop-1-yl)glycines were synthesized from *trans*-1,3-di(2-furyl)propenone. Conversion of the double bond to a cyclopropane is followed by the formation of an oxime ether. Enantioselective reduction of the oxime ether, separation of diastereomers and oxidation of the furane rings gave enantiomerically pure D- and L-CCG I and CCG II. The structure of oxime **7b** was determined by X-ray crystal structure analysis. The key step is the oxazaborolidine catalyzed enantioselective conversion of oxime ethers to amines. © 1998 Published by Elsevier Science Ltd. All rights reserved.

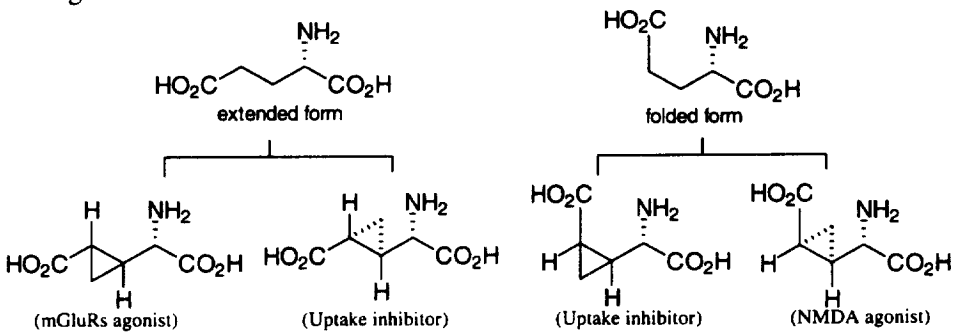
1. Introduction

L-Glutamic acid functions at many synapses in mammalian central nervous systems as an excitatory neurotransmitter[1] and is implicated in the construction of memory and early learning[2] as well as in the pathogenesis of neuron damage to cause various neuronal diseases.[3] Several classes of glutamate analogs have been used in the past as chemical probes for characterizing excitatory amino acid (EAA) receptors: among them (carboxycyclopropyl) glycines (CCGs) have represented a valuable source of potent and selective ligands for the various members of the glutamate receptor family, including ionotropic receptors, metabotropic receptors, and uptake carrier proteins. The introduction of a cyclopropyl moiety on the glutamate skeleton induces chirality, partially reduces the conformational flexibility (extended and folded form) thus allowing its selective interaction with a reduced number of recognition sites, and, most importantly, defines foreseeable orientations of the ω-carboxylate group with respect to the α-amino acid moiety, thus allowing the assessment of the conformational requirements of L-Glu acting at

* Corresponding author. E-mail: asdemi1@pop.uky.edu

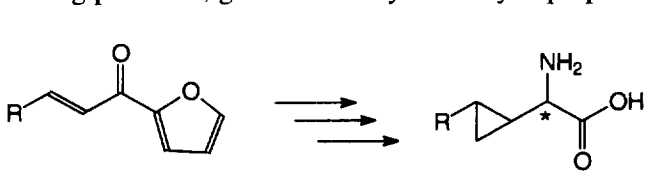
PII: S0957-4166(98)00061-5

its receptor subtypes.[4] Thus, among the eight possible CCG diastereomers, Pellicciary et al. reported that (2*S*,1′*R*,2′*S*)-(carboxycyclopropyl) glycine (L-CCG IV) **4**[5] is a potent and selective NMDA agonist, while the corresponding isomers (2*S*,1′*R*,2′*R*)- CCG II **2** and (2*S*,1′*S*,2′*R*)- CCG III **3** have been reported to be L-Glu uptake inhibitors.[6] Shinozaki et al. described the (2*S*,1′*S*,2′*S*)-CCG isomer (CCG I) **1**[7] as a potent mGluRs agonist.



