Synthesis of Syn and Anti Isomers of *trans*-Cyclopropyl Arginine

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Abstract: There is currently considerable interest in arginine and its structural analogues in the context of nitric oxide synthase (NOS) substrates and inhibitors. Of particular interest are conformationally constrained arginine analogues used to probe the active sites of the three NOS isoforms. A simple procedure is described for the preparation of *syn*- and *anti*-*trans*-cyclopropyl arginine starting from the α-OBO-protected Cbz-dehydroglutamate. Cyclopropanation is effected by diazomethane addition followed by irradiation of the resulting pyrazoline and gives a 3:1 mixture of syn:anti isomers that can be separated by crystallization. Reduction of the ester to the alcohol followed by guanylation gives the fully protected cyclopropyl arginine analogues. The CBZ protecting groups are removed by hydrogenolysis and the OBO by mild acid treatment followed by base hydrolysis.

Arginine is involved in a large number of metabolic processes and is an important component of various substrates and inhibitors of a variety of enzymes. The study of conformationally constrained arginine analogues either alone or incorporated in peptidomimetic inhibitors is currently an area of active research.[1] There are a number of reports on the synthesis of novel arginine mimetics.[2] Conformational restriction of substrate side chains facilitates the study of enzyme binding and mechanism and can result in entropically favorable binding and improve selectivity.[3]

Some cyclopropyl amino acids have been synthesized or isolated from natural sources, and some interesting biological activities have been observed.[3−5] In our study of nitric oxide synthase isoforms, we needed access to *trans*-3,4-cyclopropyl arginine to determine the conformational preference of each isoform and evaluate the impact of the cyclopropyl moiety on isoform selectivity. The isolation of 3,4-cyclopropyl arginine from natural sources or its synthesis has never been reported. The availability of *syn*- and *anti*-*trans*-L-cyclopropyl arginine derivatives will assist the examination of conformational preferences of enzymes and receptors that recognize arginine and its derivatives.

We recently reported the stereoselective synthesis of L-cyclopropyl glutamates also known as 2-(carboxycyclopropyl)glycines (CCGs)[4] via the 1,3-dipolar addition of diazomethane to a chiral dehydroglutamate derivative, followed by photolysis of the resultant pyrazoline.[5] That approach made use of the 4-methyl-2,6,7-trioxabicyclo-[2.2.2] ortho (OBO) ester function, which has been shown to be a beneficial protecting group of carboxylic acids as it prevents epimerization at the α-carbon as well as induces good diastereoselectivities in transformations performed on serine aldehyde equivalents. The OBO protection scheme enables access to a variety of nonproteinaceous amino acids.[6] In this paper we describe an extension of this approach for the synthesis of *E*-3,4-cyclopropyl L-arginine.

Olefination of Cbz-L-serine aldehyde OBO with $Ph_3P{=}CHCO_2CH_3$ provided the *E*-3,4-L-didehydroglutamate derivative **1** in very good yields (77%) after chromatography and recrystallization. Subsequent treatment with freshly distilled diazomethane provided total conversion to a pyrazoline intermediate, obtained as a white solid after evaporation of solvent. Conversion to the cyclopropane by photoirradiation was performed as previously described, though this photoreactor was constructed from standard laboratory glassware and a commercially available 175 W medium-pressure mercury-vapor security lamp. Under these conditions, longer irradiation times were required but the yields were similar (82%).

The cyclopropyl glutamate analogues **2** and **3** were obtained in a 3:1 syn:anti ratio as determined by NMR and GC-MS analysis. The 3:1 syn:anti ratio vs the 6:1 ratio obtained previously with *t*-Bu ester[5] is likely due to the use of the less bulky methyl ester. Variation of irradiation temperatures from −45 to −10 °C did not have an impact on selectivity or yield.

Flash chromatography was performed to obtain the mixture of esters, but the syn and anti isomers could not be separated in this manner. Successive recrystallization provides access to pure *syn*-**2** and *anti*-**3**. However, this time-consuming process can be avoided and the isomers separated at a later stage. The stereochemistry of cyclopropanation was confirmed by acid hydrolysis and purification of **2** as previously described.[5] The optical rotation of the free amino acid agreed with the literature value for the *syn*-cyclopropyl glutamate.[4b]

The mixture of diastereomeric esters **2**/**3** was reduced using DIBAL-H, and a mixture of **4** and **5** was obtained as an oil (81%) after chromatography. Pure samples of esters **2** and **3** were individually reduced for character-

