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Practical Syntheses of Both Enantiomers of Cyclopropylglycine and of Methyl 2-Cyclopropyl-2-*N*-Boc-iminoacetate[1]

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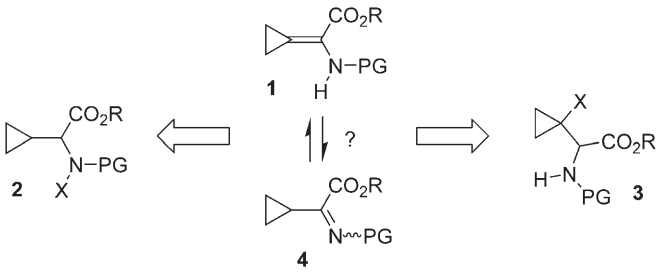
Dedicated to Professor Dieter Enders on the occasion of his 60th birthday.

Abstract: : A facile three-step synthesis of racemic cyclopropylglycine in multigram quantities from inexpensive cyclopropyl methyl ketone has been elaborated. Enzymatic hydrolysis of the *N*-Boc-protected methyl ester of cyclopropylglycine **9** with the inexpensive enzyme papain from *Carica papaya* affords both enantiomers of cyclopropylglycine (**8**) with enantiomeric excesses of 99% or better after deprotection under acidic conditions. Furthermore, the new cyclopropyl group-containing building block methyl 2-cyclopropyl-2-*N*-Boc-iminoacetate (**13**) was prepared by *N*-chlorination and subsequent dehydrochlorination with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Addition of nucleophiles to **13** offers a ready access to an unusual, orthogonally bisprotected α,α-diamino acid derivative and interesting components of rigid peptide backbones.

Keywords: amino acids; cyclopropanes; enantiomeric resolution; enzymes; furans; small rings

Introduction

2-Substituted 2-cyclopropylideneacetates have demonstrated their synthetic utility as multifunctional building blocks with unique features.[2] They significantly excel simple acrylates in their reactivity towards nucleophiles and cyclophiles.[3] Alkyl 2-chloro-2-cyclopropylideneacetates, for which an advanced simple synthesis has recently been developed by our group,[4] have emerged as most prolific of this unrivalled family. Their high reactivity combined with their four compactly arranged functionalities make them suitable precursors to various valuable complex molecules such as natural product analogues, unusual heterocyclic compounds and conformationally rigid peptidomimetics.[5] An even more facile access to the latter would be possible if 2-(acylamino)-2-cyclopropylideneacetates of type **1** were available as starting materials. At the outset of our work it was not known whether such compounds would be stable under basic conditions or would tautomerize to the potentially more stable 2-(acylimino)-2-cyclopropylacetates **4**. Since **4** also might exhibit interesting reactivities, we first tested the possibility of accessing **1** by base-promoted elimination from an *N*-protected *N*-haloaminocyclopropylacetate **2** with subsequent isomerization (Scheme 1).



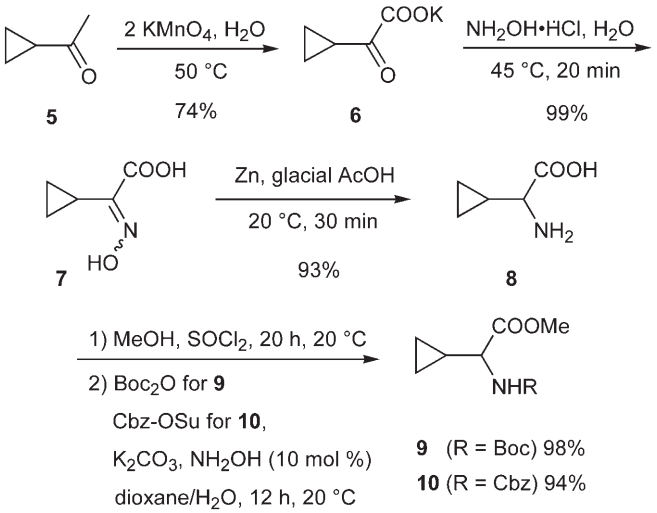
Scheme 1.

The alternative potential precursor to **1** would be **3**, a derivative of the naturally occurring amino acid cleonin, for which a new synthesis has recently been reported.[6] The route *via* **3** appeared to be considerably longer than that starting from the *N*-substituted cyclopropylglycine **2**, provided that a facile and efficient protocol for the preparation of **2** would be developed.

