Convenient Synthesis of 3,4-methano-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid and Its Derivatives as Doubly Constrained Nonproteinogenic Amino Acid Derivatives

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Three strategies for the synthesis of the novel, doubly constrained, 3,4-methano-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid and its derivatives were evaluated. Only cyclocondensation of the mono(triphenyl)phosphonium salt derived from 1,2-bis(bromomethyl)benzene with *N*-alkoxycarbonyloxamates in 1,2-dimethoxyethane in the presence of potassium carbonate and subsequent cyclopropanation with dimethylsulfoxonium methylide in dimethyl sulfoxide furnished suitable O- and N-protected derivatives of 3,4-methano-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid in a convenient way. A detailed 2D DQF-COSY and 2D NOESY NMR analysis of the rotational isomerism of the latter bicyclic amino acid derivatives was performed. Various O- and N-protection protocols were worked out to afford access to a whole range of new derivatives of the title amino acid, suitable for peptide synthesis.

Introduction

There is currently considerable interest in the synthesis of peptides incorporating conformational constraints. These peptidomimetics often provide both enhanced biological activities and greater proteolytic stabilities.[1] The concept of the topographical design of peptide ligands with improved selectivity and metabolic stability was introduced by Hruby et al.[2] A particular three-dimensional arrangement of the peptide side chains is obtained by appropriately constraining, biasing or fixing the side-chain conformers. This approach requires the availability of a set of amino acids with complementary conformational properties.

The phenylalanine side chain has been constrained by the use of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid **1** (Tic), 2-aminotetraline-2-carboxylic acid **2** (Atc), 2-aminoindane-2-carboxylic acid **3** (Aic),[3] and 4-amino-1,2,4,5-tetrahydrobenzo[*c*]azepin-3-one **4** (Aba)[4] (Figure 1). Tic has been successfully used in the synthesis of

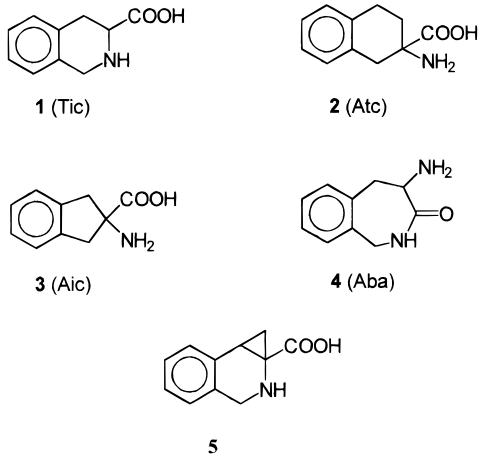

Figure 1. Depiction of various nonproteinogenic amino acids obtained by constraining the side chain in phenylalanine: 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid **1** (Tic), 2-aminotetraline-2-carboxylic acid **2** (Atc), 2-aminoindane-2-carboxylic acid **3** (Aic), and 4-amino-1,2,4,5-tetrahydrobenzo-[*c*]azepin-3-one **4** (Aba), and the newly synthesized 3,4-methano-Tic **5**.

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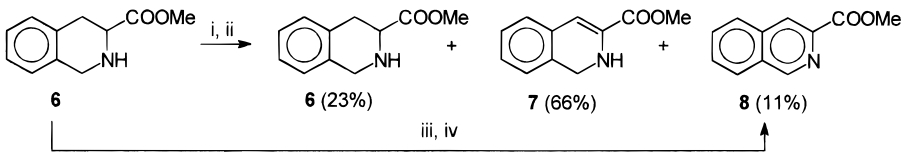
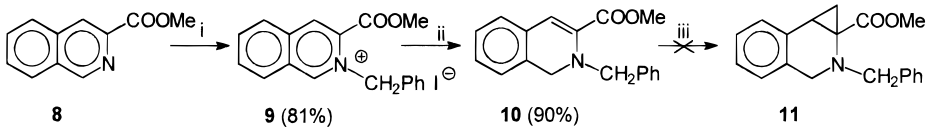
Scheme 1[a]



[a] Key: (i) 1 equiv of NCS, diethyl ether, 0 °C to rt, 1 h; (ii) 1.2 equiv of Et_3N, diethyl ether, 0 °C to rt, 2 h; (iii) 2 equiv of NCS, diethyl ether, 0 °C to rt, 1 h; (iv) 2 equiv of Et_3N, diethyl ether, 0 °C to reflux, 20 h, 90%.

Scheme 2[a]



[a] Key: (i) 5 equiv of $PhCH_2I$, acetone, rt, 4 d; (ii) 8 equiv of $NaBH_4$, ethanol, rt, 1 h; (iii) $Me_3SO^+I^-$, NaH, DMSO, rt, 1 d or CH_2N_2, diethyl ether, $Pd(OAc)_2$, rt, 2 h.

bradykinin antagonists,[5] ACE inhibitors,[6] renin inhibitors[7] and opioid antagonists.[8−10] The incorporation of a Tic residue at an internal position in a peptide has been shown to result in a gauche (+) conformation for its side chain, whereas a Tic residue at the N-terminal position takes up a gauche (−) conformation.[2] As a result of its secondary amine structure, however, the Tic residue causes a cis/trans conformational equilibrium around the peptide bond, which complicates the interpretation of the conformational data. For instance, for the δ-opioid antagonist Tyr-Tic-Phe-Phe-OH (TIPP-OH), models for the receptor-bound conformation having either a trans or a cis Tyr-Tic peptide bond have been proposed.[11]

Cyclopropane amino acids or methano amino acids are of broad interest as biological probes, enzyme inhibitors, and conformationally constrained analogues of native amino acids.[12] Since the cyclopropane ring introduces a steric constraint into the amino acid, changes in chemical reactivity of the functional groups result. The cyclopropane ring exhibits a certain "unsaturated character", which results in a restriction of the torsion angles about the $C_\alpha-C{=}O$ bond to small values, due to conjugation of the carbonyl group with the ring. More specifically, the 1-aminocyclopropane carboxylic acid residue has been shown to exhibit a marked preference for the conformational space $\phi, \psi = \pm 90°, 0°$, i.e., for the position $i + 2$ of type I and type II β-turns.[13] For methano methionine, a preference for the γ-turn conformation has been observed.[14] In peptides, significant changes are caused in the conformation, which in turn may affect the ability of the peptide to fit a receptor.[12] It is interesting, therefore, to synthesize the hitherto unknown 3,4-methano-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid **5** (Figure 1) and its derivatives as a combination of a sterically constrained 1-aminocyclopropane-1-carboxylic acid and a 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, which might reduce the structural promiscuity present in each of them separately.