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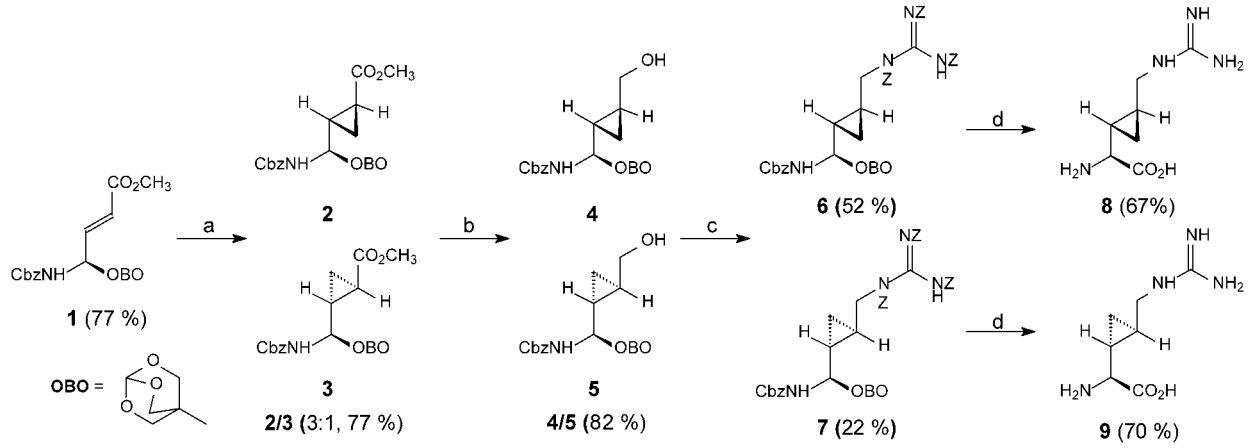
Scheme 1[a]



[a] Reaction conditions: (a) (i) CH_2N_2, EtO; (ii) *hv*, AcCN, benzophenone; (b) DIBAL-H, CH_2Cl_2; (c) *N*′,*N*,*N*-tri-Cbz guanidine, Ph_3P, DEAD, THF; (d) (i) H_2, Pd/C; (ii) 0.1% TFA/H_2O; (iii) 10% Cs_2CO_3/H_2O; (iv) Dowex 50W X4-100.

ization of each alcohol. Mitsunobu reaction of the mixture with *N*′,*N*,*N*-tri-Cbz guanidine[7] gave a mixture of fully protected cyclopropyl arginine derivatives **6** and **7** (74%). This mixture can be conveniently separated by flash chromatography, and each diastereomer **6** and **7** was obtained in a pure form. Derivatization of pure **4** provided **6** with identical characteristics.

The removal of protecting groups was performed under standard conditions,[6a] and lyophilization following cation exchange chromatography provided *syn*-3,4-cyclopropyl L-arginine **8** and *anti*-3,4-cyclopropyl L-arginine **9** as fine white powders in 67 and 70% yields, respectively. An efficient and practical method for the stereoselective synthesis of both *syn* and *anti-trans*-3,4-cyclopropyl L-arginine (18 and 8%, respectively) from a chiral serine aldehyde equivalent has been described. The biological evaluation of each diastereomer with NOS isoforms will be described in due course.

Experimental Section

General. All chemicals were purchased from Aldrich and used directly. CH_2Cl_2 was distilled from CaH_2 and THF from Na/benzophenone. Melting points are uncorrected. All reactions were performed under an argon atmosphere in oven-dried glassware. TLC was performed using Merck aluminum-backed silica gel 60 F_{254} and visualized using 5% $(NH_4)_6MoO_{24}$/0.2% $Ce(SO_4)_2$/5% H_2SO_4. Chromatography was performed using silica gel (230−400 mesh). NMR spectra were recorded in D_2O or $CDCl_3$ prefiltered through basic alumina to remove traces of acid. Elemental analyses were performed by MHW Laboratories, Phoenix, AZ. HRMS−FAB was performed by Tim Jones at Brock University, Ontario. GC-MS was performed on a 30 m × 0.25 mm HP5 column. Temperature program: initial, 70 °C for 2 min; heating rate, 10 °C/min for 18 min; final, 250 °C for 10 min.