Results and Discussion

Cyclopropylglycine (**8**) had previously been prepared, e.g., from cyclopropanecarboxaldehyde by a Strecker

reaction,[7] and by reaction of an electrophilic glycine equivalent, with cyclopropylmagnesium bromide.[8] However, both of these approaches have certain shortcomings, e.g., the toxicity of KCN, the volatility of cyclopropanecarboxaldehyde, as well as the low yield in the first case, and expensive starting materials in the second protocol. Therefore, a short route to **8** from inexpensive cyclopropyl methyl ketone (**5**) was conceived and executed. First, **5** was oxidized with aqueous $KMnO_4$ at 50 °C (Scheme 2) to give the potassium salt **6** of cyclopropyloxoacetic acid which, after concentration of the aqueous phase, was converted with hydroxylamine hydrochloride into the corresponding oxime **7** in 73% yield over 2 steps. The potassium salt **6** and the oxime **7** can be stored at room temperature for at least 6 months without decomposition. The oxime **7** raises an additional interest as it is the key structural constituent of a potent ($IC_{50} \leq 50$ μM) KSP kinesin inhibitor.[9]

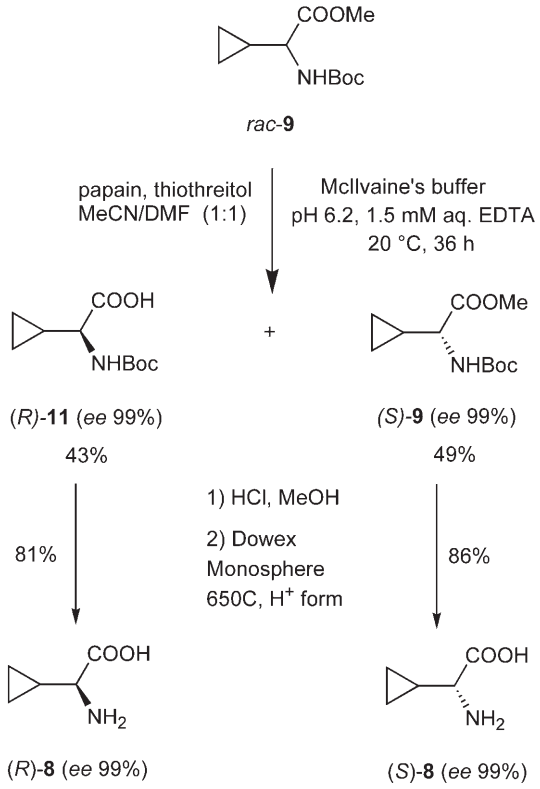


Scheme 2. New practical synthesis of cyclopropylglycine (**8**) and derivatives thereof.

Upon attempted hydrogenation of **7** over Pd/C, norvaline (*n*-propylglycine) was obtained instead of the expected cyclopropylglycine (**8**). Since several other oxime reduction methods also proved fruitless, attention was turned to reduction with zinc in glacial acetic acid which had previously been shown to be compatible with the cyclopropane ring.[10]

Indeed, the reduction proceeded cleanly to give **8** in 93% yield after DOWEX ion-exchange chromatography. The crude reduction product which, according to the ^1H NMR spectrum had an approximate composition **8**·HOAc·2 $Zn(OAc)_2$, can be directly transformed into the corresponding Boc-protected methyl ester **9** in 98% yield over 2 steps. The developed protocol, which features efficiency, simplicity and easy availability of the starting materials, could easily be performed on a 100 g scale. By analogy, the Cbz-protected methyl ester *rac*-**10** was prepared in a one-pot procedure employing *N*-benzyloxycarbonyloxysuccinimide (Cbz-OSu) instead of Boc_2O.

With the methyl *N*-Boc-cyclopropylglycinate (**9**) in hand, an enzymatic deracemization was considered as an efficient route to both enantiomers of **8**, employing papain as an inexpensive and efficient enzyme (Scheme 3).



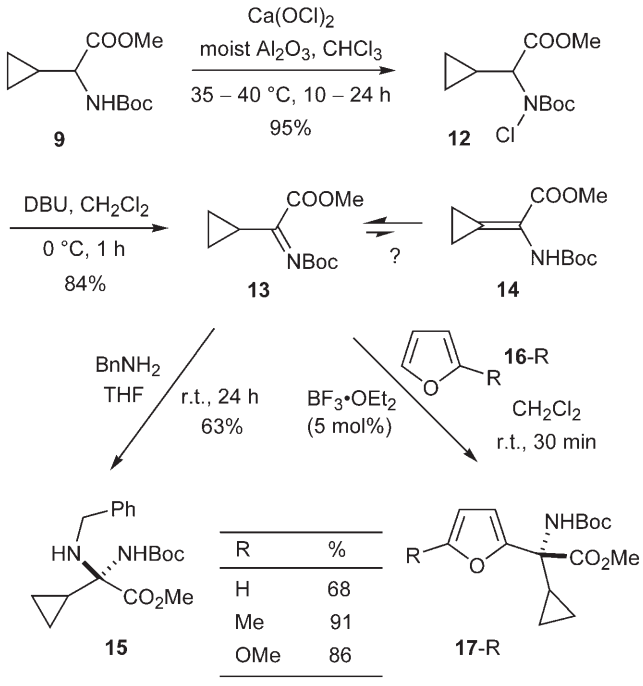
Scheme 3. The papain-catalyzed deracemization of *rac*-**9** as an efficient route to both enantiomers of **8**.