CCG-1 **1** **CCG-II** **2** **CCG-III** **3** **CCG-IV** **4**

The first reported synthesis of CCG was not enantioselective and used *cis* and *trans*-cyclopropane-1,2-dicarboxylic acids as intermediates. Three partially enantioselective syntheses using the diazo addition method have also been reported.[8] L-CCG I was also synthesized by using the Sharpless asymmetric dihydroxylation reaction and stereochemically controlled cyclopropanation reaction of a substituted diene.[8g] In our previous work we reported an enantioselective synthesis of α-amino acids in which the key step is the enantioselective reduction of *E*- and *Z*-furyl ketone oxime ethers with chiral boron complexes. The chirality of the amino acid is fully controlled by the appropriate choice of geometrical isomer of the oxime ether.[9] Application of this method to the 1-(2-furyl) enones, using the double bond function as a cyclopropane ring precursor, gives new entry to the cyclopropane amino acids as shown in Scheme 1.[9,10]



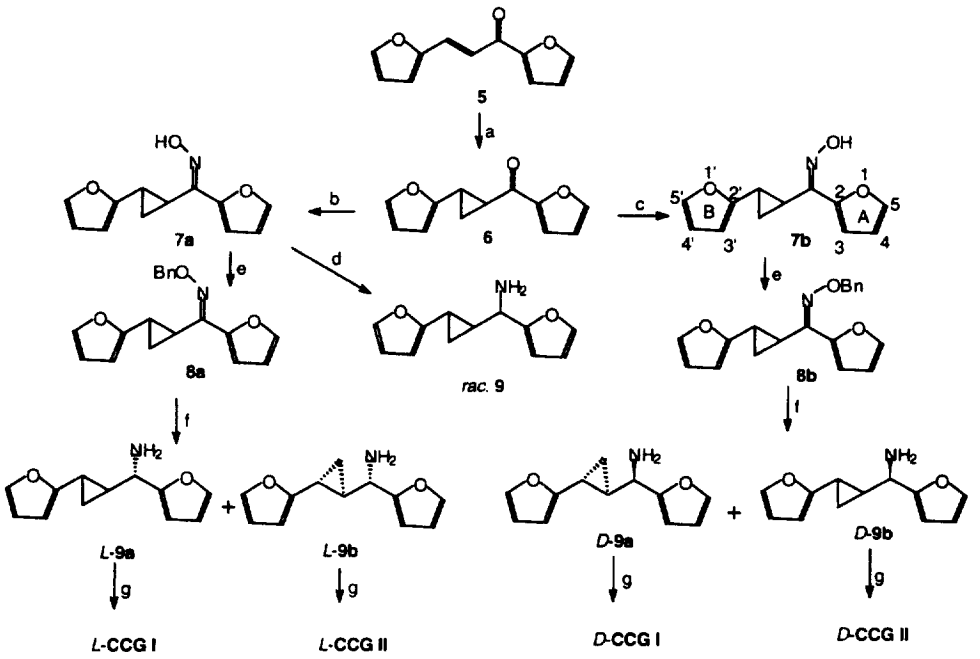
Scheme 1.

Using this simple chirality control we describe in this paper new routes to the stereoselective syntheses of D- and L-CCG I and CCG II.

2. Results and discussion

As shown in Scheme 2 *trans*-1,3-di(2-furyl)propenone **5** was chosen as the starting material for the synthesis of target molecules. The *trans*-enone **5** is synthesized from furfural and acetylfurane in 92% yield. Treatment of the enone **5** with trimethylsulfoxoniumiodide gave cyclopropylketone **6** in 94% yield. Simmons–Smith cyclopropanation gave a very low yield of the desired product. The ketone **6** was converted selectively to the *E*- and *Z*-oximes **7a** and **7b** in good yield using the following conditions. The reaction of enone with $H_2NOH \cdot HCl/NaOH$ gave *E*-oxime **7a** (mp 97–99°C) and $H_2NOH \cdot HCl/NaOAc$–EtOH gave *Z*-oxime **7b** (mp 69–71°C). From both methods the opposite isomer is isolated as a minor product. Additional purification was done by recrystallization. The *E*-oxime can also

be convert to the *Z*-oxime with HCl gas in ether at 0°C. Determination of oxime geometry was carried out using ^{1}H-NMR spectroscopy and X-ray crystal structure analysis.[11] In the ^{1}H-NMR spectra we obtained different shift values for the protons of furane rings (Scheme 2) for the *Z*-oxime [δ 6.08, 6.29, 6.55, 7.26, 7.43, 7.49) and the *E*-oxime (δ 6.06 (C-4′ H), 6.25 (C-3′ H), 6.39 (C-4 H), 6.67 (C-3 H), 7.26 (C-5′ H), 7.47 (C-5 H)].[9] In the *E*-isomer three multiplets appear at 6.39, 6.67 and 7.47 ppm from ring A. In the *Z*-isomer the signal of C-3 H shows a downfield shift and appears at 7.43 ppm because of the interaction of the oxime OH with C-3 H. Figure 1 shows the ORTEP drawing of compound **7b**.



a) Me_3SOI, NaH, DMSO b) $H_2NOHHCl$, NaOHc) $H_2NOHHCl$, NaOAc, EtOH d) BH_3-SMe_2, THF e) NaH, BnBr, DMF f) BH_3 THF, cat. g) O_3, MeOH

Scheme 2.