***N*-Cbz-(*O*-CH_3)-*E*-2,3-L-Dehydroglutamate OBO Ester (1).** Cbz-L-Ser(ald)-OBO ester[6c] (6 g, 18.58 mmol) and $Ph_3P{=}CHCO_2CH_3$ (6.52 g, 1.05 eq) were dissolved in dry CH_2Cl_2 (250 mL) and stirred for 15 min at room temperature. The reaction was quenched with 3% NH_3Cl (100 mL) and the organic layer washed with 3% NH_3Cl (3 × 50 mL) and brine (50 mL), dried ($MgSO_4$), and evaporated to dryness. Purification by flash column chromatography (silica gel, 3:2 EtOAc/hexane with 0.2% triethylamine) yielded 5.39 g (77%) of clear oil. Crystallization provided fine white crystals: mp 109−112 °C; $[\alpha]^{25}_D$ −32.9 (*c* 1.0, EtOAc); TLC (1:1 EtOAc/hexane) R_f = 0.49; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32 (m, 5H), 6.97 (dd, *J* = 15.8, 5.1 Hz, 1H), 5.98 (dd, *J* = 15.8, 1.6 Hz, 1H), 5.14 (d, *J* = 9.3 Hz, 1H), 5.11 (s, 2H), 4.55 (ddd, *J* = 8.4, 4.3, 1.4 Hz, 1H), 3.88 (s, 6H), 3.71 (s, 3H), 0.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.6, 157.0, 143.3, 136.3, 128.7, 128.6, 128.3, 122.5, 107.8, 72.9, 67.2, 56.1, 51.7, 30.8, 14.3; Anal. Calcd for $C_{19}H_{23}O_7N$: C, 60.47; H, 6.14; N, 3.71. Found: C, 60.24; H, 6.16; N, 3.71.

***N*-Cbz-(*O*-CH_3)-*trans*-2-(Carboxycyclopropyl)glycine OBO Ester (2/3).** The cyclopropanation was performed on **1** (2 g, 5.31 mmol) as previously described.[5] The reaction mixture was evaporated to a thick yellow oil, and flash chromatography (silica, 2:1 hexane/EtOAc with 0.2% triethylamine) provided a 3:1 mixture of *syn*- and *anti*-cyclopropyl derivatives as 1.7 g of clear oil (82%). Successive recrystallizations from EtOAc/hexane provided each of the diastereomers in a pure form as fine white crystals.

***N*-Cbz-(*O*-CH_3)-*trans*-2-(Carboxy-(*syn*)cyclopropyl)glycine OBO Ester 2:** mp 130−132 °C; $[\alpha]^{25}_D$ +39.9 (*c* 1.05, EtOAc); TLC (1:1 EtOAc/hexane) R_f = 0.5; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32 (m, 5H), 5.08 (m, 2H), 5.03 (m, 1H), 3.88 (s, 6H), 3.63 (s, 3H), 3.47 (m, 1H), 1.68 (m, 2H), 1.22 (m, 1H), 0.96 (m, 1H), 0.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.3, 128.7, 128.6, 128.1, 108.3, 72.8, 67.1, 57.0, 51.8, 30.7, 23.0, 16.9, 14.6, 14.4; GC-MS R_t = 17.8 min, *m*/*z* 283 (6, M^+ − Cbz),[8] 225 (22), 185 (19), 154 (39), 86 (64), 55 (100). Anal. Calcd for $C_{20}H_{25}O_7N$: C, 61.37; H, 6.44; N, 3.58. Found: C, 61.52; H, 6.40; N, 3.62.

***N*-Cbz-(*O*-CH_3)-*trans*-2-(Carboxy-*anti*)cyclopropyl)glycine OBO Ester 3:** mp 124−127 °C; $[\alpha]^{25}_D$ −38.78 (*c* 1.065, EtOAc); TLC (1:1 EtOAc/hexane) R_f = 0.5; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32 (m, 5H), 5.12 (m, 2H), 4.97 (m, 1H), 3.86 (s, 6H), 3.64 (s, 3H), 3.61 (m, 1H), 1.64 (m, 2H), 1.05 (m, 1H), 0.97 (m, 1H), 0.77 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.4, 128.7, 128.2, 128.1, 108.3, 72.8, 67.0, 56.3, 51.8, 30.7, 22.1, 18.7, 14.4, 11.6; GC-MS R_t = 17.9 min, *m*/*z* 283 (8, M^+ − Cbz),[8] 225 (23), 185 (38), 154 (35), 86 (77), 55 (100). Anal. Calcd for $C_{20}H_{25}O_7N$: C, 61.37; H, 6.44; N, 3.58. Found: C, 61.61; H, 6.49; N, 3.49.