Indeed, papain had previously been used for successful deracemizations of *N*-protected amino esters in a few cases,[11] and one of them comprised the optical resolution of ethyl *N*-Boc-vinylglycinate.[12] Gratifyingly, the papain-catalyzed ester hydrolysis yielded (*R*)-**9** and (*S*)-**11** in 49 and 43% yields, respectively, and with high enantiopurity (> 99%).[13] Although no pH control was necessary, the use of McIlvaine's buffer consisting of citric acid, disodium hydrogen phosphate and a 1.5 mM aqueous solution of the disodium salt of ethylenediamine-*N*,*N*,*N*′,*N*′-tetraacetic acid (EDTA) buffer with pH 6.2 as an aqueous component furnished the best results in terms of enantioselectivity and catalyst activity (Scheme 3). Also, utilization of dimethylformamide as an organic cosolvent

with acetonitrile played a beneficial role. *rac*-Thiothreitol was added to prevent oxidative deactivation of the enzyme. Ethanethiol can also be employed instead of *rac*-thiothreitol, although a slight decrease of the hydrolysis rate was observed. The free amino acids (*R*)- and (*S*)-**8** were then liberated by acidic hydrolysis and purified by subsequent ion-exchange chromatography on DOWEX Monosphere 650C, in close analogy to the previously described procedure for the purification of 3-(*trans*-2-nitrocyclopropyl)alanine.[14]

The *N*-Boc-protected methyl ester *rac*-**9** was cleanly chlorinated to yield the corresponding *N*-chloro derivative **12** with calcium hypochlorite on moist alumina, as has recently been described.[15]

A screening of the reaction conditions for the dehydrochlorination of **12** showed that the choice of an appropriate base was crucial for achieving high yields. Whereas potassium *tert*-butoxide and potassium carbonate led to a rapid charring of the reaction mixture, triethylamine brought about only a very sluggish reaction to an elimination product and a number of unidentified by-products. On the other hand, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) effected a much cleaner dehydrochlorination, which was complete within 1 h and could successfully be performed on an up to 250 mmol scale without decreases in yield (Scheme 4). The elimination product turned out to be the 2-cyclopropyl-(*N*-Boc-imino)acetate **13** and not the 2-(*N*-Boc-amino)-2-cyclopropylideneacetate **14**. A



Scheme 4. Dehydrochlorination of the 2-(*N*-chloro-*N*-Boc-amino)-2-cyclopropylacetate **12** and subsequent reactions of the resulting *N*-Boc-iminoacetate **13**.

small fraction of the non-chlorinated precursor **9** (*ca.* 3 – 5%) was also present and could not be separated from the Boc-imino ester **13**. As the *N*-chlorinated starting material **12** did not contain **9**, its presence in the final product can only be rationalized on the basis of a chlorine transfer onto the tertiary amine moiety in DBU, as had previously been suggested for other *N*-chloro derivatives.[16] The *N*-Boc-iminoacetate **13** appears to be the first such compound that does not readily tautomerize to the corresponding *N*-Boc-aminoacrylate in spite of its having a β-hydrogen substituent.[17] This must be due to the additional strain that a double bond experiences when it is attached to a three-membered ring.[18,19]

To test the reactivity of the *N*-Boc-imino ester **13**, it was treated with benzylamine in tetrahydrofuran. This afforded the 2,2-diamino-2-cyclopropylacetate derivative **15** in 63% yield. Since α-substituted cyclopropylglycines appear to be key constituents of many biologically active compounds,[20] the derivative **15**, possessing an α-heteroatom substituent may be of particular interest as a building block for the preparation of novel analogues.

Although a number of [4+2] cycloadditions of acceptor-substituted imines are known,[21] **13** did not undergo Diels–Alder reactions with cyclopentadiene, cyclohexa-1,3-diene, isoprene, or Danishefsky's diene under various conditions, including high pressure (10 kbar). With furan and substituted furans **16**-R under boron trifluoride-etherate catalysis, however, **13** reacted smoothly to give the corresponding Friedel–Crafts aminoalkylation products **17**-R in 68 – 91% yields. The structures of these products were unambiguously established on the basis of HMBC/HSQC NMR spectra. The adducts **17** comprise α-furyl-α-cyclopropylglycine derivatives, which are difficult to access along other routes, and might be of interest as constituents for rigid peptide frameworks.[22]

Conclusions

In conclusion, a facile and easily scalable synthesis of cyclopropylglycine and several interesting derivatives thereof, from inexpensive starting materials, has been developed.

Experimental Section

General Remarks

^{1}H and ^{13}C NMR spectra were recorded at 250 as well as 300 (^{1}H), and 62.9 MHz [^{13}C, additional DEPT (distortionless enhancement by polarization transfer)] on Bruker Aspect 3000 and Varian Unity-300 instruments. For $CDCl_3$ solutions $CHCl_3/CDCl_3$ was used as an internal reference; δ

in ppm, *J* in Hz. IR spectra of the compounds as oils between KBr plates were measured on a Bruker IFS 66 (FT-IR) spectrometer. MS (EI) were recorded on a Finnigan MAT 95 instrument. Enantiomeric purities were determined by HPLC on a chiral column [Crownpak CR (+) or (−) for the amino acid **8**, and ChiralPak for the derivatives **9** and **11**]. Moist alumina was prepared according to the published protocol.[15] 0.1 M (pH 6.2) McIlvaine's buffer containing 1.5 mM of the disodium salt of ethylenediamine-*N*,*N*,*N*′,*N*′-tetraacetic acid (EDTA) was prepared by dissolving citric acid (0.6513 g, 3.39 mmol), $Na_2HPO_4 \cdot 12\ H_2O$ (4.735 g, 13.22 mmol) in water (98.5 mL), and adding 0.1 M aqueous solution of the disodium salt of EDTA (1.5 mL). Zinc powder (Merck) was activated by rinsing with 0.5 N aqueous hydrochloric acid, then water, anhydrous ethanol, and diethyl ether, then dried under vacuum (0.05 mbar) at 150 °C overnight, and cooled to room temperature under an atmosphere of Ar. All other chemicals were used as commercially available (Merck, Acrõs, BASF, Bayer, Hoechst, Degussa AG, and Hüls AG). Organic extracts were dried over Na_2SO_4.