The oximes are converted to O-benzyloxime ethers using NaH and benzyl bromide in high yields. The purity of the *E*- and *Z* isomers was proven by GLC analysis of the corresponding O-benzyloxime ethers. The reduction of oxime **7a** with BH_3–SMe_2 in THF afforded *rac*-amine **9** in 88% yield. For the synthesis of the optically active amine, O-benzyloxime ethers are used as starting materials.

For the enantioselective reduction of *E*-oxime ether with BH_3·THF, a reaction performed in the presence of oxazaborolidine catalysts prepared from different chiral amino alcohols shown in Table 1, is used.[10,12] After reduction, the crude product was separated using flash column chromatography and two major products (*S*,*S*,*S*)-amine L-**9a** and (*S*,*R*,*R*)-amine L-**9b** were isolated (R_f=0.17 and 0.27). Under similar conditions the reduction of *Z*-oxime ether **8b** gave (*R*,*R*,*R*)-amine D-**9a** and (*R*,*S*,*S*)-amine D-**9b**. As shown in Table 1 the best enantiomeric excesses are obtained using **10**, **13** and **14** as catalysts with the ratio of oxime ether:BH_3:catalysts 0.8:2:1. The enantiomeric excess of the isomers is determined after separation of diastereomers via Mosher amides by ^{19}F-NMR and (*S*)-acetyl-lactylamide of amines by GLC analysis[13] (Table 1). The oxime geometry becomes a dominant factor in the stereoselectivity by the formation of amines. The same reduction reaction with O-methyloxime ether gave low selectivity. The use of catalytic amounts of catalysts gave very low selectivity.

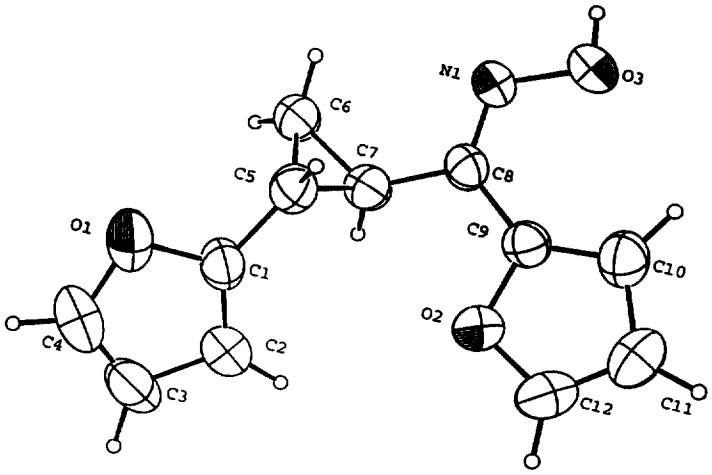
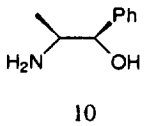
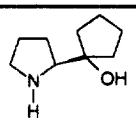
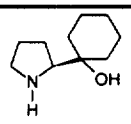
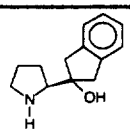
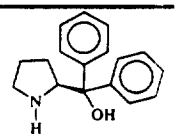


Fig. 1. X-Ray crystallographic structure of **7b**

Table 1
Reduction of oxime ethers **8a** and **8b** with different chiral catalysts

Catalyst	 10	 11	 12	 13	 14
CY% *L*-**9a**, *L*-**9b**[a,b]	37, 34	28, 21	30, 32	41, 38	36, 42
D-**9a**, *D*-**9b**[a,b,c]	33, 36			36, 39	36, 38

a)The enantiomeric excesses of the products are determined (after two chromatographic separations of the products) via Mosher amides by ^{19}F NMR and (*S*)-acetyllactylamide of amines by GLC analysis[13] (ee≥ 96%) (capillary column HP-5 crosslinked 5%PhMe silicone).b)The absolute configurations are determined from the optical rotation values of acids after oxidation of furane rings of amines. c)The reduction reactions are carried out only with **10**,**13** and **14**.