***N*-Cbz-(*trans*)-2-(Cyclopropyl)pentahomoserine OBO Ester 4/5.** The mixture of cyclopropyl esters **2**/**3** (3:1, 1.5 g, 3.84 mmol) was dissolved in dry CH_2Cl_2 (50 mL) under argon and cooled to −78 °C. DIBAL-H (1 M in hexanes) (8.45 mL, 2.2 equiv) was added dropwise over 1 h while maintaining the solution at −78 °C. The solution was stirred for an additional 2 h at −78 °C, followed by addition of methanol (3 mL), and allowed to warm to 0 °C. A saturated solution of KNa tartrate (20 mL) was added, and the suspension stirred vigorously for l6 h at room temperature. The layers were separated and the aqueous layer washed with additional CH_2Cl_2 (20 mL). The organic fractions were combined and washed with brine (20 mL), then dried ($MgSO_4$). The solution was concentrated to a yellowish clear oil that was purified by flash chromatography (silica, 3:1 EtOAc/

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(8) Cbz-protected amino acids decomposed during GC-MS analysis to the corresponding isocyanate. Thus, under these conditions, benzyl alcohol also elutes at R_t = 6.08 min.

hexane with 0.2% triethylamine). Concentration of pure fractions provided a mixture of **4** and **5** as 1.13 g (81%) of clear oil.

***N*-Cbz-(*trans*)-2-((*syn*)Cyclopropyl)pentahomoserine OBO Ester 4:** $[\alpha]^{25}_D$ −6.01 (*c* 1.015, EtOAc); TLC (3:1 EtOAc/hexane) $R_f = 0.34$; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32 (m, 5H), 5.09 (d, J = 12.21, 1H), 5.03 (d, J = 12.22 Hz, 1H), 4.93 (d, J = 8.77 Hz, 1H), 3.88 (s, 6H), 3.70 (dd, J = 6.0, 9.45 Hz, 1H), 3.66 (m, 1H), 3.08 (dd, J = 8.52, 10.62 Hz, 1H), 1.80 (br s), 1.08 (m, 1H), 0.93 (m, 1H), 0.78 (s, 3H), 0.56 (m, 1H), 0.46 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.6, 128.6, 128.2, 128.1, 108.8, 72.8, 66.9, 66.7, 55.9, 30.7, 17.1, 17.1, 14.4, 7.9; Anal. Calcd for $C_{19}H_{25}O_6N$: C, 62.80; H, 6.93; N, 3.85. Found: C, 62.85; H, 6.84; N, 3.90.

***N*-Cbz-(*trans*)-2-((*anti*)Cyclopropyl)pentahomoserine OBO Ester 5:** $[\alpha]^{25}_D$ −23.16 (*c* 1.075, EtOAc); TLC (3:1 EtOAc/hexane) $R_f = 0.34$; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30 (m, 5H), 5.17 (d, J = 9.35 Hz, 1H), 5.09 (d, J = 12.01 Hz, 1H), 5.03 (d, J = 12.01 Hz, 1H), 3.86 (s, 6H), 3.75 (m, 1H), 3.30 (app br t, J = 9.66 Hz, 1H, 2.97 (t, J = 9.67 Hz, 1H), 2.28 (br s), 1.15 (m, 1H), 0.86 (m, 1H), 0.75 (s, 3H), 0.67 (m, 1H), 0.37 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.4, 136.6, 128.5, 128.2, 128.1, 109.0, 72.8, 66.9, 66.6, 58.2, 30.7, 21.3, 18.5, 14.4, 7.3; Anal. Calcd for $C_{19}H_{25}O_6N$: C, 62.80; H, 6.93; N, 3.85. Found: C, 62.82; H, 6.95; N, 3.96.

***N*-Cbz-(*trans*)-2-((*syn/anti*)-Cyclopropyl)-δ,ω,ω'-tri-Cbz-arginine OBO Ester 6/7.** The unresolved mixture of cyclopropyl alcohols **4**/**5** (600 mg, 1.65 mmol) was dissolved in dry THF (20 mL) under argon, to which was added Ph_3P (649 mg, 1.5 equiv) and *N*′,*N*,*N*-tri-Cbz guanidine[7] (1.264 g, 1.66 equiv). This mixture was cooled to 0 °C, and DEAD (0.39 mL, 1.5 equiv) was added dropwise over 1 h. The reaction was allowed to warm to room temperature and continue to stir for 16 h. The solvent was evaporated in vacuo and the residue purified by flash chromatography (silica, 1:1 EtOAc/hexane with 0.2% triethylamine) providing **6** (687 mg) and **7** (292 mg) (74% combined yield).