Potassium Cyclopropylglyoxylate (6)[23]

To a mechanically stirred mixture of cyclopropyl methyl ketone (**5**) (54.6 g, 0.65 mol) and a solution of Na_2CO_3 (0.8 g, 7.6 mmol) in water (360 mL) at 50 °C in a 4 L flask equipped with an efficient reflux condenser and a 500 mL dropping funnel, was added dropwise over 40 h a solution of $KMnO_4$ (145 g, 0.92 mol) in water (3 L). The mixture was stirred for an additional 10 h, then cooled to room temperature, and MeOH (360 mL) was added. The solids were filtered off and washed with warm (50 °C) water (3 × 200 mL). The combined filtrates were concentrated under reduced pressure at 50 °C. The solid residue was dried under vacuum (0.05 mbar) to give the salt **6**·KOH, which also contained ca. 10 % potassium cyclopropanecarboxylate (due to partial decarboxylative overoxidation); yield: 75 g (*ca.* 74% based on $KMnO_4$ and taking in account, that KOH is formed as a by-product according to the stoichiometry of the reaction); mp 241 °C (decomp.). ^{1}H NMR (300 MHz, D_2O): $\delta = 0.97 - 1.35$ (4H, m), 2.38 – 2.47 (1H, m); ^{13}C NMR (62.9 MHz): $\delta =$ 13.67 ($2CH_2$), 19.57 (CH), 172.01 (C), 208.90 (C); IR (film): $\tilde{\nu} = 3340$, 1557, 1417, 1358, 1188, 1102, 1026, 884, 702, 624 cm^{-1}.

2-Cyclopropyl-2-hydroxyiminoacetic Acid (7)[7]

A mixture of the salt **6**·KOH (66 g, *ca.* 0.3 mol) and water (60 mL) in a 250 mL flask was stirred at 45 °C until a clear solution had formed. Hydroxylamine hydrochloride ($NH_2OH \cdot HCl$) (43.4 g, 0.62 mol) was added over 15 min in small portions to avoid foaming. The mixture was stirred for an additional 20 min, then at 0 °C for 2 h. The fine precipitate was filtered off to give the first crop (32.6 g) of **7** as a colorless solid. The filtrate was acidified to pH 2 with 12 N HCl and extracted with CH_2Cl_2 (5 × 60 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure and then under vacuum (0.05 mbar) to give the second crop (5.9 g) as a colorless oil, slowly solidifying upon standing; total yield: 38.5 g (99%); mp 95 °C. ^{1}H NMR (300 MHz, D_2O): $\delta = 0.85 - 0.96$ (4H, m), 1.97 – 2.06 (1H, m); ^{13}C NMR (62.9 MHz): $\delta = 9.51$ (CH_2), 13.47 (CH), 162.38 (C), 171.04 (C).

Reduction of the Oxime 7 with Zinc. Synthesis of Cyclopropylglycine[24] (*rac*-8) and Methyl 2-(*N*-*tert*-Butoxycarbonylamino)-2-cyclopropylacetate [Boc-*c*PrGly-OMe] (*rac*-9)[25]

Activated zinc powder (see general remarks on reagents and chemicals, 45.4 g, 0.69 mol) was added in portions within 10 min to a solution of the oxime **7** (11.2 g, 86.7 mmol) in glacial AcOH (260 mL), maintaining the reaction temperature at 20 – 30 °C. The mixture was stirred at room temperature for 30 min, and then filtered. The filtrate was concentrated under reduced pressure at 40 °C to give a glassy solid which, according to its ^{1}H NMR spectrum, had an approximate composition **8**·HOAc·2 $Zn(OAc)_2$ (yield: 49 g). A sample of this (2.3 g) was applied onto a DOWEX column, as described elsewhere,[14] to give, after recrystallization from ethanol/water, the amino acid *rac*-**8** as a colorless solid; yield: 0.44 g (93%); mp 251 °C (lit. 249 °C). ^{1}H NMR (300 MHz, D_2O): $\delta = 0.20 - 0.25$ (1H, m), 0.35 – 0.43 (1H, m), 0.48 – 0.56 (2H, m), 0.92 – 0.98 (1H, m), 2.86 (1H, s); ^{13}C NMR (62.9 MHz): $\delta = 4.8$ (CH_2), 5.6 (CH_2), 13.7 (CH), 61.2 (CH), 176.0 (C); IR (KBr): $\tilde{\nu} = 3547$, 3440, 3386, 1624, 1580, 1490, 1417, 1390, 1260, 1030, 710 cm^{-1}.