The oxidation of the furane ring carried out with ozone at −78°C and the product amino acids L-CCG I **1** {from the less polar amine, $[\alpha]_D^{25}$=+103 (c 0.5, H_2O) [lit.[8a] $[\alpha]_D^{21}$=102.0 (c 0.50, H_2O)], mp 244–248°C, dec. [lit.[8a] mp 243–247°C, dec.]} and L-CCG II (**2**) {from the more polar amine, $[\alpha]_D^{25}$=−19.5 (c 0.6, H_2O) [lit.[8a] $[\alpha]_D^{25}$=−20.2 (c 0.51, H_2O)] mp 255–257°C, dec. [lit.[8a] mp 255–258°C dec.]} are obtained in 41 and 38% yield, respectively. The same procedure gave D-CCG I (**1**) {$[\alpha]_D^{25}$=−98.3 (c 0.8, H_2O) [lit.[8a] $[\alpha]_D^{25}$=−97.4 (c 0.5, H_2O)] mp 238–240°C, dec. [lit.[8a] mp 240–242°C]} and D-CCG II (**2**) {$[\alpha]_D^{25}$=+20.33 (c 0.5, H_2O) [lit.[8a] $[\alpha]_D^{25}$=21.6 (c 0.5, H_2O)] mp 255–259°C dec. [lit.[8a] mp 254–258°C, dec.]}.

3. Experimental

All reagents were of commercial quality, and reagent quality solvents were used without further purification. IR spectra were determined on a Philips model PU9700 spectrometer. ^1H-NMR spectra were determined on a Bruker AC 80 MHz FT, AC 200 MHz and Bruker DPX 400 MHz FT spectrometers. GC

analyses were determined on an HP 5890 gas chromatograph. Optical rotations were measured on a Perkin–Elmer 241 polarimeter.

3.1. (E)-1,3-Di(2-furyl)-2-propen-1-one 5

To a suspension of 6.6 g (0.08 mol) 2-acetylfurane and 7.68 g (6.6 ml, 0.06 mol) furfural in water was added 10 ml 0.1% KOH solution. The mixture was stirred for 4 h at r.t., neutralized with 10% H_2SO_4 and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$. The purification of the crude product by flash column chromatography (silica gel 60, EtOAc:*n*-hexane=1:8) afforded 10.3 g (92%) of a product as a yellow solid (mp 85–86°C; lit.[14] mp 88–89°C). IR (KBr): 2990–3020, 1660, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 5.75–6.74 (m, 1H, furane H), 6.61–6.60 (m, 1H, furane H), 6.54–6.53 (m, 1H, furane H), 7.34 (d, 1H, olefinic H, J=16 Hz), 7.32–7.33 (m, 1H, furane H), 7.551–7.548 (m, 1H, furane H), 7.65 (d, 1H, olefinic H, J=16 Hz), 7.66–7.67 (m, 1H, furane H).

3.2. trans-2-Furyl(2-(2-furyl)cyclopropyl)methanone 6

Trimethylsulfoxonium iodide (2.29 g, 10.4 mmol) was added slowly to a suspension of 0.24 g (10 mmol) NaH in dry DMSO under Ar. An exothermic reaction took place with the evolution of H_2. After 20 min a clear solution was obtained. To this solution 1.89 g (10 mmol) of **5** dissolved in 15 ml dry DMSO was added in one portion. The color of the solution immediately changed to black. The reaction was checked by TLC. After 1 h the mixture was poured into ice and extracted with ether. The ether layer was washed with water and brine, and dried over anhydrous $MgSO_4$. Purification of the crude product by flash column chromatography (flash silica gel, EtOAc:*n*-hexane=1:10, R_f: 0.28) afforded 1.89 g (94%) colorless solid (mp 46–48°C). IR (KBr) 3020, 1660, 1600 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.57–1.61 (m, 1H, cyclopropane H), 1.77–1.82 (m, 1H, cyclopropane H), 2.70–2.75 (m, 1H, cyclopropane H), 2.93–2.98 (m, 1H, cyclopropane H), 6.13 (d, 1H, furane H, J=3.12 Hz), 6.32 (dd, 1H, furane H, J=3.22 and 1.92 Hz), 6.57 (dd, 1H, furane H, J=3.62 and 1.69 Hz), 7.26–7.27 (m, 1H, furane H), 7.30 (dd, 1H, furane H, J=1.95 and 0.66 Hz), 7.62–7.63 (m, 1H, furane H). ^{13}C-NMR ($CDCl_3$): δ 17.17 (CH), 22.65 (CH), 26.95 (CH), 105.91 (CH), 110.92 (CH), 112.71 (CH), 117.39 (CH), 141.46 (CH), 146.92 (CH), 153.46 (C), 154.02 (C), 187.07 (C). Anal. calcd For $C_{12}H_{10}O_3$ (202.21): C, 71.27; H, 4.98. Found: C, 71.41; H, 5.12.