To synthesize the title compound **5**, two important problems had to be solved. First, it was necessary to prepare a 1,2-dihydroisoquinoline-3-carboxylic acid derivative, e.g., **7** (Scheme 1), which has often been considered to be a very unstable species. Second, the cyclopropanation of a 1,2-dihydroisoquinoline moiety, bearing an electron-attracting carboxyl function adjacent to the double bond, should be accomplished, with subsequent focus on a suitable deprotection protocol, leaving the cyclopropane unit untouched. Many of the substituted 1,2-dihydroisoquinolines are rather difficult to prepare and to purify.[15−17] Common methods for the synthesis can be classified in two approaches: (1) reduction of isoquinolines or isoquinolinium salts,[15] and (2) construction of the 1,2-dihydroisoquinoline skeleton either by cyclization of *N*-benzylaminoacetaldehyde dialkyl acetals[15,16] or by Wittig reaction of *N*-alkoxycarbonylcarbamates with ω-halogenated phosphorus ylides.[17] Ethyl 1,2-dihydro isoquinoline-3-carboxylate was previously prepared in six steps in an overall yield of 20% by intramolecular 1,3-dipolar cycloaddition, but the compound proved unstable in air.[18]

The present paper describes a facile synthesis of 3,4-methano-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid **5** via cyclopropanation of the corresponding N- and O-protected 1,2-dihydroisoquinoline derivatives **17a**,**b** with dimethylsulfoxonium methylide (Schemes 3 and 4). The N-protected dihydro compounds **17a**−**c** were prepared via Wittig reaction of the phosphorus ylide of **16** with N-alkoxycarbonyloxamates **14a**−**c** and subsequent ring closure (Scheme 3).[17]

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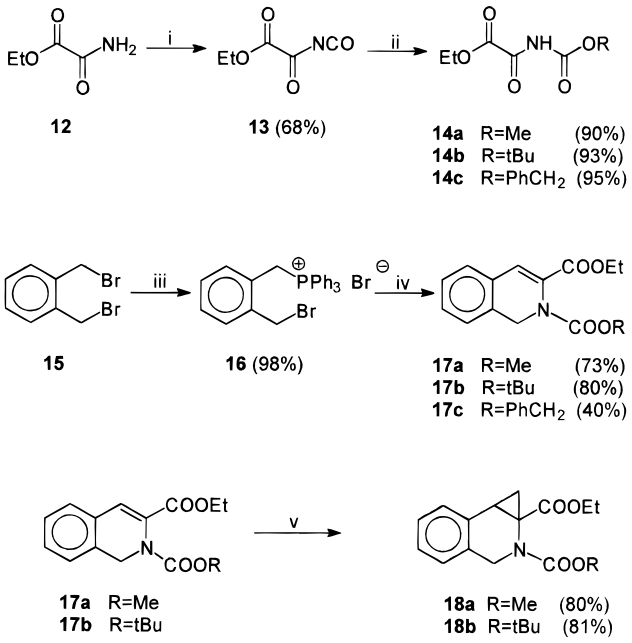
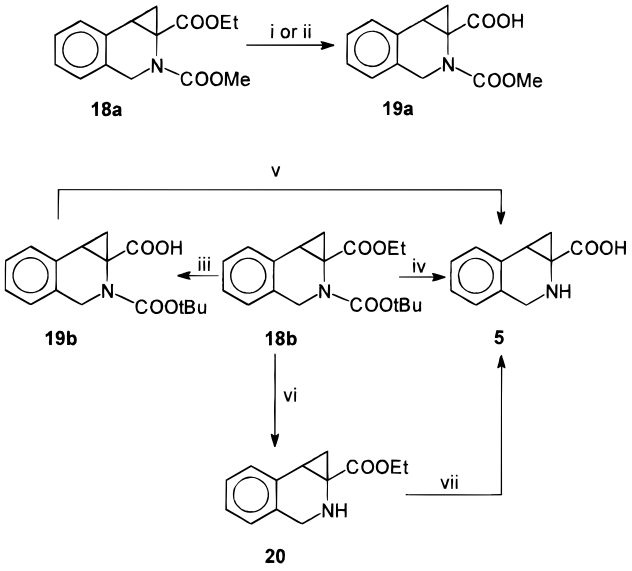
Scheme 3[a]



[a] Key: (i) 1.1 equiv of $(COCl)_2$, 1,2-dichloroethane, Δ, 16 h; (ii) 2 equiv of ROH, diethyl ether, 0 °C to rt, 2−4 h; (iii) 2.2 equiv of PPh_3, benzene, Δ, 8 h; (iv) 1.5 equiv of **14a**−**c**, DME, 2 equiv of K_2CO_3, Δ, 8 h; (v) 1.34 equiv of $Me_3SO^+I^-$, 1.28 equiv of NaH, DMSO, rt, 1 d.

Scheme 4[a]



[a] Key: (i) 10 equiv of 6 N HCl, Δ, 1 d, 57%; (ii) 1.5 equiv of 1 N NaOH, rt, 1 d, 91%; (iii) 5 equiv of 4 N NaOH, Δ, 1 d, 95%; (iv) 10 equiv of 6 N HCl, Δ, 1 d, then propylene oxide, EtOH, rt, 30 min, 69%; (v) HCl, diethyl ether, rt, 30 min, then propylene oxide, EtOH, rt, 30 min, 86%; (vi) 12 N HCl, EtOAc, rt, 30 min, $NaHCO_3$ 92% or HCl, diethyl ether, rt, 30 min, 90% (hydrochloride); (vii) 2.5 equiv of 1 N NaOH, rt, 1 d, ion exchange, 42%.

Results and Discussion

The first approach to the preparation of methyl 1,2-dihydroisoquinoline-3-carboxylate **7** was the selective oxidation of Tic methyl ester[19] **6** by means of N-chlorination with *N*-chlorosuccinimide (NCS) and subsequent dehydrochlorination with triethylamine (Scheme 1). The N-chlorination of Tic methyl ester **6** in dry diethyl ether with 1 equiv of NCS at 0 °C to room temperature for 1 h proceeded well, as monitored by TLC. The corresponding *N*-chloro compound was fairly stable in solution under an inert atmosphere, but all attempts to isolate it resulted in significant decomposition. The addition of 1.2 equiv of triethylamine to the reaction mixture of the *N*-chloro compound at 0 °C and further stirring at room temperature for 2 h resulted in a complex mixture of which the ^1H NMR spectrum showed the presence of starting material **6** (23%), 1,2-dihydroisoquinoline derivative **7** (66%), and the aromatized isoquinoline derivative **8** (11%). When 2 equiv of NCS and 2 equiv of triethylamine were used and the reaction was run for 20 h under reflux, a complete conversion to methyl isoquinoline-3-carboxylate **8** was attained. Any attempt to produce an N-protected derivative of **7** by reaction of the crude reaction mixture (containing 66% of dihydro compound **7**) with methyl chloroformate, di-*tert*-butyl dicarbonate, or acetic anhydride failed.