The remaining crude product (46.7 g) was covered with MeOH (100 mL). In a separate flask, a mixture of MeOH (200 mL), and $SOCl_2$ (50 mL) was prepared at –10 °C. This was added into the flask with the crude product at –10 °C within 5 min, and the resulting mixture was stirred at room temperature for 20 h. It was then concentrated under reduced pressure. The glassy residue was dried under vacuum (0.05 mbar), then covered with dioxane (140 mL) and water (140 mL). Then K_2CO_3 (120 g, 0.87 mol) was added in portions with vigorous stirring maintaining the reaction temperature within 0 – 10 °C. Boc_2O (19.8 g, 91.0 mmol), and $NH_2OH \cdot HCl$ (0.6 g, 8.63 mmol) were added, the mixture was stirred at room temperature for 12 h, and then 3-dimethylaminopropylamine (5 mL) was added to scavenge the excess of Boc_2O. The mixture was stirred for an additional 1 h, then concentrated to *ca.* 50 mL under reduced pressure at room temperature and extracted with CH_2Cl_2 (4 × 200 mL). The extracts were washed with 1 N aqueous $KHSO_4$ (2 × 200 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The oily residue solidified upon standing to give the *N*-Boc-protected ester *rac*-**9** as a colorless waxy solid; yield: 18.5 g (98%); mp 49 °C. ^{1}H NMR (300 MHz): $\delta = 0.32 - 0.42$ (1H, m), 0.44 – 0.58 (3H, m), 0.98 – 1.11 (1H, m), 1.42 (9H, s), 3.69 (1H, m), 3.74 (3H, s), 5.04 (1H, br s); ^{13}C NMR (62.9 MHz): $\delta = 2.62$ (CH_2), 2.75 (CH_2), 13.47 (CH), 27.51 (CH_3), 51.99 (CH_3), 56.50 (CH), 79.57 (C), 155.14 (C), 172.69 (C); IR (film): $\tilde{\nu} = 3369$, 2976, 1747, 1717, 1507, 1367, 1163, 1025, 784 cm^{-1}; LR-MS (DCI): $m/z = 247.3$ (100) [M + NH_4^+], 230.2 (14) [M + H^+], 191.2

(5); HR-MS (ESI): $m/z = 230.1392$, calcd for $C_{11}H_{20}NO_4^+$ [M + H$^+$]: 230.1387.

Methyl *rac*-2-(*N*-Benzyloxycarbonylamino)-2-cyclopropylacetate (*rac*-10)[26]

This ester was prepared as described for *rac*-**9**, except that Cbz-OSu (*N*-benzyloxycarboxysuccinimide) was used instead of Boc_2O. *rac*-**10**: oxime **7** (1.18 g, 9.13 mmol) was reduced with the activated zinc powder (see general remarks on reagents and chemicals, 4.78 g, 72.63 mol) in AcOH (27 mL) as described for *rac*-**9**, and the obtained glassy solid was covered with MeOH (10 mL). In a separate flask, a mixture of MeOH (20 mL), and $SOCl_2$ (5 mL) was prepared at –10 °C. This was added into the flask with the crude product at –10 °C within 5 min, and the resulting mixture was stirred at room temperature for 20 h. It was then concentrated under reduced pressure. The glassy residue was dried under vacuum (0.05 mbar), then covered with dioxane (14 mL) and water (14 mL). Then K_2CO_3 (12 g, 0.087 mol) was added in portions with vigorous stirring while maintaining the reaction temperature within 0 – 10 °C. Cbz-OSu (2.49 g, 10 mmol) was added, the mixture was stirred at room temperature for 16 h, and then 3-dimethylaminopropylamine (0.8 mL) was added to scavenge the excess of Cbz-OSu. The mixture was stirred for an additional 1 h, then concentrated to ca. 50 mL under reduced pressure at room temperature and extracted with CH_2Cl_2 (4 × 20 mL). The extracts were washed with 1 N aqueous $KHSO_4$ (2 × 20 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give the *N*-Cbz-protected ester *rac*-**10** as a colorless solid; yield: 2.27 g (94%); mp 55 °C. ^{1}H NMR (300 MHz): δ = 0.25 – 0.62 (4H, m), 0.98 – 1.11 (1H, m), 3.74 (3H, s), 3.82 (1H, dd, J = 7.6, 7.6 Hz), 5.08 (2H, s), 5.33 (1H, d, J = 7.6 Hz), 7.27 – 7.39 (5H, m) ppm; ^{13}C NMR (62.9 MHz): δ = 2.97 (CH_2), 13.86 (CH), 52.32 (CH_3), 57.11 (CH), 67.00 (CH_2), 128.11 (CH), 128.16 (CH), 128.49 (CH), 136.15 (C), 155.82 (C), 172.48 (C); IR (film): $\tilde{\nu}$ = 3347, 1734, 1710, 1522, 1275, 1235, 1056, 975, 758, 698, 668 cm^{-1}.

