A Short and Efficient Diastereoselective Synthesis of 2′-Substituted 2-Cyclopropylglycines

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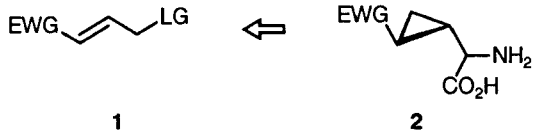
Received 24 June 1993

Diastereomerically pure 2-cyclopropylglycines **2**, 2′-substituted with an electron-withdrawing group, were prepared in two steps by Michael addition of the glycine equivalent 2-(diphenylmethyleneamino)acetate **11** to various Michael acceptors of type **1** with subsequent γ-elimination of bromide and followed by acid mediated deprotection.

Cyclopropylglycines are an important subgroup of naturally occurring amino acids containing a cyclopropane ring.[1-3] They are quite regularly found in plants and microorganisms, and have received attention as enzyme inhibitors, phytochemical agents or probes in metabolism studies.[4,5] We now report a short and efficient synthesis of 2-cyclopropylglycines **2** substituted at C-2′ with an electron-withdrawing group (EWG) starting from Michael acceptors of type **1** with a suitable leaving group (LG) at the γ-position (Scheme 1).



LG = Br

EWG = NO_2, CO_2Me, COMe, SO_2Ph

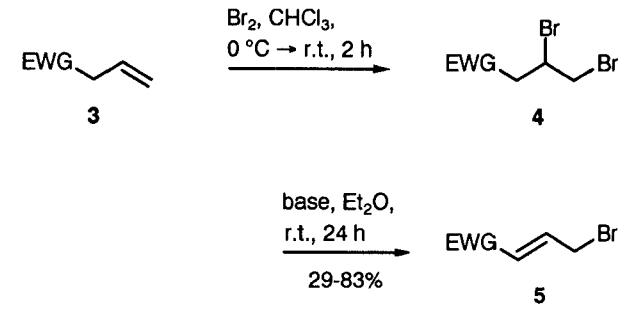
Scheme 1

This approach has previously been used to prepare protected 2-(2′-carboxycyclopropyl)glycine,[6,7] the only known natural cyclopropylglycine of type **2**.[8] All four possible stereoisomers of 2-(2′-carboxycyclopropyl)glycine have also been prepared by addition of various carbenes to olefins, suitable precursors were ethyl diazoacetate, diazomethane or an enantiopure diazoamide for intramolecular cyclopropanation.[9,10]

γ-Bromo Substituted Michael Acceptors

The γ-bromo substituted Michael acceptors **5** were prepared by an addition–elimination sequence starting from readily available allyl derivatives **3**.[11-14] After addition of bromine to the double bonds in compounds **3**, carried out in chloroform, the resulting dibromides **4** were treated with a suitable base in diethyl ether to give the expected γ-bromo substituted Michael acceptors **5** (Scheme 2, Table 1).[15-19]

The β-substituted Michael acceptor **10** was prepared in a sequence starting with addition of methylenenitronate to THP-protected hydroxyacetone **6**[20] in methanol. The resulting tertiary β-nitro alcohol **7** was acetylated in diethyl ether with acetic anhydride and a catalytic amount of 4-dimethylaminopyridine. Subsequent elimination of acetic acid with sodium acetate gave the THP-protected allyl alcohol **8** which was deprotected with *p*-toluenesulfonic acid in methanol. The primary allyl alcohol **9** was converted to the bromide **10** by treatment with tetrabromomethane/triphenylphosphine[21] in dichloromethane at 0 °C (Scheme 3).

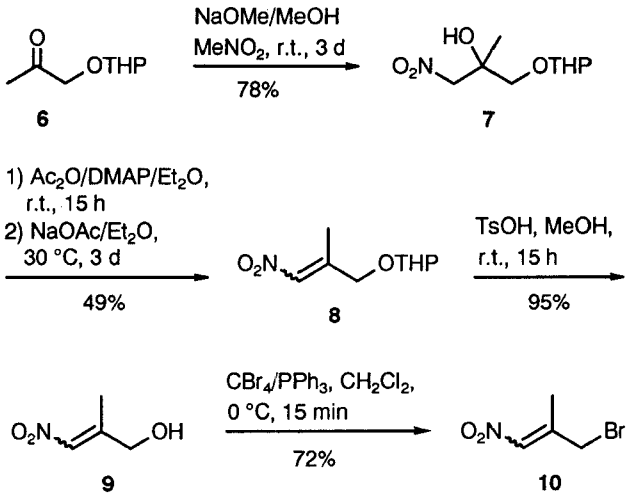


Scheme 2

Table 1. Formation of γ-Bromo Substituted Michael Acceptors **5**

Starting Material	EWG	Base	Product	Yield (%)	Ratio *E*/*Z*[a]
3a	NO_2	NaOAc	**5a**	68	> 19 : 1
	CO_2Me		**5b**[b]		2 : 1
3c	COMe	Na_2CO_3	**5c**	29	> 19 : 1
3d	CN	Na_2CO_3	**5d**	83	2 : 1
3e	SO_2Ph	Na_2CO_3	**5e**	53	> 19 : 1
3f	PO_3Me_2	DBU[c]	**5f**	42	> 19 : 1

[a] Determined by ^1H NMR spectroscopy.
[b] Commercially available (Fluka).
[c] DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene.



Scheme 3

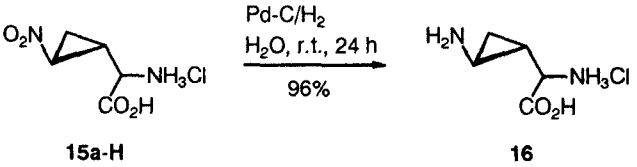
2′-Substituted 2-Cyclopropylglycines

The lithiated glycine equivalent **11**[22] reacted with various Michael acceptors **5** and **10** to yield either the protected 2′-substituted 2-cyclopropylglycines **12-R** or the 5-substituted 4-pentenoates **13-R**. At −78 °C the reaction should produce 2′-substituted 2-cyclopropylglycines **12-**

R.[6] The competitive formation of 5-substituted 4-pentenoates **13-R** is preferred in the presence of strongly solvating solvent additives (HMPA,[6] DME[19]) or under phase-transfer conditions at room temperature.[23] All 2′-substituted 2-cyclopropylglycines **12-R** obtained were diastereomerically pure and *trans* configurated (R = H). The *E*/*Z* isomer ratios of 5-substituted 4-pentenoates **13d-H, 13f-H** were identical to those of the corresponding starting materials **5d,f**. Deprotection of compounds **12-R** with 1 N hydrochloric acid provided the amino acid hydrochlorides **15-R**, which were pure according to their ^{1}H NMR spectra (Scheme 4, Table 2).