***N*-Cbz-(*trans*)-2-((*syn*)-Cyclopropyl)-δ,ω,ω'-tri-Cbz-arginine OBO Ester 6:** $[\alpha]^{25}_D$ −3.6 (*c* 1.0, EtOAc); TLC (1:1 EtOAc/hexane) $R_f = 0.48$; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36 (m, 20H), 5.0 (m, 9H), 4.08 (m, 1H), 3.77 (s, 6H), 3.54 (m, 1H), 3.53 (m, 1H), 1.18 (m, 2H), 0.69 (s, 3H), 0.50 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.8, 134.7, 128.8, 128.7, 128.6, 128.5, 128.2, 128.0, 108.7, 72.7, 69.3, 68.2, 66.0, 56.36, 50.9, 30.6, 17.7, 14.4, 13.9, 9.52; Anal. Calcd for $C_{44}H_{46}O_{11}N_4$: C, 65.50; H, 5.75; N, 6.94. Found: C, 65.38; H, 5.53; N, 7.00.

***N*-Cbz-(*trans*)-2-((*anti*)-Cyclopropyl)-δ,ω,ω'-tri-Cbz-arginine OBO Ester 7:** $[\alpha]^{25}_D$ −1.5 (*c* 1.0, EtOAc); TLC (1:1 EtOAc/hexane) $R_f = 0.53$; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36 (m, 20H), 5.0 (m, 9H), 3.98 (dd, J = 5.1, 14.2, 1H), 3.71 (s, 6H), 3.64 (m, 1H), 3.10 (m, 2H), 1.29 (m, 1H), 1.09 (m, 1H), 0.69 (s, 3H), 0.59 (m, 1H), 0.36 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.9, 136.7, 134.6, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 128.2, 128.1, 108.6, 72.7, 69.3, 68.2, 66.8, 58.65, 50.2, 30.5, 18.6, 17.7, 14.4, 8.3. Anal. Calcd for $C_{44}H_{46}O_{11}N_4$: C, 65.50; H, 5.75; N, 6.94. Found: C, 65.62; H, 5.81; N, 7.09.

Removal of Protecting Groups. A sample of pure, fully protected arginine analogue was dissolved in 1:1 EtOH/EtOAc with an equal mass of Pd/C. The suspension was stirred vigorously under a pure H_2 atmosphere for 16 h. The mixture was filtered and the solvent evaporated. The clear oil was dissolved in 0.1% TFA in distilled deionized water and stirred for 10 min, and then the solvent was removed in vacuo. The clear oil was suspended in 10% Cs_2CO_3, stirred for 16 h, and then lyophilized. The residue was dissolved in minimal H_2O (distilled), acidified with doubly distilled 6 N HCl to pH 3, and then loaded onto Dowex 50W X4−100 cation-exchange resin. After being washed with pure H_2O, the product was eluted with a gradient to 0.5 N NH_4OH. Fractions were combined and lyophilized to provide the free amino acid as a fine white powder.

***syn*-3,4-Cyclopropyl L-Arginine 8.** The deprotection procedure above was applied to **6** (289 mg) to provide 44.5 mg of **8** (67%) as a white pwoder: mp 196−200 °C dec; $[\alpha]^{25}_D$ +40.0 (*c* 1.0, H_2O); ^{1}H NMR (D_2O, 300 MHz) δ 2.97 (dd, J = 7.03, 13.82 Hz, 1H), 2.88 (dd, J = 7.26, 13.83 Hz, 1H), 2.54 (d, J = 8.67 Hz, 1H), 0.88 (m, 1H), 0.75 (m, 1H), 0.52, 0.37 (m, 2 × 1H); ^{13}C NMR (D_2O, 75 MHz) δ 178.59, 156.64, 58.51, 44.43, 20.44, 15.89, 8.71; HR-MS (FAB) calcd for $C_7H_{15}N_4O_2$ 187.1195, found 187.1161.

***anti*-3,4-Cyclopropyl L-Arginine 9.** The deprotection procedure above was applied to **7** (100 mg) to provide 16.1 mg of **9** (70%): mp 198−201 °C dec; $[\alpha]^{25}_D$ +30.67 (*c* 0.6, H_2O); ^{1}H NMR (D_2O, 300 MHz) δ 3.12 (dd, J = 6.63, 13.91, 1H), 2.97 (d, J = 10.28 Hz, 1H), 2.89 (dd, J = 7.71, 13.91, 1H), 1.23 (m, 1H), 0.95 (m, 1H), 0.62 (m, 2H); ^{13}C NMR (D_2O, 75 MHz) δ 173.88, 156.60, 58.44, 44.17, 18.32, 17.01, 8.90; HR-MS (FAB) calcd for $C_7H_{15}N_4O_2$ 187.1195, found 187.1158.

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