Kinetic Resolution by the Papain-Catalyzed Hydrolysis of *rac*-9

To a solution of *rac*-**9** (1.52 g 6.63 mmol) in MeCN (7 mL) and DMF (7 mL) was added 0.1 M McIlvaine's buffer, containing 1.5 mM EDTA (7 mL, see general remarks on reagents and chemicals). In a separate flask, a solution of thiothreitol (20 mg) and papain (10 mg) in the buffer (1 mL) was prepared. This was added into the first flask, and the resulting mixture was stirred at room temperature for 36 h. It was then concentrated under reduced pressure at room temperature. The residue was diluted with 10% citric acid (10 mL) and Et_2O (50 mL). The ethereal phase was extracted with 0.1 M pH 9.6 $NaHCO_3/Na_2CO_3$ buffer (see general remarks on reagents and chemicals, 7 × 10 mL). The combined aqueous phases were washed with Et_2O (10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to give the ester (*S*)-**9**; yield: 0.75 g (49%).

The combined $NaHCO_3/Na_2CO_3$ buffer extracts were cooled to 0 °C, acidified to pH 2, and then extracted with Et_2O (5 × 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to give the acid (*R*)-**11**; yield: 0.61 g (43%); mp 79 °C; $[\alpha]_D^{20}$: +0.38 (*c* 1.4, $CHCl_3$). ^{1}H NMR (300 MHz): δ = 0.43 (1H, dd, J = 5.3, 5.3 Hz),0.47 – 0.68 (3H, m), 0.98 – 1.15 (1H, m), 1.43 (9H, s), 3.69 – 3.80 (1H, m), 5.11 (1H, br s), 6.42 (1H, br s); ^{13}C NMR (62.9 MHz): δ = 2.92 (CH_2), 3.12 (CH_2), 13.51 (CH), 28.24 (CH_3), 56.76 (CH), 80.23 (C), 155.54 (C), 177.13 (C); IR (film): $\tilde{\nu}$ = 3336, 3007, 2979, 1735 1683, 1528, 1303, 1167, 1050, 979, 784, 601 cm^{-1}; LR-MS (DCI): m/z = 247.3 (100) [M + NH_4^+], 230.2 (14) [M + H$^+$], 191.2 (5); anal. calcd. for $C_{10}H_{17}NO_4$ (215.25): C 55.80, H 7.96, N 6.51; found: C 55.96, H 8.11, N 6.59.

(*S*)-**9**: mp 52 °C; $[\alpha]_D^{20}$: –0.31 (*c* 0.9, $CHCl_3$). The spectral data (^{1}H and ^{13}C NMR, IR) of (*S*)-**9** were identical to those of *rac*-**9**.

General Procedure (GP1) for the Hydrolysis of (*S*)-9 and (*R*)-11, and Liberation of Enantiomerically Pure (*S*)- and (*R*)-Cyclopropylglycine (8)

A solution of (*S*)-**9** (0.46 g, 2 mmol) or (*R*)-**11** (0.43 g, 2 mmol) in methanol (5 mL) and 12 N aqueous HCl (5 mL) was heated under reflux for 8 h. It was then concentrated under reduced pressure, and the residue was purified by ion exchange chromatography on DOWEX Monosphere 650C to give the cyclopropylglycine enantiomers (*S*)-**8**; yield: 0.20 g (86%); $[\alpha]_D^{20}$: +59 (*c* 0.3, $CHCl_3$) or (*R*)-**8**; yield: 0.19 g (81%); $[\alpha]_D^{20}$: –60.1 (*c* 0.32, $CHCl_3$)}, respectively. The spectral data (^{1}H and ^{13}C NMR, IR) of the both enantiomers of **8** were virtually identical to those of *rac*-**8**.

Methyl 2-(*N*-*tert*-Butoxycarbonyl-*N*-chloroamino)-cyclopropylacetate (12)[15]

From **9** (57.4 g, 250.3 mmol), $Ca(OCl)_2$ (108.5 g, 759 mmol), and moist Al_2O_3 (398 g) in $CHCl_3$ (700 mL), compound **12** was obtained according to the literature procedure[15] as a colorless oil; yield: 62.5 g (95%). ^{1}H NMR: δ = 0.40 – 0.46 (m, 1H), 0.51 – 0.59 (m, 1H), 0.61 – 0.68 (m, 1H), 0.78 – 0.85 (m, 1H), 1.37 – 1.45 (m, 1H), 1.49 (s, 9H), 3.78 (s, 3H), 3.95 (d, J = 9.5 Hz, 1H); ^{13}C NMR: δ = 3.38 (CH_2), 5.72 (CH_2), 11.55 (CH), 27.81 (CH_3), 52.29 (CH_3), 68.42 (CH), 83.39 (C), 154.88 (C), 169.94 (C); IR (film): $\tilde{\nu}$ = 2981, 1751, 1705, 1457, 1436, 1371, 1341, 1287, 1262, 1158, 1063, 1027, 969, 853, 752, 461 cm^{-1}; MS (EI): m/z = 263.3 (1) [M$^+$], 160.2 (5), 104.1 (23), 57.1 (100), 41.0 (17).