It is remarkable that with three new stereogenic centers generated in the sequence of Michael addition of the lithiated glycine equivalent **11** to compounds **5** and subsequent cyclisation of the intermediates **14-R**, only a single pair of enantiomers of the 2′-substituted 2-cyclopropylglyclines **12-R** was obtained in each case, independent of the *E*/*Z* ratios in the starting materials **5**. The substituents on the three-membered ring were always *trans* orientated. This complete diastereoselectivity can be rationalized if only two out of four possible stereoisomeric intermediates **14-R** are formed due to a chelation of the lithium counterion of the enolate **14-R**. With a suitable chiral auxiliary in the glycine equivalent it should be possible to create the new stereogenic centers in these 2′-substituted 2-cyclopropylglycines with a high enantiomeric excess.[7,24]

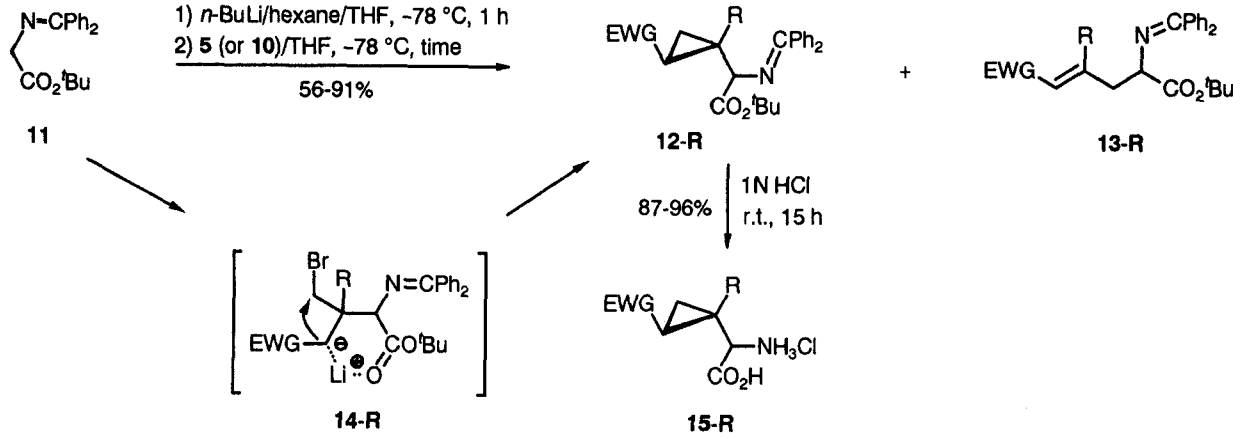
The nitro group in **15a-H** could be hydrogenated[25] to give the α,γ-diaminocarboxylic acid **16** in quantitative yield. Compound **16** is an interesting methano bridged, and thereby conformationally restricted,[26,27] analogue of the natural 2,4-diaminobutanoic acid (Scheme 5).



Scheme 5

The 2′-nitrocyclopropylglycine **15a-H** is the lower homologue to the unusual natural amino acid 3-(*trans*-2′-nitrocyclopropyl)alanine.[28]

IR spectra were recorded with a Perkin-Elmer 298 spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker AM 250 spectrometer, ^{13}C NMR spectra on Varian XL 200 or VXR 200 spectrometers. Mass spectra were measured with Varian MAT CH-7 and MAT 731 instruments. Merck Kieselgel 60 (200–400 mesh) was used for flash column chromatography, Merck Kieselgel 60 F_{254} on aluminium was used for TLC tests. Mps are uncorrected. Combustion analyses were carried out by the microanalytical laboratory at the Georg-August-Universität Göttingen. Compounds **7–10, 12a-H,b-H,e-H,a-Me, 13d-H,f-H**, and **15a-H,b-H,c-H,e-H,a-Me** gave C,H ± 0.3%, except: **12a-H**, C + 0.96, H + 0.63; **13f-H**, H − 0.36; and **15e-H**, C − 0.71%. All reactions with organometallic reagents were performed in anhydrous solvents under dry nitrogen.



Scheme 4

Table 2. Synthesis of Diastereopure 2-Cyclopropylglycines **12-R** Substituted at C-2′ with an Electron-Withdrawing Group and Deprotection to the Amino Acid Hydrochlorides **15-R**

Starting Material	EWG	R	Time (h)	Product	Yield (%)	Isomer Ratio d.e. or *E*/*Z*[a]	Product	Yield (%)
5a	NO_2	H	15	**12a-H**	63	≥ 95	**15a-H**	93
5b	CO_2Me	H	1	**12b-H**	91	≥ 95	**15b-H**	90
5c	COMe	H	1	**12c-H**	83	≥ 95	**15c-H**	87
5d	CN	H	48	**13d-H**	64	2 : 1		
5e	SO_2Ph	H	15	**12e-H**	69	≥ 95	**15e-H**	96
5f	PO_3Me_2	H	24	**13f-H**	59	> 19 : 1		
10	NO_2	Me	15	**12a-Me**	56	≥ 95	**15a-Me**	94

[a] Determined by ^{1}H NMR spectroscopy after chromatography over silica gel.