An alternative route was evaluated by reduction of a functionalized quaternary isoquinolinium salt **9** (Scheme 2). Reduction of the *N*-methyl quaternary salt derived from ethyl isoquinoline-3-carboxylate proceeded in a facile way with $NaBH_4$ in ethanol.[18] In an analogous manner, the *N*-benzyl quaternary salt **9** was prepared in 81% yield by reaction with 5 equiv of benzyl iodide in acetone at room temperature for 4 days in the dark. Benzyl iodide was prepared from benzyl bromide with NaI in acetone at room temperature for 1 day. Reduction of compound **9** with an excess of $NaBH_4$ in ethanol at room temperature for 1 h took place quantitatively, as monitored by TLC. The isolated dihydro compound **10** proved to be quite unstable in air. However, it was possible to analyze it by ^1H and ^{13}C NMR, IR, and mass spectroscopy. Attempts to produce compound **11** via the cyclopropanation of methyl 2-benzyl-1,2-dihydroisoquinoline-3-carboxylate **10** with diazomethane and dimethylsulfoxonium methylide failed (Scheme 2).

The third attempted approach consisted in building up the skeleton of the 1,2-dihydroisoquinoline-3-carboxylic acid derivatives, following the synthesis of 2-methoxycarbonyl-1,2-dihydroisoquinoline-3-carboxylic acid ester **17a** in a Wittig reaction and ring closure[17] (Scheme 3). Ethoxycarbonylcarbonyl isocyanate **13** was prepared by a known method[21] from ethyl oxamate **12** with a slight excess of oxalyl chloride in 1,2-dichloroethane under reflux for 16 h. The functionalized isocyanate **13** reacted with the corresponding dry alcohols in diethyl ether at 0 °C to room temperature to afford the 2-alkoxycarbonyloxamates **14a**−**c** in 90−95% yield. The monophosphonium salt **16** was prepared from 1,2-bis(bromomethyl)benzene **15** and an excess of triphenylphosphine in benzene under reflux for 8 h according to a literature method.[22] Ethyl 2-alkoxycarbonyl-1,2-dihydroisoquinoline-3-carboxylates **17a**−**c** were prepared in one step from an excess of oxamate **14a**−**c** and the phosphorus ylide derived of **16** in 1,2-dimethoxyethane at 85 °C for

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8 h[17] (Scheme 3). The reaction products **17a**−**c** were purified by Kugelrohr distillation and/or silica gel chromatography. In contrast with the N-unprotected or *N*-benzyl-protected methyl 1,2-dihydroisoquinoline-3-carboxylates[18] **7** or **10**, these urethanes proved stable for months at room temperature. During the synthesis, minor amounts of numerous unstable compounds were formed, as detected by TLC. These impurities decomposed during standing for a few days at room temperature, which facilitated purification of the main compounds **17a**−**c**. Thus, **17a** was purified by Kugelrohr distillation and silica gel chromatography, while **17b** could not be distilled, but column chromatography resulted in a pure crystalline compound in high yield. In contrast, the 2-benzyloxycarbonyl derivative **17c** was formed in much lower yield, with many side-products. Most of the contaminants were separated by silica gel chromatography (30% diethyl ether/hexane) but the purified product (yield 40%) was still a mixture of two compounds (according to ^{1}H NMR), displaying a single R_f value in any solvent combination, and it was therefore not characterized further, nor transformed into the corresponding 3,4-methano-Tic.

In the ^{1}H NMR spectra of compounds **17a**−**c**, the δ value of the olefinic hydrogen at position 4 is very characteristic, close to the aromatic region ($\delta \sim 7$ ppm). However, a literature report published a much lower δ value.[18] The chemical shift of the hydrogen at position 4 of ethyl 1,2-dihydroisoquinoline-3-carboxylate was assigned to 5.15 ppm in $CDCl_3$.[18] We have located this hydrogen signal at 6.41 ppm for compound **7**, 7.07 ppm for **17a** and 6.96 ppm for **17b**, all in $CDCl_3$.

Cyclopropanation of ethyl 2-alkoxycarbonyl-1,2-dihydroisoquinoline-3-carboxylate **17a**,**b** with diazomethane failed when CuCl[23] or Pd(II) acetate[24] catalysis was applied. Dimethylsulfoxonium methylide[25] can cyclopropanate compounds which are susceptible to Michael addition. Enhancement of the withdrawal of electron density from the C−C double bond facilitates the reaction.[26] Dimethylsulfoxonium methylide proved a very efficient cyclopropanating agent for compounds **17a**,**b** (Scheme 3). Using a literature procedure[27] to generate the ylide from trimethylsulfoxonium iodide with NaH in DMSO, the cyclopropanation reaction with compounds **17a**,**b** was monitored by ^{1}H NMR spectroscopy (disappearance of the olefinic H-4 signal). Quantitative reaction took place during 24 h at room-temperature yielding **17a**,**b** (Scheme 3). A higher temperature, e.g., 60 °C, did not reduce the reaction time significantly.

The N-protected methano amino acid derivatives **18a**,**b** exist as mixtures of two conformational isomers, as indicated by their ^{1}H NMR spectra. The ratio of the two conformers was 7:3 for **18a** and 8:2 for **18b**. A complete assignment of all the signals of the major and the minor isomers of **18a** was performed at 500 MHz, using 2D DQF-COSY and 2D NOESY spectra recorded at 40 °C. Clear proof of the conformational isomerism was obtained from a temperature study between 30 and 80 °C, which revealed a gradual broadening and finally a coalescence of the major with the minor signals. Moreover, in the 2D NOESY spectra at 40 °C, intense exchange cross-peaks were observed between the major and minor resonances of the CH_2 protons at C-1. Since the largest chemical shift differences between the major and the minor conformers are observed for the CH_2 protons at C-1 and for the methyl protons of the carbamate function, the isomerism can be attributed to a slow rotation about the urethane amide bond, as expected.