3.3. (E)-trans-2-Furyl(2-(2-furyl)cyclopropyl)methanone oxime 7a

To a 10 ml 2 N NaOH solution was added 2.1 g (30 mmol) of $NH_2OH \cdot HCl$ at 5°C then 4.04 g (20 mmol) of **6** was added at 35–40°C and stirred for 4 h. After adding saturated ammonium chloride solution the product was extracted with ether. The ether layer was washed with water and brine and dried over anhydrous $MgSO_4$. The purification of the product by flash column chromatography (flash silica gel, EtOAc/*n*-hexane=1:10) and additional crystallization in ethanol gave 4.92 g (75.5%) of **7a**. 0.93 g (14%) of **7b** (mp 97–99°C) was also isolated after chromatographic purification. ^{1}H-NMR ($CDCl_3$): δ 1.25–1.78 (m, 2H, cyclopropane H), 2.22–2.72 (m, 2H, cyclopropane H), 6.06 (m, 1H, furane H), 6.25 (m, 1H, furane H), 6.39 (m, 1H, furane H), 6.67 (m, 1H, furane H), 7.26 (m, 1H, furane H), 7.47 (m, 1H, furane H), 9.45 (broad s, 1H, OH).

3.4. (Z)-trans-2-Furyl(2-(2-furyl)cyclopropyl)methanone oxime 7b

A mixture of 2.12 g (10.5 mmol) of **6**, 0.95 g (13.59 mmol) of $NH_2OH \cdot HCl$ and 1.12 g (13.59 mmol) of CH_3CO_2Na were refluxed for 10 h in 20 ml absolute ethanol. The reaction was checked by TLC. After 10 h the hot solution was filtered and ethanol was evaporated. The remaining solid was dissolved in water and extracted with diethyl ether. The ether layer was washed with water and brine and dried over anhydrous $MgSO_4$. Separation of the crude product by flash column chromatography (flash silica, EtOAc:*n*-hexane=1:10) gave 1.83 g (81%) **7b** as a colorless solid (mp 69–71°C) and 0.20 g (9%) **7a** is obtained as minor product (colorless solid, mp 97–99°C). IR (KBr): 3340, 2990, cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.34–1.39 (m, 1H, cyclopropane H), 1.49–1.53 (m, 1H, cyclopropane H), 2.34–2.39 (m, 1H, cyclopropane H), 2.51–2.56 (m, 1H, cyclopropane H), 6.08 (d, 1H, furane H, J=3.0 Hz), 6.29 (m, 1H, furane H), 6.55 (d, 1H, furane H, J=3.0 Hz), 7.26 (s, 1H, furane H), 7.43 (d, 1H, furane H, J=3.42 Hz), 7.49 (s, 1H, furane H), 8.70 (broad s, 1H, OH); ^{13}C-NMR ($CDCl_3$): 13.81, 18.53, 20.96, 104.90, 110.75, 112.43, 118.30, 141.15, 143.25, 146.16, 147.01, 155.66. Anal. calcd for $C_{12}H_{11}NO_3$ (217.23): C, 66.34; H, 5.10; N, 6.45. Found: C, 66.33; H, 5.28; N, 6.22.

3.5. Crystal data for 7b[11]

The X-ray data were collected on an Enraf–Nonius CAD-4 automatic diffractometer with graphite-monochromated MoKα radiation (λ=0.71073 Å) at ambient temperature. The structure was solved by the Direct method (SIR88) and was refined by a full-matrix least-square technique. $C_{12}H_{11}NO_3$, M=217.23. Monoclinic-P, *a*=12.9167(12), *b*=6.3480(11), *c*=13.6453(12) Å, α=90.00°, β=105.197(3)°, δ=90.00°, space group=P21/n (No. 14), *V*=1079.7(2) $Å^3$, *Z*=4, D_c=1.336 g/cm^3, crystal size=0.3×0.35×0.4 mm, F(000)=456, a total of 2649 reflections in the range of $3.17° \leq \theta \leq 26.93°$ were measured, the $\Delta\rho_{max}$ and $\Delta\rho_{min}$ are 0.286 and −0.165 e $Å^{-3}$, goodness of fit=1.24, 1469 independent reflections with $I/\sigma(I) \geq 2.0$, *R*=0.05.