Michael Acceptors 5 from Allyl Compounds 3; Typical Procedure:

(E)-3-Bromo-1-nitro-1-propene **(5a):**

To a stirred solution of 3-nitro-1-propene **(3a)**[11] (8.71 g, 100 mmol) in $CHCl_3$ (100 mL), a solution of Br_2 (5.12 mL, 100 mmol) in $CHCl_3$ (50 mL) was added dropwise at 0 °C. The mixture was stirred for 2 h at r.t., the solvent was evaporated under reduced pressure, and the product was purified by bulb-to-bulb distillation in vacuo (0.1 mbar). The resulting dibromo compound **4a** was dissolved in Et_2O (200 mL) and NaOAc (16.4 g, 200 mmol) was added. The mixture was stirred for 24 h at r.t., the solids were collected on a filter, the filtrate was concentrated under reduced pressure, and the product was purified by bulb-to-bulb distillation in vacuo (0.1 mbar) to give 11.3 g (68%) of **5a**.

IR (film): ν = 3100, 3050, 1650 (C=C), 1525 (NO_2), 1350 (NO_2), 1205, 950, 870, 740 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 4.05 (dd, 2H, ^3J = 7.1, ^4J = 1.0 Hz, 3-H), 7.16 (dt, 1H, $^3J_{trans}$ = 13.2, ^4J = 1.0 Hz, 1-H), 7.35 (dt, 1H, ^3J = 7.1, $^3J_{trans}$ = 13.2 Hz, 2-H).

^{13}C NMR (50.3 MHz, $CDCl_3$, APT): δ = 23.97 (−, C-3), 135.99 and 141.80 (+, C-1 and C-2).

MS (70 eV): *m/z* (%) = 167/165 (7/7, M^+), 121/119 (16/16, $M^+ - NO_2$), 95/93 (15/15, CH_2Br^+), 86 (29, $M^+ - Br$).

2-Methyl-3-nitro-1-(tetrahydro-2′*H*-pyranyloxy)propan-2-ol (7):

To a solution of 1-(tetrahydro-2′*H*-pyranyloxy)propan-2-one **(6)**[20] (15.8 g, 100 mmol) in $MeNO_2$ (8 mL), NaOMe (0.27 g, 5 mmol) dissolved in MeOH (5 mL) was added. The mixture was stirred for 3 d at r.t. and then poured into H_2O (150 mL). The aqueous solution was extracted three times with Et_2O (50 mL), and the combined organic extracts were dried ($MgSO_4$). After filtration and evaporation of the solvent under reduced pressure the crude product was purified by flash chromatography eluting with Et_2O/light petroleum (1:1) to give **7**, yield 17.1 g (78%); mp 63 °C; R_f = 0.35.

IR (KBr): ν = 3600–3200 (OH), 2950, 1550 (NO_2), 1375 (NO_2) 1130, 1070, 1035 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$) (both isomers): δ = 1.36 (s, 3H, CH_3), 1.52–1.90 [m, 6H, $(CH_2)_3$], 3.48 (s, 1H, OH), 3.44–3.62 and 3.75–3.92 (m, 4H, 1-H and 6′-H), 4.48–4.69 (m, 3H, 3-H and 2′-H).

^{13}C NMR (50.3 MHz, $CDCl_3$, APT) (1st isomer): δ = 21.94 (+, CH_3), 19.41, 25.18, and 30.62 [−, $(CH_2)_3$], 62.66 (−, C-6′), 71.23 (−, C-2), 74.38 (−, C-1), 81.83 (−, C-3), 99.60 (+, C-2′).

(2nd isomer): 22.48 (+, CH_3), 20.14, 25.01, and 30.34 [−, $(CH_2)_3$], 63.83 (−, C-6′), 71.01 (−, C-2), 72.83 (−, C-1), 81.67 (−, C-3), 100.90 (+, C-2′).

MS (70 eV): *m/z* (%) = 118 (4, $M^+ - C_5H_9O_2$), 101 (3, $C_5H_9O_2^+$), 85 (100, $C_5H_9O^+$).

2-Methyl-3-nitro-2-propenyl Tetrahydro-2*H*-pyran-2-yl Ether (8):

A solution of alcohol **7** (16.4 g, 75 mmol) in Et_2O (200 mL) was treated with Ac_2O (8.5 mL, 90 mmol) and DMAP (367 mg, 3.0 mmol). The mixture was stirred for 15 h at r.t., washed with aq 1 N $NaHCO_3$ (100 mL), dried ($MgSO_4$) and the solvent was evaporated in vacuo. The resulting yellowish oil was dissolved in Et_2O (200 mL), and NaOAc (12.3 g, 150 mmol) was added. The mixture was stirred for 3 d at 30 °C. After filtration and evaporation of the solvent under reduced pressure, the crude product was purified by flash chromatography eluting with Et_2O/light petroleum (1:10) to give 7.36 g (49%) of **8**: R_f = 0.21.

IR (film): ν = 2950, 1650 (C=C), 1520 (NO_2), 1345 (NO_2), 1130, 1085, 1040 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$) (1st isomer): δ = 1.49–1.93 [m, 6H, $(CH_2)_3$], 2.18 (d, 3H, ^4J = 0.7 Hz, CH_3), 3.48–3.61 and 3.74–3.90 (m, 2H, 6-H), 3.99–4.10 and 4.29–4.41 (m, 2H, 1′-H), 4.60–4.71 (m, 1H, 2-H), 7.23 (s br, 1H, 3′-H).

(2nd isomer): 1.49–1.93 [m, 6H, $(CH_2)_3$], 2.05 (d, 3H, ^4J = 0.7 Hz, CH_3), 3.48–3.61 and 3.74–3.90 (m, 2H, 6-H), 4.60–4.71 (m, 1H, 2-H), 4.76–4.81 and 4.86–4.91 (m, 2H, 1′-H), 6.95 (s, br, 1H, 3′-H).

^{13}C NMR (50.3 MHz, $CDCl_3$, APT) (1st isomer): δ = 15.66 (+, CH_3), 19.03, 25.21, and 30.18 [−, $(CH_2)_3$], 62.18 (−, C-6), 68.37 (−, C-1′), 98.30 (+, C-2), 134.82 (+, C-3′), 148.81 (−, C-2′).

(2nd isomer): 18.44 (+, CH_3), 19.14, 25.25, and 30.25 [−, $(CH_2)_3$], 62.56 (−, C-6), 69.17 (−, C-1′), 99.08 (+, C-2), 134.10 (+, C-3′), 153.26 (−, C-2′).