Methyl 2-(*N*-*tert*-Butoxycarbonylimino)-2-cyclopropylacetate (13)

To a solution of **12** (4.47 g, 17 mmol) in CH_2Cl_2 (100 mL) was added dropwise within 20 min at 0 °C a solution of DBU (2.57 g, 16.9 mmol) in CH_2Cl_2 (5 mL), and the mixture

was stirred at room temperature until the starting material had completely disappeared (*ca.* 1 h, TLC, hexane/Et_2O, 2:1). The solvent was then removed under reduced pressure at *ca.* 10 – 15 °C. The residue was covered with hexane (40 mL), the precipitate was filtered off and washed with hexane (3 × 10 mL). The combined filtrates were concentrated under reduced pressure, and the residue was immediately applied onto a column of neutral alumina [Brockmann activity N 4, prepared by deactivation of alumina ICN, Super I (40 g) with 10% (w/w, 4 g) of water]. This was eluted with a hexane/Et_2O, 5:1 mixture, to give, after concentration of the fraction with the product [R_f = 0.25 (hexane/Et_2O, 2:1)] the desired *N*-Boc-imino ester **13** as a colorless oil. The product turned yellow on standing at room temperature, and, therefore, should be stored at –18 °C. The product contained some of the precursor **9** (ca. 3 mol%), which could not be removed. Yield: 3.26 g (84%); bp 240 °C (0.05 mbar, bulb-to-bulb distillation). ^{1}H NMR (300 MHz): δ = 0.99 – 1.09 (2H, m), 1.10 – 1.21 (2H, m), 1.51 (9H, s), 2.06 – 2.22 (1H, m), 3.84 (3H, s); ^{13}C NMR (62.9 MHz): δ = 12.46 (CH_2), 14.47 (CH) 27.90 (CH_3), 52.82 (CH_3), 82.32 (C), 160.58 (C), 164.62 (C), 219.29 (C); IR (film): $\tilde{\nu}$ = 3413, 2978, 1746, 1663 (-N=C), 1483, 1392, 1295, 1249, 1159, 857 cm^{-1}; LR-MS (DCI): *m/z* = 245.2 (44) [M + NH_4^+], 228.2 (100) [M + H^+], 128.1 (21); HR-MS (ESI): *m/z* = 228.1233, calcd. for $C_{11}H_{18}NO_4^+$ [M + H^+]; 228.1230.

Methyl 2-Benzylamino-2-(*N*-*tert*-butoxycarbonylamino)-2-cyclopropylacetate (15)

To a solution of benzylamine (1.5 g, 14 mmol) in THF (15 mL) was added dropwise within 30 min at room temperature a solution of **13** (2.27 g, 10 mmol) in THF (15 mL), and the mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (hexane/Et_2O, 4:1) to give an oil, which solidified on standing. This was dissolved in boiling Et_2O (6 mL), and hexane (6 mL) was added. The mixture was stirred at 0 °C for 1 h, and the precipitate was filtered off to give the product **15** as a colorless solid; yield: 2.12 g (63%); mp 52 °C. ^{1}H NMR (300 MHz): δ = 0.36 – 0.54 (3H, m), 0.55 – 0.64 (1H, m), 1.27 – 1.40 (1H, m), 1.44 (9H, s), 3.01 (1H, br s), 3.47 (1H, d, *J* = 12.2 Hz), 3.68 (1H, d, *J* = 12.2 Hz), 3.74 (3H, s), 5.59 (1H, s), 7.17 – 7.75 (5H, m); ^{13}C NMR (62.9 MHz): δ = 1.6 (CH_2), 2.1 (CH_2), 18.4 (CH), 28.20 (CH_3), 47.8 (CH_2), 52.9 (CH_3), 74.9 (C), 79.7 (C), 126.9 (CH), 128.3 (CH), 128.4 (CH), 139.6 (C), 154.2 (C), 172.4 (C); IR (KBr): $\tilde{\nu}$ = 3347, 3088, 3009, 1745, 1685, 1616, 1534, 1384, 1365, 1260, 1165, 1072, 882, 788, 741, 698, 629 cm^{-1}; LRMS (EI): *m/z* = 334.2 (3) [M^+], 271.5 (22), 219.1 (100), 175.1 (9); anal. calcd, for $C_{18}H_{26}N_2O_4$ (334.4): C 64.65, H 7.84, N 8.38; found: C 64.33, H 7.98, N 8.25.

General Procedure (GP2) for the Friedel–Crafts Aminoalkylation of Furans 16-R with *N*-Boc-iminoacetate 13

To a solution of the imino ester **13** (2.27 g, 10 mmol) and the respective furan **16**-R (22 mmol) in CH_2Cl_2 (5 mL) was added at room temperature $BF_3{\cdot}OEt_2$ (71 mg, 0.5 mmol, 5 mol%), and the mixture was stirred at room temperature for 30 min (24 h without catalyst). The volatiles were removed under reduced pressure, and the residue was purified by column chromatography to give the corresponding amino acid derivative **17**-R.