Because of the steric constraint caused by the cyclopropane ring, a decreased chemical reactivity of the functional groups is anticipated.[15] Hydrolysis of the ethyl ester **18a** to carboxylic acid **19a** with 1 N NaOH proceeded at room temperature during 1 day, but the sterically more hindered **18b** reacted only under more drastic conditions toward **19b**: 5 equiv of 4 N NaOH at 100 °C for 1 day (Scheme 4). Under these conditions, **18a** decomposed completely to give numerous ninhydrine-positive spots on TLC. With 6 N HCl under reflux for 1 day, **18a** was converted into N-protected amino acid **19a**, together with some decomposition products. The Boc protecting group of **18b** and **19b** was removed conventionally with trifluoroacetic acid,[28] with EtOAc/aqueous 12 N HCl[29] or preferably with HCl/diethyl ether (17 g of dry HCl in 100 mL of diethyl ether) because the hydrochlorides of **20** and **5** were easily handled, in contrast to the corresponding TFA salts. The hydrochloride salt of amino acid **5** was readily prepared in 71% yield from the fully protected compound in one step by hydrolysis with an excess of 6 N HCl at 100 °C for 1 day. The new free amino acid **5** was prepared in 97% yield from its hydrochloride with an excess of propylene oxide in ethanol[30] at room temperature for 30 min, this completing the first synthesis of this doubly sterically constrained bicyclic amino acid.

Experimental Section

Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra, including DEPT[31] spectra, were recorded at 270 and 67.8 MHz, respectively, except for the NMR temperature study and the 2D DQF-COSY[32] and 2D NOESY[33] spectra, which were recorded at 500 MHz on a spectrometer equipped with a digital lock system and an SGI O2 system for spectrometer control. All 2D spectra were recorded in the phase-sensitive mode, using TPPI.[34] The total recycling delay was 2 s. Processing consisted in multiplication with a π/2-shifted squared sinebell in F_2 and F_1, followed by zero-filling along F_1, yielding a final 2K by 2K complex data matrix after Fourier transformation and polynomial baseline correction. For the DQF-COSY[32] and NOESY[33] spectra, 512 FIDs of 4096 data points, 32 scans each were recorded. For the NOESY[33] spectrums, a mixing time of 500 ms was used. IR spectra were obtained on a Perkin-Elmer spectrometer. Mass spectra were recorded at 70 eV. HRMS spectra were recorded on a Finnigan 8200 instrument with

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an electron impact ionization technique (70 eV). Column chromatography was performed on silica gel (0.035−0.07 mm) with different solvent combinations, via initial TLC analysis. TLC solvent systems: A: $CHCl_3$/acetone = 9/1, B: $CHCl_3$/MeOH = 9/1, C: diethyl ether/hexane = 4/6, D: diethyl ether/hexane = 1/1, E: *n*-BuOH/AcOH/H_2O = 4/1/1.

Ethyl oxamate and 1,2-bis(bromomethyl)benzene were commercially available products and were used as received.

2-Benzyl-3-methoxycarbonylisoquinolinium Iodide 9. A solution of 2.24 g (12 mmol) of methyl isoquinoline-3-carboxylate[19] **8** and 13.08 g (60 mmol) of benzyl iodide in 5 mL of dry acetone was kept in the dark at room temperature for 4 days. The reaction could be monitored by TLC. Dry diethyl ether (50 mL) was added to the deep-brown solution in order to precipitate the oily quaternary salt. Trituration several times with diethyl ether resulted in a solid material, which was recrystallized from methanol/diethyl ether to afford 3.92 g (81%) of light-brown crystals: R_f 0.1 (A); mp 112−114 °C; ^{1}H NMR ($CDCl_3$) δ 4.01 (3H, s, OCH_3), 6.62 (2H, s, Ph-CH_2), 7.35−7.46 (5H, m, *Ph*-CH_2), 8.1−8.26 (3H, m, aromatic H), 8.81 (1H, s, aromatic H), 9.07 (1H, s, H-4), 11.74 (1H, s, H-1);^{13}C NMR ($CDCl_3$) δ 54.7 (O−CH_3), 62.1 (Ph-CH_2), 128.0, 132.7, 133.0 (aromatic quaternary C), 128.7, 129.3, 129.7, 131.8, 133.6 (aromatic CH), 136.8 (C-3), 138.8 (C-4), 153.7 (C-1), 160.7 (COO); IR (KBr, cm^{-1}) 1755 (C=O).

Methyl 2-Benzyl-1,2-dihydroisoquinoline-3-carboxylate 10. To a stirred suspension of 1.22 g (3 mmol) of quaternary salt **9** in 30 mL of ethanol was added 0.23 g (6 mmol) of $NaBH_4$ in small portions under nitrogen at 0 °C. The as yet undissolved portion of the salt dissolved immediately, and the brown color changed to yellow. Stirring was continued for 1 h at room temperature. TLC analysis revealed a quantitative reaction and a single product. The reaction mixture was evaporated to dryness at 30 °C in vacuo, 10 mL of water was added to the residue, and the solution was extracted with diethyl ether. The combined extracts were washed with 10 mL of water and dried over $MgSO_4$. Evaporation in vacuo afforded 0.75 g (90%) of a pale-yellow oil, which was immediately subjected to analysis: R_f 0.9 (A); ^{1}H NMR ($CDCl_3$) δ 3.83 (3H, s, O−CH_3), 4.13 (2H, s, Ph-CH_2 or H-1), 4.15 (2H, s, Ph-CH_2 or H-1), 6.99 (1H, s, H-4), 7.17−7.39 (9H, m, aromatic H); ^{13}C NMR ($CDCl_3$) δ 51.1 and 55.1 (Ph-CH_2 and C-1), 52.1 (O−CH_3) 118.5 (C-4), 125.1, 125.5, 127.2, 127.4, 128.3, 128.4, 128.6 (aromatic CH), 129.6, 131.8, 137.8, 138.5 (aromatic quaternary C and C-3), 165.4 (COO); IR (NaCl, cm^{-1}) 1711 (C=O), 1600 (C=C); MS *m*/*z* (rel int) 279 (14, M^+), 91 (100).

Ethoxycarbonylcarbonyl Isocyanate 13. This compound was prepared analogously to a literature method.[21] A total of 58.5 g (0.5 mol) of ethyl oxamate **12** was suspended in 500 mL of dry 1,2-dichloroethane, and 69.8 g (0.55 mol) of oxalyl chloride was added. The resulting mixture was refluxed for 16 h, moisture being rigorously excluded. The solvent was distilled off at normal pressure, using a 30 cm Vigreux column, and the residue was further distilled under reduced pressure without a column, to afford 48.8 g (68%) of compound **13**: bp 78 °C (10 Torr); ^{1}H NMR ($CDCl_3$) δ 1.44 (3H, t, J = 7.1 Hz, CH_3−CH_2), 4.46 (2H, q, J = 7.1 Hz, O−CH_2); ^{13}C NMR ($CDCl_3$) δ 13.9 (CH_3−CH_2), 65.6 (O−CH_2), 134.3 (NCO), 157.6, 158.1, (2 × C=O); IR (NaCl, cm^{-1}) 1715, 1737, 1780 (C=O), 2239 (N=C=O); MS *m*/*z* (rel int) 142 (4, $M^+ - 1$), 91 (100).