2-Methyl-3-nitro-2-propen-1-ol (9):

To a solution of the acetal **8** (7.04 g, 35 mmol) in MeOH (80 mL), *p*-TsOH (190 mg, 1.0 mmol) was added. The mixture was stirred for 15 h at r.t., poured into conc. aq NaCl (300 mL). The aqueous solution was extracted three times with Et_2O (100 mL), and the combined organic layers were dried ($MgSO_4$). After filtration and evaporation of the solvent under reduced pressure the crude product was purified by flash chromatography eluting with Et_2O/light petroleum (1:3) to give 3.89 g (95%) of **9**; R_f = 0.15.

IR (film): ν = 3600–3200 (OH), 2940, 1650 (C=C), 1515 (NO_2), 1345 (NO_2), 1080, 835 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$) (1st isomer): δ = 2.13 (d, 3H, ^4J = 0.7 Hz, CH_3), 3.10 (t, 1H, ^3J = 6.5 Hz, OH), 4.26 (dd, 2H, ^3J = 6.5, ^4J = 0.6 Hz, 1-H), 7.23 (s br, 1H, 3-H).

(2nd isomer): 2.05 (d, 3H, ^4J = 0.7 Hz, CH_3), 2.96 (t, 1H, ^3J = 6.5 Hz, OH), 4.76 (dd, 2H, ^3J = 6.5, ^4J = 0.6 Hz, 1-H), 6.95 (s br, 1H, 3-H).

^{13}C NMR (50.3 MHz, $CDCl_3$, APT) (1st isomer): δ = 15.43 (+, CH_3), 64.79 (−, C-1), 134.37 (+, C-3), 152.44 (−, C-2).

(2nd isomer): 18.76 (+, CH_3), 61.96 (−, C-1), 134.21 (+, C-3), 155.51 (−, C-2).

MS (70 eV): *m/z* (%) = 117 (4, M^+), 100 (6, $M^+ - OH$), 71 (18, $M^+ - NO_2$).

3-Bromo-2-methyl-1-nitro-1-propene (10):

To a stirred solution of the alcohol **9** (3.51 g, 30 mmol) and CBr_4 (12.6 g, 38 mmol) in anhydr. CH_2Cl_2 (60 mL), PPh_3 (11.8 g, 45 mmol) was added in small doses at 0 °C. The mixture was stirred for 15 min, half of the solvent was evaporated under reduced pressure, and the mixture was treated with Et_2O (100 mL). The filtrate was concentrated under reduced pressure, and the crude product was purified by flash chromatography eluting with Et_2O/light petroleum (1:3) to give 3.89 g (72%) of **10**; R_f = 0.40.

IR (film): ν = 3100, 1640 (C=C), 1525 (NO_2), 1440, 1350 (NO_2), 1225, 970, 835, 770, 630 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$) (1st isomer): δ = 2.38 (d, 3H, ^4J = 0.7 Hz, CH_3), 3.96 (d, 2H, ^4J = 0.6 Hz, 3-H), 7.17 (s br, 1H, 1-H).

(2nd isomer): 2.11 (d, 3H, ^4J = 0.7 Hz, CH_3), 4.45 (d, 2H, ^4J = 0.6 Hz, 3-H), 6.94 (s, br, 1H, 1-H).

^{13}C NMR (50.3 MHz, $CDCl_3$, APT) (1st isomer): δ = 17.51 (+, CH_3), 33.75 (−, C-3), 137.22 (+, C-1), 146.18 (−, C-2).

(2nd isomer): 20.82 (+, CH_3), 26.64 (−, C-3), 135.83 (+, C-1), 145.55 (−, C-2).

MS (70 eV): *m/z* (%) = 181/179 (6/6, M^+), 135/133 (9/9, $M^+ - NO_2$), 100 (100, $M^+ - Br$).

Reactions of the Glycine Equivalent 11 with γ-Bromo Michael Acceptors 5; General Procedure:

To a stirred solution of *tert*-butyl 2-(diphenylmethyleneamino) ethanoate **(11)**[22] (591 mg, 2.0 mmol) in THF (60 mL) a solution of butyllithium in hexane (2.36 N, 0.89 mL, 2.1 mmol) was added dropwise at −78 °C. After being stirred for 1 h at −78 °C the γ-bromo Michael acceptor **5** (2.0 mmol) dissolved in THF (1 mL) was added dropwise. The mixture was stirred at −78 °C for the time given in Table 2. The solvent was removed in vacuo at r.t., and H_2O (100 mL) was added to the residue. The mixture was extracted three times with Et_2O (50 mL), and the combined organic layers were dried ($MgSO_4$). After filtration and evaporation of the solvent under reduced pressure the crude product was purified by flash chromatography eluting with Et_2O/light petroleum containing NEt_3 (1%) to give **12**.

***tert*-Butyl 2-(Diphenylmethyleneamino)-2-(*trans*-2′-nitrocyclopropyl)ethanoate (12a-H):**

3-Bromo-1-nitro-1-propene **(5a)**[15] (332 mg) gave after purification [Et_2O/light petroleum (1:5)] 479 mg (63%) of **12a-H**; $R_f = 0.34$.

IR (film): ν = 2970, 1720 (C=O), 1620 (N=C), 1535 (NO_2), 1440, 1365 (NO_2), 1265, 1150, 695 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.28 (ddd, 1 H, ^2J = 5.8, $^3J_{cis}$ = 7.1, $^3J_{trans}$ = 7.1 Hz, 3′-H), 1.43 [s, 9 H, $C(CH_3)_3$], 1.83 (ddd, 1 H, ^2J = 5.8, $^3J_{cis}$ = 10.5, $^3J_{trans}$ = 3.7 Hz, 3′-H), 2.54 (dddd, 1 H, ^3J = 4.5, $^3J_{cis}$ = 10.5, $^3J_{trans}$ = 3.4, $^3J_{trans}$ = 7.1 Hz, 1′-H), 4.05 (d, 1 H, ^3J = 4.5 Hz, 2-H), 4.65 (ddd, 1 H $^3J_{cis}$ = 7.1, $^3J_{trans}$ = 3.4, $^3J_{trans}$ = 3.7 Hz, 2′-H), 7.12–7.19 and 7.28–7.62 (m, 10 H, Ar-H).