Methyl 2-(*N*-*tert*-Butoxycarbonylamino)-2-cyclopropyl-2-furanylacetate (17-H)

According to **GP2**, **17**-H (2.0 g, 68%) was obtained from imino ester **13** (2.27 g, 10 mmol) and furan **16**-H (1.5 g, 22 mmol), and purified by column chromatography (hexane/Et_2O, 6:1). R_f = 0.5, (hexane/Et_2O, 2:1). Light brown oil; ^{1}H NMR (300 MHz): δ = 0.26 – 0.37 (1H, m), 0.38 – 0.69 (3H, m), 1.35 (4H, s, rotamers), 1.43 (5H, s, rotamers), 1.56 – 1.71 (1H, m), 3.76 (2H, s, rotamers), 3.89 (1H, s, rotamers), 5.05 (0.2H, br s, rotamers), 5.55 (0.8H, br s, rotamers), 6.35 (1H, s), 6.50 (1H, d, *J* = 3.2 Hz), 7.33 (1 H, br s); ^{13}C NMR (62.9 MHz): δ = 1.32 (CH_2), 2.11 (CH_2), 17.10 (C), 28.04 (CH_3), 52.98 (CH_3), 62.11 (C), 79.94 (C), 108.65 (CH), 110.36 (CH), 141.49 (CH), 151.34 (C), 154.08 (C), 171.05 (C); IR (film): $\tilde{\nu}$ = 3397 cm, 2978, 2522, 1714, 1490, 1367, 1258, 1164, 1052, 1023, 737, 599 cm^{-1}; LR-MS (EI): *m/z* = 296.1 (5) [M + H^+], 240.0 (24), 181.0 (100); HR-MS (ESI): *m/z* = 296.1490, calcd. for $C_{15}H_{22}NO_5^+$ [M + H^+]: 296.1493.

Methyl 2-(*N*-*tert*-Butoxycarbonylamino)-2-cyclopropyl-(5-methylfuran-2-yl)acetate (17-Me)

According to **GP2**, **17**-Me (2.82 g, 91%) was obtained from imino ester **13** (2.27 g, 10 mmol) and 2-methylfuran **16**-Me (1.8 g, 22 mmol), and purified by column chromatography (hexane/Et_2O, 4:1). R_f = 0.45, (hexane/Et_2O, 2:1). Light brown oil. ^{1}H NMR (300 MHz): δ = 0.26 – 0.63 (4H, m), 1.40 (4H, s, rotamers), 1.43 (5H, s, rotamers), 1.61 – 1.77 (1H, m), 2.23 (3H, s), 3.73 (3H, s), 5.53 (1H, br s), 5.91 (1H, d, *J* = 5.0 Hz), 6.33 (1H, d *J* = 5.0 Hz); ^{13}C NMR (62.9 MHz): δ = 1.21 (CH_2), 2.15 (CH_2), 13.70 (CH_3), 16.87 (CH), 28.07 (CH_3), 52.94 (CH_3), 62.14 (C), 79.86 (C), 106.35 (CH), 109.27 (CH), 149.23 (C), 151.39 (C), 154.14 (C), 171.29 (C); IR (film): $\tilde{\nu}$ = 3447, 2926, 1734, 1707, 1363, 1158, 1094, 1020, 748, 668, 620 cm^{-1}; LR-MS (EI): *m/z* = 309.1 (5) [M^+], 253.0 (12), 194.0 (90), 150.1 (40), 57.1 (100); HR-MS (ESI): *m/z* = 332.1471, calcd. for $C_{16}H_{23}NNaO_5^+$ [M + Na^+]: 332.1468.

Methyl 2-*N*-*tert*-Butoxycarbonylamino-2-cyclopropyl-(5-methoxyfuran-2-yl)acetate (17-OMe)

According to **GP2**, **17**-OMe (2.8 g, 86%) was obtained from imino ester **13** (2.27 g, 10 mmol) and 2-methoxyfuran **16**-OMe (2.16 g, 22 mmol), and purified by column chromatography (hexane/Et_2O, 5:1). $R_f = 0.25$, (hexane/Et_2O, 2:1). Colorless solid; mp 70 °C. ^1H NMR (300 MHz): $\delta = 0.31 - 0.67$ (4H, m), 1.37 (9H, s), 1.61 – 1.74 (1H, m), 3.75 (3H, s), 3.80 (3H, s), 5.15 (1H, d, $J = 3.3$ Hz), 5.48 (1H, br s), 6.37 (1H, d, $J = 3.3$ Hz); ^{13}C NMR (62.9 MHz): $\delta = 1.27$ (CH_2), 2.05 (CH_2), 16.63 (C), 28.11 (CH_3), 52.98 (CH_3), 57.75 (CH_3), 61.78 (C), 79.79 (C), 80.28 (CH), 110.01 (CH), 140.91 (C), 154.02 (C), 160.7 (C), 171.14 (C); IR (KBr): $\tilde{\nu} = 3426$, 3119, 2980, 2944, 1722, 1623, 1581, 1493, 1262, 1164, 1004, 962, 832, 777, 730, 666, 542 cm^{-1}; LR-MS (EI): $m/z = 325.1$ (6) [M^+], 266.1 (10), 210.0 (55), 166.0 (20), 114.0 (28), 57.1 (100); HR-MS (ESI): $m/z = 326.1599$, calcd. for $C_{16}H_{24}NO_6^+$ [M + H^+]: 326.1598.

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