General Procedure for Ethyl *N*-Alkoxycarbonyloxamates 14a−c. A solution of 7.15 g (0.05 mol) of ethoxycarbonylcarbonyl isocyanate **13** in 50 mL of dry diethyl ether was cooled in an ice bath. To this stirred solution, 0.1 mol of the corresponding dry alcohol in 10 mL of dry ether was added dropwise over a period of 15 min. The reaction mixture was stirred further for 2−4 h at room temperature. Evaporation of the solvent in vacuo afforded oily or crystalline products which were generally sufficiently pure (>95%) for the next step.

Ethyl *N*-Methoxycarbonyloxamate 14a. During the addition of methanol, this compound partially crystallized: yield 90%; purity 100% (by ^{1}H NMR); mp 90−92 °C (diethyl ether), slightly hygroscopic; R_f 0.46 (A); ^{1}H NMR ($CDCl_3$) δ 1.41 (3H, t, J = 7.1 Hz, CH_3−CH_2), 3.86 (3H, s, O−CH_3), 4.41 (2H, q, J = 7.1 Hz, O−CH_2), 8.86 (1H, br s, NH); ^{13}C NMR ($CDCl_3$) δ 13.9 (CH_3−CH_2), 53.6 (O−CH_3), 64.0 (O−CH_2), 150.9, 155.4, 159.4 (3 × C=O); IR (KBr, cm^{-1}) 1710, 1738, 1788 (C=O); MS *m*/*z* (rel int) 175(0.3, M^+), 59 (100); HRMS analysis $C_6H_9NO_5$ requires M^+ 175.04807, found M^+ 175.04803.

Ethyl *N*-*tert*-butoxycarbonyloxamate 14b: oil; yield 93%; R_f 0.66 (A); ^{1}H NMR ($CDCl_3$) δ 1.40 (3H, t, J = 7.1 Hz, CH_3-CH_2), 1.52 (9H, s, $((CH_3)_3)$), 4.39 (2H, q, J = 7.1 Hz, OCH_2), 9.13 (1H, br s, NH); ^{13}C NMR ($CDCl_3$) δ 13.9 (CH_3-CH_2), 27.9 ($(CH_3)_3$), 63.5 (OCH_2), 83.6 ($(CH_3)_3$ *C*-O), 149.3, 155.6, 159.8 (3 × C=O); IR (NaCl, cm^{-1}) 1710, 1739, 1786 (C=O); MS *m*/*z* (rel int), no M^+, 57(100). Anal. Calcd for $C_9H_{15}NO_5$: C, 49.76; H, 6.96; N, 6.45. Found: C, 49.98; H, 6.79; N, 6.49.

Ethyl *N*-Benzyloxycarbonyloxamate 14c. A total of 1.1 equiv of benzyl alcohol was used, with stirring for 4 h at room temperature, giving an oil, yield 95% (containing about 5% of benzyl alcohol), R_f 0.62 (A). Compound **14c** is quite unstable, and no satisfactory elemental analysis or HRMS data could be obtained: ^{1}H NMR ($CDCl_3$) δ 1.38 (3H, t, J = 7.2 Hz, CH_3-CH_2), 4.37 (2H, q, J = 7.2 Hz, OCH_2), 5.24 (2H, s, Ph-CH_2), 7.33−7.42 (5H, m, *Ph*-CH_2), 8.92 (1H, br s, NH); ^{13}C NMR ($CDCl_3$) δ 13.8 (CH_3-CH_2), 63.9 (OCH_2), 68.4 (Ph-CH_2), 128.4, 128.6, 128.7, 128.8, 128.9 (aromatic CH), 134.6 (aromatic quaternary C) 150.2, 155.5, 159.3 (3 × C=O); IR (NaCl, cm^{-1}) 1710, 1732, 1790 (C=O); MS *m*/*z* (rel int) 251 (3, M^+), 145 (81), 91 (100).

2-(Bromomethyl)benzyltriphenylphosphonium Bromide 16. This phosphonium salt was prepared according to a literature procedure[22] from 1,2-bis(bromomethyl)benzene **15** and triphenylphosphine in benzene under reflux during 8 h: yield 98%; mp 238−240 °C (lit.[22] mp 253−256 °C, yield 92%). The crude product was used for the next step. A purified sample, still containing 3−4% of the bis-phosphonium salt (^{1}H NMR) was obtained by recrystallization from ethanol/diethyl ether: ^{1}H NMR ($CDCl_3$) δ 3.92 (2H, s, CH_2Br), 5.39 (2H, d, $^2J_{HP}$ =14.2 Hz, CH_2-P), 7.09−7.28 and 7.64−7.86 (19H, m, aromatic H); ^{31}P NMR ($CDCl_3$ 109 MHz, ref 85% H_3PO_4) δ 22.31. Anal. Calcd for $C_{26}H_{23}Br_2P$: C, 59.34; H, 4.41. Found: C, 59.99; H, 4.46.

Ethyl 2-Alkoxycarbonyl-1,2-dihydroisoquinoline-3-carboxylate 17a−c. These N-protected enaminoesters were prepared according to a general literature method.[17] A mixture of 20 mmol (1.5 equiv) of carbamate **14a−c**, 7.02 g (13.3 mmol) of phosphonium salt **16** and 2.7 g (26.6 mmol) of dry K_2CO_3 in 50 mL of dry 1,2-dimethoxyethane was stirred at 85 °C for 8 h under a nitrogen atmosphere. After the reaction mixture was cooled, 50 mL of water was added, and the solution was extracted with dichloromethane (3 × 40 mL) and dried over $MgSO_4$. The solvent was evaporated off at reduced pressure, and the residue was extracted with diethyl ether. The ethereal solution was cooled in order to remove triphenylphosphine oxide by crystallization. After filtration and evaporation of the solvent, the crude products were purified by Kugelrohr distillation and/or silica gel chromatography.