^{13}C NMR (50.3 MHz, $CDCl_3$, APT): δ = 14.89 (−, C-3′), 27.86 (+, C-1′), 27.95 [+, $C(\underline{C}H_3)_3$], 56.63 (+, C-2′), 62.91 (+, C-2), 82.17 [−, $\underline{C}(CH_3)_3$], 127.62, 128.13, 128.67, 128.82, 128.96, and 130.84 (+, Ar-C), 135.80 and 138.79 (−, Ar-C), 169.07 and 172.29 (−, C=N and C=O).

***tert*-Butyl 2-(Diphenylmethyleneamino)-2-(*trans*-2′-methoxycarbonylcyclopropyl)ethanoate (12b-H):**

Methyl 4-bromo-2-butenoate **(5b)** (0.24 mL) gave after purification [Et_2O/light petroleum (1:5)] 716 mg (91%) of **12b-H**; $R_f = 0.23$.

IR (film): ν = 2970, 1725 (C=O), 1620 (N=C), 1445, 1260, 1155, 695 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 0.92 (ddd, 1 H, ^2J = 4.5, $^3J_{cis}$ = 9.0, $^3J_{trans}$ = 6.6 Hz, 3′-H), 1.18 (ddd, 1 H, ^2J = 4.5, $^3J_{cis}$ = 9.0, $^3J_{trans}$ = 4.5 Hz, 3′-H), 1.44 [s, 9 H, $C(CH_3)_3$], 1.83 (ddd, 1 H, $^3J_{cis}$ = 9.0, $^3J_{trans}$ = 4.5, $^3J_{trans}$ = 4.5 Hz, 2′-H), 2.04 (dddd, 1 H, ^3J = 6.5, $^3J_{cis}$ = 9.0, $^3J_{trans}$ = 4.5, $^3J_{trans}$ = 4.5 Hz, 1′-H), 3.67 (s, 3 H, CH_3), 3.77 (d, 1 H, ^3J = 6.5 Hz, 2-H), 7.12–7.19 and 7.29–7.65 (m, 10 H, Ar-H).

^{13}C NMR (50.3 MHz, $CDCl_3$, APT): δ = 12.17 (−, C-3′), 16.92 (+, C-1′), 25.22 (+, C-2′), 28.00 [+, $C(\underline{C}H_3)_3$], 51.68 (+, OCH_3), 65.63 (+, C-2), 81.33 [−, $\underline{C}(CH_3)_3$], 127.78, 128.01, 128.52, 128.68, 128.84, and 130.42 (+, Ar-C), 136.26 and 139.31 (−, Ar-C), 170.16, 170.81, and 174.51 (−, C=N and C=O).

***tert*-Butyl 2-(Diphenylmethyleneamino)-2-[*trans*-2′-(1-oxoethyl)cyclopropyl]ethanoate (12c-H):**

5-Bromo-3-pentene-2-one **(5c)**[16] (326 mg) gave after purification [Et_2O/light petroleum (1:5)] 627 mg (83%) of **12c-H**; $R_f = 0.15$.

IR (film): ν = 2970, 2920, 1730 (C=O), 1695 (C=O), 1620 (N=C), 1440, 1365, 1150, 695 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 0.97 (ddd, 1 H, ^2J = 3.9, $^3J_{cis}$ = 7.1, $^3J_{trans}$ = 6.7 Hz, 3′-H), 1.26 (ddd, 1 H, ^2J = 3.9, $^3J_{cis}$ = 8.6, $^3J_{trans}$ = 4.7 Hz, 3′-H), 1.42 [s, 9 H, $C(CH_3)_3$], 1.99 (dddd, 1 H, ^3J = 5.1, $^3J_{cis}$ = 8.6, $^3J_{trans}$ = 3.5, $^3J_{trans}$ = 6.7 Hz, 1′-H), 2.23–2.32 (m, 1 H, 2′-H), 2.26 (s, 3 H, CH_3), 3.89 (d, 1 H, ^3J = 5.1 Hz, 2-H), 7.12–7.19 and 7.28–7.66 (m, 10 H, Ar-H).

^{13}C NMR (50.3 MHz, $CDCl_3$, APT): δ = 13.77 (−, C-3′), 15.21 (+, C-1′), 24.84 (+, C-2′), 27.95 [+, $C(\underline{C}H_3)_3$], 30.43 (+, CH_3), 64.76 (+, C-2), 81.25 [−, $\underline{C}(CH_3)_3$], 127.67, 127.97, 128.36, 128.62, 128.75, and 130.41 (+, Ar-C), 136.22 and 139.25 (−, Ar-C), 170.34 and 171.03 (−, C=N and C=O), 207.96 (−, C=O).

***tert*-Butyl (*E*)- and (*Z*)-5-Cyano-2-diphenylmethyleneamino-4-pentenoate (13d-H):**

4-Bromo-2-butenenitrile **(5d)**[17] (292 mg) gave after purification [Et_2O/light petroleum (1:5)] 461 mg (64%) of **13d-H**; $R_f = 0.26$.

IR (Film): ν = 2965, 2920, 2220 (C≡N), 1730 (C=O), 1620 (N=C and C=C), 1445, 1370, 1155, 700 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$) (both isomers): δ = 1.46 [s, 9 H, $C(CH_3)_3$], 2.72–3.11 (m, 2 H, 3-H), 4.04–4.17 (m, 1 H, 2-H), 5.36–5.45 (m, 1 H, 5-H), 6.60–6.73 (m, 1 H, 4-H), 7.14–7.51 and 7.61–7.69 (m, 10 H, Ar-H).

^{13}C NMR (50.3 MHz, $CDCl_3$, APT) (1st isomer): δ = 27.98 [+, $C(\underline{C}H_3)_3$], 35.84 (−, C-3), 64.22 (+, C-2), 81.73 [−, $\underline{C}(CH_3)_3$], 101.23 (+, C-5), 115.76 (−, C≡N), 127.64, 128.01, 128.57, 128.76, 128.83, and 130.47 (+, Ar-C), 136.12 and 139.19 (−, Ar-C), 151.06 (+, C-4), 169.72 and 171.08 (−, C=N and C=O).