3.6. General procedure for the synthesis of O-benzyloxime ethers

To the suspension of 6.5 mmol of NaH (washed from oil with hexane) in 50 ml DMF under argon atmosphere at 0°C was added 5 mmol of oxime slowly over 15 minutes. To this mixture 5.2 mmol of benzyl bromide was added and stirred for 6 h at r.t. (the reaction was monitored by TLC). After addition of 25 ml of water the resulting mixture was extracted with ethyl acetate. The organic layer was washed with water and brine and dried over $MgSO_4$. The purification of crude product done by flash column chromatography (flash silica, EtOAc:*n*-hexane=1:10).

3.7. (E)-trans-2-Furyl(2-(2-furyl)cyclopropyl)methanone O-benzyloxime ether 8a

Viscose oil. Yield 1.44 g (92%). ^{1}H-NMR ($CDCl_3$): δ 1.17–1.68 (m, 2H, cyclopropane H), 2.21–2.70 (m, 2H, cyclopropane H), 5.18 (s, 2H, CH_2), 6.05 (m, 1H, furane H), 6.27 (1H, furane H), 6.37 (m, 1H, furane H), 6.59 (m, 1H, furane H), 7.20–7.50 (m, 7H, 2 furane and 5 phenyl H). Anal. calcd for $C_{19}H_{17}NO_3$ (307.35): C, 74.25; H, 5.57; N, 4.55. Found: C, 74.51; H, 5.68; N, 4.28.

3.8. (Z)-trans-2-Furyl(2-(2-furyl)cyclopropyl)methanone O-benzyloxime ether **8b**

Viscose oil. Yield 1.43 g (94%). ^{1}H-NMR ($CDCl_3$): δ 1.15–1.70 (m, 2H, cyclopropane H), 2.20–2.68 (m, 2H, cyclopropane H), 5.24 (s, 2H, CH_2), 6.08 (m, 1H, furane H), 6.28 (m, 1H, furane H), 6.53 (m, 1H, furane H), 7.21–7.49 (m, 8H, 3 furane H, 5 phenyl H). Anal. calcd for $C_{19}H_{17}NO_3$ (307.35): C, 74.25; H, 5.57; N, 4.55. Found: C, 74.41; H, 5.63; N, 4.33.

3.9. *Racemic synthesis of* trans-2-furyl(2-(2-furyl)cyclopropyl)methanamine rac-**9**

To a solution of **7a** (0.34 g,1.6 mmol) in 20 ml abs. THF was added BH_3–SMe_2 (3 mmol) dropwise over 1 h. Then the mixture was stirred for 34 h at r.t., hydrolyzed with 2 N HCl and extracted with ether. The water layer was separated, basified with ammonium hydroxide solution and extracted with ether. The organic layer was separated, washed with water and dried over anhydrous $MgSO_4$. The crude product was purified by the flash column chromatography (flash silica gel, EtOAc:*n*-hexane:methanol=1:1:1). The product was obtained in 88% yield (0.27 g). IR (neat): 3660, 3365 cm^{-1}; ^{1}H-NMR (CD_3OD): δ 0.94–1.44 (m, 4H, CH_2 of cyclopropane H and NH_2), 1.88–2.44 (m, 2H, cyclopropane H), 3.65 (d, 1H, CH, J=8.2 Hz), 6.05–6.60 (m, 3H, furan) 7.22–7.55 (m, 3H, furan). ^{13}C-NMR ($CDCl_3$): δ 17.14, 22.21, 25.12, 52.45, 101.24, 102.86, 108.12, 113.26, 139.72, 143.40, 154.25, 155.32. Anal. calcd for $C_{12}H_{13}NO_2$ (203.24): C, 70.91; H, 6.44. Found: C, 70.72; H, 6.41.