Ethyl 2-Methoxycarbonyl-1,2-dihydroisoquinoline-3-carboxylate 17a. The crude product was purified by Kugelrohr distillation: bp 120−130 °C (0.05 Torr) (lit.[17] bp 135 °C (1.3 Torr, yield 61%), followed by silica gel chromatography (40% diethyl ether/hexane); colorless oil; yield 73%; R_f 0.44 (D); ^{1}H NMR ($CDCl_3$) δ 1.35 (3H, t, J = 7.1 Hz, CH_3-CH_2), 3.71 (3H, s, OCH_3), 4.31 (2H, q, J = 7.1 Hz, O−CH_2), 4.81 (2H, s, H-1), 7.07 (1H, s, H-4), 7.14−7.31 (4H, m, aromatic H); ^{13}C NMR ($CDCl_3$) δ 14.3 (CH_3-CH_2), 47.0 (C-1), 53.2 (OCH_3), 61.3 (OCH_2), 123.4, 125.3, 127.0, 127.9, 129.6 (aromatic CH and C-4), 130.0, 130.6, 132.8 (aromatic quaternary C and C-3), 154.1 (NCOO), 163.7 (C-*C*OO); IR (NaCl, cm^{-1}) 1622 (C=C), 1710, 1760 (C=O); MS *m*/*z* (rel int) 261 (13, M^+), 132 (100).

Ethyl 2-*tert*-Butoxycarbonyl-1,2-dihydroisoquinoline-3-carboxylate 17b. The oily crude product was purified by silica gel chromatography (20% diethyl ether/hexane), affording a crystalline product: mp 85−86 °C (MeOH/H_2O); yield 80%; R_f 0.58 (C); ^{1}H NMR ($CDCl_3$) δ 1.38 (3H, t, J = 7.2 Hz, CH_3-CH_2), 1.43 (9H, s, $(CH_3)_3$), 4.31 (2H, q, J = 7.2 Hz, OCH_2), 4.80 (2H, s, H-1), 6.96 (1H, s, H-4), 7.18−7.29 (4H, m, aromatic

H); ^{13}C NMR ($CDCl_3$) δ 14.3 (CH_3−CH_2), 28.0 (($CH_3)_3$), 46.5 (C-1), 61.3 (O−CH_2), 81.8 (($CH_3)_3$ *C*), 122.1 (C-4), 125.4, 126.8, 127.7, 129.3 (aromatic CH), 130.2, 131.1, 132.9 (aromatic quaternary C and C-3), 152.3 (NCOO), 164.2 (C-*C*OO); IR (KBr, cm^{-1}) 1630 (C═C), 1709, 1720 (C═O); MS *m*/*z* (rel int) 303 (9, M$^+$), 202 (100); HRMS analysis $C_{17}H_{21}NO_4$ requires M$^+$ 303.14705. found M$^+$ 303.14747. Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31, H, 6.98, N, 4.62; found. C, 67.77, H, 7.35, N,5.02.

General Procedure for Ethyl 2-Alkoxycarbonyl-3,4-methano-1,2,3,4-tetrahydroisoquinoline-3-carboxylate 18a,b. Sodium hydride (0.31 g, 12.8 mmol, 0.51 g of 60% oily dispersion) was washed three times with hexane. After decantation, the remaining hexane was removed under vacuum. The vacuum was released to a dry nitrogen source, and 2.95 g (13.4 mmol) of dry trimethylsulfoxonium iodide was added. The mixture was stirred, and 10 mL of dry dimethyl sulfoxide (distilled over CaH_2) was added dropwise. A vigorous evolution of hydrogen ensued, which ceased after 15−20 min. After additional stirring for 15 min, 10 mmol of the dihydroisoquinoline compound **17a**,**b** in 10 mL of dry dimethyl sulfoxide was added at room temperature and stirring was continued for 1 day. The reaction could be monitored by ^{1}H NMR. The reaction mixture was poured into 50 mL of cold water and extracted with diethyl ether (3 × 60 mL). The combined extracts were washed with water, dried over $MgSO_4$ and evaporated in vacuo, giving an oily or crystalline crude product. The compounds were obtained as mixtures of rotational isomers, as shown by their ^{1}H and ^{13}C NMR spectra. The NMR data on the minor isomer (if resolved) are given between square brackets. In most cases, the *J* values for the minor isomers in the ^{1}H NMR spectra were exactly the same as those for the major isomers, unless otherwise indicated.

Ethyl 2-Methoxycarbonyl-3,4-methano-1,2,3,4-tetrahydroisoquinoline-3-carboxylate 18a: an oil, which solidified on standing; yield 80%; mp 72−73 °C (diethyl ether/hexane); R_f 0.46 (D); ^{1}H NMR ($CDCl_3$) δ 1.13 [1.19] (1H, dd, J = 4.5, 7.1 Hz, cyclopropane CH_2) 1.27 (3H, t, J = 7.1 Hz, CH_3-CH_2), 2.21 [2.28] (1H, dd, J = 4.6, 9.9 Hz, cyclopropane CH_2), 2.69 [2.70] (1H, dd, J = 6.9, 9.9 Hz, H-4), 3.72 [3.74] (3H, s, OCH_3), 4.1−4.34 (3H, m, OCH_2 and one H-1), 4.86 [4.72] (1H, d, J = 15.8 Hz, one H-1), 7.8−7.39 (4H, m, aromatic H); ^{13}C NMR ($CDCl_3$) δ 14.3 [14.2] (CH_3-CH_2), 27.0 [26.5] (C-4), 28.1 [27.6] (cyclopropane CH_2), 39.9 [40.3] (C-3) 44.4 [44.9] (C-1), 59.5 [59.8] (OCH_3), 61.4 (O−CH_2), 126.1 [125.9], 126.6, [126.4] 127.4 [127.6], 129.0 [129.2] (aromatic CH), 133.0 [133.4], 134.9 (aromatic quaternary C), 156.7 [155.7] (NCOO), 171.8 [171.4] (C-*C*OO); IR (NaCl, cm^{-1}) 1710, 1740 (C═O); MS *m*/*z* (rel int) 275 (9, M$^+$), 202 (80), 115 (100); HRMS analysis $C_{15}H_{17}NO_4$ requires M$^+$ 275.11575, found M$^+$ 275.11531. Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.23; H, 6.63; N, 5.44.