(2nd isomer): 27.98 [+, $C(\underline{C}H_3)_3$], 37.20 (−, C-3), 64.32 (+, C-2), 81.79 [−, $\underline{C}(CH_3)_3$], 102.01 (+, C-5), 117.12 (−, C≡N), 127.64, 128.07, 128.57, 128.76, 128.83, and 130.57 (+, Ar-C), 136.12 and 139.07 (−, Ar-C), 152.04 (+, C-4), 169.60 and 171.21 (−, C=N and C=O).

***tert*-Butyl 2-(Diphenylmethyleneamino)-2-(*trans*-2′-phenylsulfonylcyclopropyl)ethanoate (12e-H):**

3-Bromo-1-phenylsulfonyl-1-propene **(5e)**[18] (522 mg) gave after purification [Et_2O/light petroleum (1:1)] 656 mg (69%) of **12e-H**; mp 136°C; $R_f = 0.47$.

IR (KBr): ν = 2980, 1730 (C=O), 1620 (N=C), 1445, 1370, 1305, 1130, 890, 790, 735, 700 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.07 (ddd, 1 H, ^2J = 4.8, $^3J_{cis}$ = 9.6, $^3J_{trans}$ = 6.1 Hz, 3′-H), 1.39 [s, 9 H, $C(CH_3)_3$], 1.57 (ddd, 1 H, ^2J = 4.8, $^3J_{cis}$ = 9.6, $^3J_{trans}$ = 4.8 Hz, 3′-H), 2.37 (dddd, 1 H, ^3J = 5.7, $^3J_{cis}$ = 9.6, $^3J_{trans}$ = 4.8, $^3J_{trans}$ = 6.1 Hz, 1′-H), 2.68 (ddd, 1 H, $^3J_{cis}$ = 9.6, $^3J_{trans}$ = 4.8, $^3J_{trans}$ = 4.8 Hz, 2′-H), 3.75 (d, 1 H, ^3J = 5.7 Hz, 2-H), 6.92–6.99, 7.28–7.54 and 7.91–7.97 (m, 15 H, Ar-H).

^{13}C NMR (50.3 MHz, $CDCl_3$, APT): δ = 9.09 (−, C-3′), 22.87 (+, C-1′), 27.92 [+, $C(\underline{C}H_3)_3$], 36.13 (+, C-2′), 64.28 (+, C-2), 81.90 [−, $\underline{C}(CH_3)_3$], 127.50, 127.64, 127.94, 128.56, 128.80, 129.11, 130.61, and 133.17 (+, Ar-C), 135.83, 138.73, and 140.65 (−, Ar-C), 169.39 and 171.34 (−, C=N and C=O).

MS (70 eV): m/z (%) = 374 [100, $M^+ - CO_2C(CH_3)_3$], 233 [9, $M^+ - CO_2C(CH_3)_3 - C_6H_5SO_2$].

***tert*-Butyl (*E*)-5-Dimethylphosphonyl-2-diphenylmethyleneamino-4-pentenoate (13f-H):**

Dimethyl 3-bromo-1-propene-1-phosphonate **(5f)**[19] (458 mg) gave after purification [Et_2O/light petroleum (3:1)] 523 mg (59%) of **13f-H**; $R_f = 0.15$.

IR (film): ν = 2970, 1725 (C=O), 1625 (N=C and C=C), 1445, 1370, 1250, 1155, 1040, 830, 700 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.44 [s, 9 H, $C(CH_3)_3$], 3.05–3.16 (m, 2 H, 3-H), 3.61 (d, 3 H, $^3J_{HP}$ = 9.2 Hz, OCH_3), 3.66 (d, 3 H, $^3J_{HP}$ = 9.2 Hz, OCH_3), 4.08 (t, 1 H, ^3J = 6.0 Hz, 2-H), 5.62 (ddt, 1 H, $^2J_{HP}$ = 19.3, $^3J_{trans}$ = 13.2, ^4J = 1.0 Hz, 5-H), 6.63 (ddt, 1 H, $^3J_{HP}$ = 53.1, $^3J_{trans}$ = 13.2, ^3J = 7.3 Hz, 4-H), 7.16–7.47 and 7.60–7.66 (m, 10 H, Ar-H).

^{13}C NMR (50.3 MHz, $CDCl_3$, APT): δ = 27.93 [+, $C(\underline{C}H_3)_3$], 34.43 (−, d, $^3J_{CP}$ = 7.7 Hz, C-3), 51.84 and 51.95 (+, OCH_3), 64.72(+, d, $^4J_{CP}$ = 1.5 Hz, C-2), 81.31 [−, $\underline{C}(CH_3)_3$], 116.64 (+, d, $^1J_{CP}$ = 183.9 Hz, C-5), 127.72, 127.88, 128.41, 128.54, 128.73, and 130.25 (+, Ar-C), 136.22 and 139.31 (−, Ar-C), 150.71 (+, d, $^2J_{CP}$ = 3.6 Hz, C-4), 170.24 and 170.47 (−, C=N and C=O).

***tert*-Butyl 2-(Diphenylmethyleneamino)-2-(1′-methyl-2′-nitrocyclopropyl)ethanoate (12a-Me):**

3-Bromo-2-methyl-1-nitro-1-propene **(10)** (360 mg) gave after purification [Et_2O/light petroleum (1:5)] 442 mg (56%) of **12a-Me**; mp 78°C; $R_f = 0.55$.

IR (KBr): ν = 2990, 1730 (C=O), 1625 (N=C), 1545 (NO_2), 1435, 1365 (NO_2), 1145, 880, 785, 710, 695 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.37 (s, 3 H, CH_3), 1.36–1.47 (m, 1 H, 3′-H), 1.46 [s, 9 H, $C(CH_3)_3$], 1.73 (dd, 1 H, ^2J = 5.5, $^3J_{trans}$ = 5.0 Hz, 3′-H), 3.81 (s, 1 H, 2-H), 4.78 (dd, 1 H, $^3J_{cis}$ = 6.5, $^3J_{trans}$ = 5.0 Hz, 2′-H), 7.11–7.18 and 7.30–7.63 (m, 10 H, Ar-H).