3.10. *General procedure for asymmetric reduction*

A solution of borane (20 mmol) in THF (20 ml) was added dropwise under argon to a 10 mmol catalyst dissolved in 10 ml THF at −20°C. The resulting mixture was warmed to −5°C and stirring continued at this temperature for 16 h before 8 mmol of oxime ether in 10 ml of THF was added dropwise. The resulting solution was stirred at 30°C for 48 h (monitored by TLC) and was decomposed by slow addition of 2 M HCl. The mixture was then extracted with ether, treated with ammonium hydroxide, and extracted again with ether. The ether layer was dried over $MgSO_4$ and evaporated to give a colorless oil. The diastereomers were separated by flash column chromatography (silica gel, EtOAc).

3.11. trans-2-Furyl(2-(2-furyl)cyclopropyl)methanamine L-**9a**, L-**9b**

According to the general procedure 2.4 g (8 mmol) of **8a** gave 1.44 g (89%) of crude oil. The chromatographic separation of diastereomers gave 0.66 g (41%, **13** is used as catalyst) of L-**9a** ($[\alpha]_D^{20}$=−176.5 (c 1, $CHCl_3$)) and 0.61 g (38%) of L-**9b** ($[\alpha]_D^{20}$=−117.5 (c 1, $CHCl_3$)) isolated. 2.4 g (8 mmol) of **8b** gave 0.58 g (36%) D-**9a** ($[\alpha]_D^{20}$=+175.7 (c 1, $CHCl_3$)) and 0.62 g (39%) of D-**9b** ($[\alpha]_D^{20}$=+114.3 (c 1, $CHCl_3$)). For diastereomers R_f: 0.17 and 0.27 (silica gel, EtOAc).

3.12. *General procedure for ozonolysis*

2 mmol of amine was dissolved in methanol and the solution was cooled to −78°C. Ozone gas was passed through the solution. After 30 minutes the reaction was stopped and N_2 was passed through the mixture to remove the excess ozone. Evaporation of solvent gave the product which was purified by crystallization (water). (2*S*,3*S*,4*S*)-(-(Carboxycyclopropyl)glycine): yield 91% (^{1}H-NMR ($CDCl_3$): δ 1.22 (m, 1H), 12.9 (m, 1H), 1.68 (m, 1H), 1.77 (m, 1H), 3.21 (d, 1H, J=9.5 Hz). (2*S*,3*R*,4*R*)-(-(Carboxycyclopropyl)glycine): yield 93%; (2*R*,3*S*,4*S*)-(-(carboxycyclopropyl)glycine): yield 93%;

(2*R*,3*R*,4*R*)-(-(carboxycyclopropyl)glycine): yield 90%. The ^{1}H-NMR data of the products are in agreement with the published data.[8]

Acknowledgements

We thank the Middle East Technical University for a grant (AFP-1997), the Turkish State Planning Organization for a grant (DPT-1996) and the Turkish Scientific and Technical Research Council for a grant.