Ethyl 2-*tert*-butoxycarbonyl-3,4-methano-1,2,3,4-tetrahydroisoquinoline-3-carboxylate 18b: yield 81%; mp 97−98 °C (MeOH/H_2O); R_f 0.59 (C); ^{1}H NMR ($CDCl_3$) δ 1.11 [1.17] (1H, dd, J = 4.6, 7.1 Hz, cyclopropane CH_2), 1.30 [1.27] (3H, t, J = 7.1 Hz, CH_3-CH_2), 1.44 [1.49] (3H, s, $(CH_3)_3$), 2.19 [2.27] (1H, dd, J = 4.6, 9.9 Hz, cyclopropane CH_2), 2.68 [2.67] (1H, dd, J = 7.1, 9.8 Hz, H-4), 4.13 (1H, d, J = 15.8 Hz, H-1), 4.23 (3H, Hz, q, J = 7.1, OCH_2) 4.82 [4.65] (1H, d, J = 15.8 Hz, H-1), 7.12−7.42 (4H, m, aromatic H); ^{13}C NMR ($CDCl_3$) δ 14.4 [14.23] (CH_3CH_2), 27.7 [26.5] (C-4), 28.1 [27.5] (cyclopropane CH_2), 28.4 (($CH_3)_3$), 40.0 (C-3), 43.5 [45.2] (C-1), 61.3 [61.2] (O−CH_2), 80.1 [80.5] (($CH_3)_3$C), 126.1, 127.3, 128.9, 133.2 [125.9, 126.5, 127.4, 129.1] (aromatic CH), 133.2, 135.2 [133.5, 135.3] (aromatic quaternary C), 155.0 [154.5] (NCOO), 172.3 [171.8] (CCOO); IR (KBr, cm^{-1}) 1705, 1730 (C═O); MS *m*/*z* (rel int) 317 (11, M$^+$), 217 (87), 144 (96); HRMS analysis $C_{18}H_{23}NO_4$ requires M$^+$ 317.16271, found M$^+$ 317.16278.

2-Methoxycarbonyl-3,4-methano-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid 19a. A. Hydrolysis with 1 N NaOH. To a solution of 0.55 g (2 mmol) of compound **18a** in 3 mL of methanol was added 3 mL (3 mmol) of 1 N NaOH, and the mixture was stirred at room temperature for 1 day. The hydrolysis could be monitored by TLC. The methanol was evaporated off at 40 °C in vacuo, and the cold aqueous solution was cautiously acidified with 2 N HCl. The resulting white precipitate was filtered off, washed with water, and dried to afford 0.45 g (91%) of compound **19a**: mp 199−200 °C (ethyl acetate/hexane); R_f 0.47 (B); ^{1}H NMR ($CDCl_3$) δ 1.24 [1.29] (1H, dd, J = 4.6, 6.9 Hz, cyclopropane CH_2), 2.26 [2.32] (1H, dd, J = 4.6, 9.9 Hz, cyclopropane CH_2), 2.81 (1H, dd, J = 7.3, 9.9 Hz, H-4), 3.75 [3.77] (3H, s, OCH_3), 4.18 [4.28] (1H, d, J = 15.8 Hz, H-1), 4.87 [4.73] (1H, d, J = 15.8 Hz, H-1) 7.11−7.41 (4H, m, aromatic H), 10.50 (1H, br s, COOH); ^{13}C NMR δ 27.7 [27.4] (C-4), 28.7 [28.2] (cyclopropane CH_2), 39.6 [39.9] (C-3), 44.3 [44.9] (C-1), 53.2 [53.1] (OCH_3), 126.2, 126.8, 127.5, 128.9 [125.9, 127.7, 129.1] (aromatic CH), 132.6, 134.7 [133.0, 134.6] (aromatic quaternary C), 156.7 [156.1] (NCOO), 178.1 [177.8] (C-*C*OO); IR (KBr, cm^{-1}) 1690, 1720 (C═O); MS *m*/*z* (rel int) 247 (32, M$^+$); HRMS analysis $C_{13}H_{13}NO_4$ requires M$^+$ 247.08446, found M$^+$ 247.08454.

B. Hydrolysis with 6 N HCl. 0.55 g (2 mmol) of compound **18a** was refluxed with 3.3 mL (20 mmol) of 6 N HCl for 1 day. The oily compound gradually solidified. The cooled suspension was filtered and the precipitate was washed with water and dried in vacuo to give 0.28 g (57%) of compound **19a**, mp 199 °C (ethyl acetate/hexane). TLC and all spectral data were identical to the data given above.

2-*tert*-Butoxycarbonyl-3,4-methano-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid 19b. To a solution of 0.64 g (2 mmol) of compound **18b** in 4 mL of 1,4-dioxane was added 2.5 mL (10 mmol) of 4 N NaOH, and the mixture stirred for 1 day at 100 °C. The hydrolysis could be checked by TLC. The reaction mixture was evaporated in vacuo to half its volume, and 5 mL of water was added to dissolve the solid mass. This aqueous solution was acidified with 10% aqueous citric acid, and the resulting white precipitate was filtered off, washed with water and dried in vacuo (alternatively, the precipitate could be extracted with 3 × 15 mL of ethyl acetate) to afford 0.55 g (95%) of compound **19b**: mp 196−198 °C dec (diethyl ether/hexane); R_f 0.61 (B); ^{1}H NMR ($CDCl_3$) δ 1.20 [1.25] (1H, dd, J = 4.5 Hz, J = 7.1 Hz, cyclopropane CH_2), 1.45 [1.49] (9H, s, $(CH_3)_3$), 2.23 [2.31], (1H, dd, J = 4.6, 9.9 Hz, cyclopropane CH_2), 2.79 (1H, dd, J = 7.3, 9.6 Hz, H-4), 4.13 [4.19] (1H, d, J = 15.8 Hz, H-1) 4.83 [4.66] (1H, d, J = 15.8 Hz, H-1), 7.14−7.39 (4H, m, aromatic H); ^{13}C NMR ($CDCl_3$) δ 27.8 [27.3] (C-4), 28.3 [28.2] (($CH_3)_3$), 28.6 (cyclopropane CH_2), 39.8 [39.7] (C-3), 43.5 [45.1] (C-1), 80.6 [81.0] (($CH_3)_3$−C), 126.3, 126.7, 127.3, 128.8 [126.0, 126.3, 127.5, 129.1] (aromatic CH), 133.1, 135.0 [132.8] (aromatic quaternary C), 155.1 [154.7] (NCOO), 178.7 [178.3] (C-*C*OO); IR (KBr, cm^{-1}) 1700, 1715 (C═O); MS *m*/*z* (rel int) 289 (2, M$^+$); HRMS analysis $C_{16}H_{19}NO_4$ requires M$^+$ 289.13141, found 289.13148.