^{13}C NMR (50.3 MHz, $CDCl_3$, APT): δ = 14.59 (+, CH_3), 19.46 (−, C-3′), 27.97 [+, $C(\underline{C}H_3)_3$], 31.77 (−, C-1′), 63.08 (+, C-2′), 69.34 (+, C-2), 82.12 [−, $\underline{C}(CH_3)_3$], 127.72, 128.13, 128.65, 128.87, 128.98, and 130.79 (+, Ar-C), 135.80 and 138.95 (−, Ar-C), 168.70 and 171.47 (−, C=N and C=O).

MS (70 eV): m/z (%) = 394 (1, M^+), 293 [100, $M^+ - CO_2C(CH_3)_3$], 247 [38, $M^+ - CO_2C(CH_3)_3 - NO_2$].

Deprotection of Cyclopropylglycines 12-R to Amino Acid Hydrochlorides 15-R; General Procedure:

The protected amino acid **12-R** (1 mmol) was treated with aq 1 N HCl (40 mL). The mixture was stirred for 15 h at r. t. and the aqueous

layer was extracted two times with Et_2O (20 mL). Evaporation of the aqueous solvent in vacuo gave **15-R**.

2-(trans-2'-Nitrocyclopropyl)glycine Hydrochloride (**15a-H**):

12a-H (380 mg) gave 183 mg (93%) of **15a-H**.

IR (KBr): ν = 3300–2700 (NH_3^+ and CO_2H), 1750 (C=O), 1550 (NO_2), 1490, 1370 (NO_2), 1215, 1100, 910, 850, 695 cm^{-1}.

^1H NMR (250 MHz, D_2O): δ = 1.53 (ddd, 1 H, ^2J = 7.2, $^3J_{cis}$ = 7.2, $^3J_{trans}$ = 7.2 Hz, 3'-H), 1.94 (ddd, 1 H, ^2J = 7.2, $^3J_{cis}$ = 10.8, $^3J_{trans}$ = 3.6 Hz, 3'-H), 2.32 (dddd, 1 H, ^3J = 9.9, $^3J_{cis}$ = 10.8, $^3J_{trans}$ = 3.6, $^3J_{trans}$ = 7.2 Hz, 1'-H), 3.48 (d, 1 H, ^3J = 9.9 Hz, 2-H), 4.52 (ddd, 1 H, $^3J_{cis}$ = 7.2, $^3J_{trans}$ = 3.6, $^3J_{trans}$ = 3.6 Hz, 2'-H).

^{13}C NMR (50.3 MHz, D_2O, APT): δ = 17.22 (–, C-3'), 24.72 (+, C-1'), 54.00 (+, C-2), 58.35 (+, C-2'), 170.29 (–, C=O).

2-(trans-2'-Methoxycarbonylcyclopropyl)glycine Hydrochloride (**15b-H**):

12b-H (394 mg) gave 189 mg (90%) of **15b-H**.

IR (KBr): ν = 3300–2800 (NH_3^+ and CO_2H), 1745 (C=O), 1730 (C=O), 1435, 1320, 1150, 705 cm^{-1}.

^1H NMR (250 MHz, D_2O): δ = 1.10–1.35 (m, 2 H, 3'-H), 1.66–1.74 (m, 1 H, 2'-H), 1.85–1.94 (m, 1 H, 1'-H), 3.40 (d, 1 H, ^3J = 9.7 Hz, 2-H), 3.55 (s, 3 H, CH_3).

2-[trans-2'-(1-Oxoethyl)cyclopropyl]glycine Hydrochloride (**15c-H**):

12c-H (377 mg) gave 168 mg (87%) of **15c-H**.

IR (KBr): ν = 3300–2800 (NH_3^+ and CO_2H), 1740 (C=O), 1700 (C=O), 1440, 1360, 1190, 845 cm^{-1}.

^1H NMR (250 MHz, D_2O): δ = 1.12–1.28 (m, 2 H, 3'-H), 1.63–1.75 (m, 1 H, 1'-H), 2.10–2.23 (m, 1 H, 2'-H), 2.14 (s, 3 H, CH_3), 3.38 (d, 1 H, ^3J = 9.9 Hz, 2-H).

^{13}C NMR (50.3 MHz, D_2O, APT): δ = 17.35 (–, C-3'), 24.49 (+, C-1'), 28.13 (+, C-2'), 30.60 (+, CH_3), 56.50 (+, C-2), 171.41 and 213.46 (–, C=O).

2-(trans-2'-Phenylsulfonylcyclopropyl)glycine Hydrochloride (**15e-H**):

12e-H (476 mg) gave 280 mg (96%) of **15e-H**.

IR (KBr): ν = 3200–2800 (NH_3^+ and CO_2H), 1755 (C=O), 1500, 1315, 1210, 1155, 745 cm^{-1}.

^1H NMR (250 MHz, D_2O): δ = 1.35 (ddd, 1 H, ^2J = 6.3, $^3J_{cis}$ = 9.2, $^3J_{trans}$ = 6.3 Hz, 3'-H), 1.57 (ddd, 1 H, ^2J = 6.3, $^3J_{cis}$ = 10.3, $^3J_{trans}$ = 4.6 Hz, 3'-H), 2.07 (dddd, 1 H, ^3J = 9.4, $^3J_{cis}$ = 10.3, $^3J_{trans}$ = 4.6, $^3J_{trans}$ = 6.3 Hz, 1'-H), 2.97 (ddd, 1 H, $^3J_{cis}$ = 9.2, $^3J_{trans}$ = 4.6, $^3J_{trans}$ = 4.6 Hz, 2'-H), 3.44 (d, 1 H, ^3J = 9.4 Hz, 2-H), 7.50–7.72 and 7.78–7.84 (m, 5 H, Ar-H).

^{13}C NMR (50.3 MHz, D_2O, APT): δ = 11.53 (–, C-3'), 19.19 (+, C-1'), 37.45 (+, C-2'), 54.25 (+, C-2), 127.61, 129.96, and 135.03 (+, Ar-C), 137.82 (–, Ar-C), 170.25 (–, C=O).

2-(1'-Methyl-2'-nitrocyclopropyl)glycine Hydrochloride (**15a-Me**):

12a-Me (394 mg) gave 198 mg (94%) of **15a-Me**.