References

1. (a) Monaghan, D. T.; Bridges, R. J.; Cotman, C. W. *Annu. Rev. Pharmacol. Toxicol.* **1989**, *29*, 365. (b) Watkins, J. C.; Krogsgaard-Larsen, P.; Honore, T. *Trends Pharmacol. Sci.* **1990**, *11*, 25.
2. (a) Collingridge, G. L.; Bliss, T. V. P. *Trends Neurosci.* **1987**, *10*, 288. (b) Madison, D. V.; Malenka, R. C.; Nicoll, R. A. *Annu. Rev. Neurosci.* **1991**, *14*, 379. (c) Kaba, H.; Hayashi, Y.; Higuchi, T.; Nakanashi, S. *Science* **1994**, *265*, 262.
3. (a) Meldrum, B.; Garthwaite, J. *Trends Pharmacol. Sci.* **1990**, *11*, 379. (b) Olney, J. W. *Annu. Rev. Pharmacol. Toxicol.* **1990**, *30*, 47. (c) Choi, D. W.; Rothman, S. M. *Annu. Rev. Neurosci.* **1990**, *13*, 171.
4. (a) Pellicciari, R.; Marinozzi, M.; Natalini, B.; Costantino, G.; Lunieia, R.; Giorgi, G.; Moroni, F.; Thomsen, C. *J. Med. Chem.* **1996**, *39*, 2259. (b) Shimamoto, K.; Ohfune, Y. *J. Med. Chem.* **1996**, *39*, 407. (c) Knopfel, T.; Kuhn, R.; Allgeir, H. *J. Med. Chem.* **1995**, *38*, 1417. (d) Knopfel, T.; Gasparini, F. *Drug Discovery Today*, **1996**, *1*, 103.
5. (a) Pellicciari, R.; Natalini, B.; Marinozzi, M.; Selvi, L.; Chiorri, C.; Monahan, J. B.; Lanthorn, T. H.; Snyder, J. P. In *Frontiers in Excitatory Amino Acid Research*; Cavalheiro, E. A.; Lehman, J.; Turksi, L., Eds.; Alan R. Liss, Inc.: New York, 1988; p. 67. (b) Shinozaki, H.; Ishida, M.; Shimamoto, K.; Ohfune, Y. *Br. J. Pharmacol.* **1989**, *98*, 1213.
6. Kwai, M.; Horikava, Y.; Ishihara, T.; Shimamoto, K.; Ohfune, Y. *Eur. J. Pharmacol.* **1992**, *211*, 195.
7. Ishida, M.; Akagi, H.; Shimamoto, K.; Ohfune, Y.; Shinozaki, H. *Brain Res.* **1990**, *537*, 311.
8. (a) Shimamoto, K.; Ishida, M.; Shinozaki, H.; Ohfune, Y. *J. Org. Chem.* **1991**, *56*, 4167. (b) Shimamoto, K.; Ohfune, Y. *Tetrahedron Lett.* **1989**, *30*, 3803. (c) Yamanoi, K.; Ohfune, Y.; Watanabe, K.; Li, P. N.; Takeuchi, H. *Tetrahedron Lett.* **1988**, *29*, 1181. (d) Kurokawa, N.; Ohfune, Y. *Tetrahedron Lett.* **1985**, *26*, 83. (e) Shimamoto, K.; Ohfune, Y. *Synlett.* **1993**, 919. (f) Ohfune, Y.; Shimamoto, K.; Ishida, M.; Shinozaki, H. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 15. (g) Ma, D.; Ma, Z. *Tetrahedron Lett.* **1997**, *38*, 7599. (h) Stammer, C. H. *Tetrahedron* **1990**, *46*, 2231. (i) Barrett, G. C. *Chemistry and Biochemistry of the Amino Acids*; Chapman and Hall: London, 1985. (j) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon Press: Oxford, 1989.
9. (a) Demir, A. S. *Pure & Appl. Chem.* **1997**, *69*, 108. (b) Cagir, A. PhD Thesis, Middle East Technical University; Gercek, Z. PhD Thesis, Middle East Technical University, Demir, A. S.: Tanyeli, C. unpublished results. (c) Ocskay, G.; Wargha, L. *Tetrahedron* **1958**, *2*, 140. (d) Borsche, W.; Leditschke, H.; Lange, K. *Chem. Ber.* **1938**, *5*, 62. (e) Gruber, W. *Can. J. Chem.* **1953**, *31*, 19. (f) Gilman, H.; Calloway, N.O. *J. Am. Chem. Soc.* **1933**, *55*, 4197. (g) Demir, A. S.; Tanyeli, C.; Altinel, E. *Tetrahedron Lett.* **1997**, *38*, 7267.
10. (a) Itsuno, S.; Sakurai,Y.; Ito, K.; Hirao, A.; Nakahama, S. *Bull. Chem. Soc. Jpn* **1987**, *60*, 395. (b) Itsuno, S.; Hirao, A.; Nakahama, S.; Yamazaki, Y. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1673. (c) Itsuno, S.; Nakano, M.; Miyazaki, K.; Masuda, H.; Ito, K. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2039. (d) Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc., Chem. Commun.* **1983**, 469. (e) Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2887.
11. The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this article.
12. Demir, A. S.; Mecitoglu, I.; Tanyeli, C.; Gulbeyaz, V. *Tetrahedron: Asymmetry*, **1996**, *7*, 3359.
13. (a) Monsadi, A.; Gessner, M.; Gunther, G.; Deger, W.; Singer, G. *J. High Res. Chromatography & Chromatography Commun.* **1987**, *10*, 67. (b) Slessor, K. N.; King, G. G. S.; Miller, D. R.; Winson, M. L.; Cutforth, T. L. *J. Chem. Ecol.* **1985**, *11*, 1659. (c) Demir, A. S.; Akhmedov, I. M.; Tanyeli, C.; Gercek, Z. Gadzhili, R. A. *Tetrahedron: Asymmetry*, **1997**, *8*, 753.
14. Weygand, C.; Strobelt, F. *Chem. Ber.* **1935**, *68*, 1839.