Ethyl 3,4-Methano-1,2,3,4-tetrahydroisoquinoline-3-carboxylate 20. To a solution of 0.37 g (1 mmol) of compound **18b** in 10 mL of ethyl acetate was added 4 mL of 12 N HCl, and the mixture was stirred for 30 min at room temperature. The reaction mixture was next treated cautiously with 20 mL of saturated $NaHCO_3$ and additional solid $NaHCO_3$ until it became slightly basic. The organic layer was separated and the aqueous phase was extracted twice with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and evaporated in vacuo to afford 0.2 g (92%) of compound **20** as a colorless oil: R_f 0.63 (E); ^{1}H NMR ($CDCl_3$) δ 1.30 (3H, t, J = 7.3 Hz, CH_3-CH_2), 1.55 (1H, t, J = 5.9 Hz, cyclopropane CH_2), 1.80 (1H, dd, J = 5.8, 9.8 Hz, cyclopropane CH_2), 2.47 (1H, dd, J = 5.9, 9.9 Hz, H-4), 3.76, (1H, d, J = 16.0 Hz, H-1), 3.93 (1H, d, J = 16.0 Hz, H-1), 4.23 (2H, q, J = 7.3 Hz, OCH_2), 7.02−7.31 (4H, m, aromatic H); ^{13}C NMR ($CDCl_3$) δ 14.2 (CH_3-CH_2), 18.0 (cyclopropane CH_2), 23.7 (C-4), 43.9 (C-3), 44.9 (C-1), 61.3 (O−CH_2), 125.9, 126.0, 126.9, 128.4 (aromatic CH), 133.2, 134.7 (aromatic quaternary C), 173.3 (COO); IR (NaCl, cm^{-1}) 1717 (C═O), 3318 (NH); MS *m*/*z* (rel int) 217 (22, M$^+$), 144 (100); HRMS analysis $C_{13}H_{15}NO_2$ requires M$^+$ 217.11028, found M$^+$ 217.11032. The hydrochloride of compound **20** was prepared in ether with HCl/diethyl ether from the base **20**, (98% yield) or from compound **18b** with HCl/diethyl ether (17 g of dry HCl in 100 mL of diethyl ether) at room temperature for 30 min (90% yield). Recrystallized from MeOH/diethyl ether: mp 166−167 °C; ^{1}H NMR ($CDCl_3$) δ 1.22 (3H, t, J =

7.1 Hz, CH_3CH_2), 1.97 (2H, d, J = 8,6 Hz, cyclopropane CH_2), 2.93 (1H, t, J = 8.6 Hz, H-4), 4.14 (1H, d, J = 15.5 Hz, H-1), 4.27 (2H, q, J = 7.1 Hz, O−CH_2), 4.31 (1H, d, J = 15.5 Hz, H-1), 7.17−7.41 (4H, m, aromatic H); ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_3-CH_2), 17.9 (cyclopropane CH_2), 23.2 (C-4), 41.6 (C-3), 43.1 (C-1), 62.9 (O−CH_2), 125.7, 131.2 (aromatic quaternary C), 127.5, 127.7, 128.6, 128.7 (aromatic CH), 168.1 (COO). Anal. Calcd for $C_{13}H_{16}NO_2Cl$: C, 61.54; H, 6.36; N, 5.52. Found: C, 61.60; H, 6.84; N, 5.16.

3,4-Methano-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid 5. Method A. A suspension of 0.289 g (1 mmol) of compound **19b** in 3 mL of dry CH_2Cl_2 was treated with 4 mL of HCl/diethyl ether (17 g of dry HCl in 100 mL of diethyl ether), and the mixture was stirred for 30 min at room temperature. The reaction mixture was next evaporated to dryness in vacuo. The solid hydrochloride was treated with dry diethyl ether and the mixture was filtered to afford 0.20 g (89%) of the amino acid hydrochloride (**5**·HCl), which was recrystallized from MeOH/diethyl ether: mp 191−192 °C dec; ^{1}H NMR (D_2O, ref 1,4-dioxane) δ 1.88 (2H, d, J = 7.9 Hz, cyclopropane CH_2), 2.88 (1H, t, J = 8.2 Hz, H-4), 4.12 (1H, d, J = 15.5 Hz, H-1), 4.28 (1H, d, J = 15.5 Hz, H-1), 7.15−7.42 (4H, m, aromatic H); ^{13}C NMR (D_2O, ref. acetonitrile) δ 16.4 (cyclopropane CH_2), 23.6 (C-4), 42.6 (C-3), 43.2 (C-1), 125.3, 132.4 (aromatic quaternary C), 128.1, 129.4, 129.8 (aromatic CH), 172.3 (COO); IR (KBr, cm^{-1}) 1740 (C=O). To 0.160 g (0.7 mmol) of the above hydrochloride, dissolved in 5 mL of ethanol, 2.5 mL of propylene oxide was added. The mixture was stirred at room temperature for 30 min, during which the amino acid **5** precipitated. The reaction mixture was evaporated to dryness in vacuo at 30 °C. The white solid residue was treated with dry diethyl ether, the mixture was filtered and the solid was dried in a desiccator to afford 0.13 g (97%) of amino acid **5**: mp 188 °C dec; R_f 0.63 (E); ^{1}H NMR (D_2O, ref 1,4-dioxane) δ 1.62 (1H, dd, J = 6.6, 6.9 Hz, cyclopropane CH_2), 1.68 (1H, dd, J = 6.9, 9.9 Hz, cyclopropane CH_2), 2.63 (1H, dd, J = 6.6, 9.9 Hz, H-4), 4,03 (1H, d, J = 15.5 Hz, H-1), 4.18 (1H, d, J = 15.5 Hz, H-1) 7.11−7.38 (4H, m, aromatic H); ^{13}C NMR (D_2O, ref. acetonitrile) δ 14.4 (cyclopropane CH_2), 20.6 (C-4), 42.4 (C-3), 43.4 (C-1), 126.2, 131.1 (aromatic quaternary C), 126.4, 126.7, 127.8, 128.1 (aromatic CH), 172.8 (COO); HRMS analysis $C_{11}H_{11}NO_2$ requires M^+ 189.07898, found M^+ 189.07878; MS m/z (rel int) 189 (2, M^+), 144 (100).

Method B. A mixture of 0.159 g (0.5 mmol) of compound **18b** and 0.83 mL (1.25 mmol) of 6 N HCl was heated at 100 °C for 1 day. The reaction mixture was then evaporated to dryness *in vacuo*. The white solid residue was recrystallized from MeOH/diethyl ether resulting in 0.08 g (71%) of **5**.HCl. The free amino acid **5** was prepared with propylene oxide as described above. HRMS of the α-amino acid hydrochloride **5**.HCl: at high temperature (225 °C), the salt dissociated into HCl and the free α-amino acid, which requires M^+ 189.07898 for $C_{11}H_{11}NO_2$, found M^+ 189.07848.

Method C. A mixture of 0.127 g (0.5 mmol) of compound **20**.HCl and 1.25 mL (1.25 mmol) of 1 N NaOH was stirred at room temperature for 1 day. The free amino acid was isolated by chromatography on a column containing Dowex-50X 8-100 ion-exchange resin (elution with 5% NH_4OH), resulting in 0.04 g (42%) of compound **5**. This material was identical to the compound obtained according to the procedures described above.

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