IR (KBr): ν = 3300–2600 (NH_3^+ and CO_2H), 1735 (C=O), 1560 (NO_2), 1440, 1370 (NO_2), 1205, 1080, 890, 695 cm^{-1}.

^1H NMR (250 MHz, D_2O): δ = 1.15 (s, 3 H, CH_3), 1.71 (dd, 1 H, ^2J = 7.0, $^3J_{cis}$ = 7.0 Hz, 3'-H), 1.93 (dd, 1 H, ^2J = 7.0, $^3J_{trans}$ = 4.8 Hz, 3'-H), 3.43 (s, 1 H, 2-H), 4.57 (dd, 1 H, $^3J_{cis}$ = 7.0, $^3J_{trans}$ = 4.8 Hz, 2'-H).

^{13}C NMR (50.3 MHz, D_2O, APT): δ = 11.45 (+, CH_3), 23.00 (–, C-3'), 29.55 (–, C-1'), 59.83 (+, C-2), 64.95 (+, C-2'), 170.51 (–, C=O).

2-(*trans*-2'-Aminocyclopropyl)glycine Hydrochloride (16):

A solution of the hydrochloride **15a-H** (98 mg, 0.5 mmol) in H_2O (5 mL) was treated with Pd–C (25 mg, 10% Pd) and stirred for 24 h at r.t. under H_2 (1 bar). Filtration and evaporation of the solvent in vacuo gave 80 mg (96%) of **16**.

IR (KBr): ν = 3300–2600 (NH_3^+ and CO_2H), 1745 (C=O), 1450, 1180, 875, 700 cm^{-1}.

^1H NMR (250 MHz, D_2O): δ = 1.07–1.27 (m, 2 H, 3'-H), 1.59 (dddd, 1 H, ^3J = 9.6, $^3J_{cis}$ = 9.6, $^3J_{trans}$ = 3.5, $^3J_{trans}$ = 6.7 Hz, 1'-H), 2.78 (ddd, 1 H, $^3J_{cis}$ = 7.4, $^3J_{trans}$ = 3.5, $^3J_{trans}$ = 3.7 Hz, 2'-H), 3.54 (d, 1 H, ^3J = 9.6 Hz, 2-H).

^{13}C NMR (50.3 MHz, D_2O, APT): δ = 9.67 (–, C-3'), 16.86 (+, C-1'), 27.49 (C-2'), 54.14 (+, C-2), 170.06 (–, C=O).

(1) Wagner, I.; Musso, H. *Angew. Chem.* **1983**, *95*, 827; *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 816.
(2) Stammer, C.H. *Tetrahedron* **1990**, *46*, 2231.
(3) Rosenthal, G.A. *Plant Nonproteinogenic Amino and Imino Acids. Biological and Toxicological Properties*; Academic: New York, 1982.
(4) Suckling, C.J. *Angew. Chem.* **1988**, *100*, 555; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 537.
(5) Baldwin, J.E.; Adlington, R.M.; Domayne-Hayman, B.P.; Knight, G.; Ting, H.-H. *J. Chem. Soc., Chem. Commun.* **1987**, 1661.
(6) Joucla, M.; el Goumzili, M.; Fouchet, B. *Tetrahedron Lett.* **1986**, *27*, 1677.
(7) McIntosh, J.M.; Leavitt, R.K.; Mishra, P.; Cassidy, K.C.; Drake, J.E.; Chadha, R. *J. Org. Chem.* **1988**, *53*, 1947.
(8) Fowden, L.; Smith, A.; Millington, D.S.; Sheppard, R.C. *Phytochemistry* **1969**, *8*, 437.
(9) Yamanoi, K.; Ohfune, Y.; Watanabe, K.; Li, P.N.; Takeuchi, H. *Tetrahedron Lett.* **1988**, *29*, 1181.
Shimamoto, K.; Ohfune, Y. *Tetrahedron Lett.* **1989**, *30*, 3803.
(10) Pellicciari, R.; Natalini, B.; Marinozzi, M.; Monahan, J.B.; Snyder, J.P. *Tetrahedron Lett.* **1990**, *31*, 139.
(11) Hesse, G.; Jäger, V. *Liebigs Ann. Chem.* **1970**, *740*, 79.
(12) Rousseau, G.; Conia, J.M. *Tetrahedron Lett.* **1981**, *22*, 649.
(13) Backer, H.J.; Dost, N. *Recl. Trav. Chim. Pays-Bas* **1949**, *68*, 1143.
(14) Bride, M.H.; Gummings, W.A.W.; Pickles, W. *J. Appl. Chem.* **1961**, *11*, 357.
(15) Calderari, G.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1592.
(16) Font, J.; March, P. de *Tetrahedron* **1981**, *37*, 2391.
(17) Glattfeld, J.W.E.; Rietz, E. *J. Am. Chem. Soc.* **1940**, *62*, 974.
(18) Eisch, J.J.; Galle, J.E. *J. Org. Chem.* **1979**, *44*, 3277.
(19) Ornstein, P.L. *J. Org. Chem.* **1989**, *54*, 2251.
(20) Severin, T.; Supp, W.; Manninger, G. *Chem. Ber.* **1979**, *112*, 3013.
(21) Kocienski, P.J.; Cernigliaro, G.; Feldstein, G. *J. Org. Chem.* **1977**, *47*, 353.
(22) O'Donnell, M.J.; Polt, R.L. *J. Org. Chem.* **1982**, *47*, 2663.
(23) Allan, R.D. *J. Chem. Res. (S)* **1980**, 392; (*M*) **1980**, 4658.
(24) Bremer, C.; de Meijere, A., unpublished results.
(25) Häner, R.; Seebach, D. *Chimia* **1985**, *39*, 356.
(26) Burgess, K.; Ho, K.-K. *J. Org. Chem.* **1992**, *57*, 5931.
(27) Ohfune, Y.; Shimamoto, K.; Ishida, M.; Shinaschi, H. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 15.
(28) Zindel, J.; Zeeck, A.; König, A.W.; de Meijere, A. *Tetrahedron Lett.* **1993**, *34*, 1917.