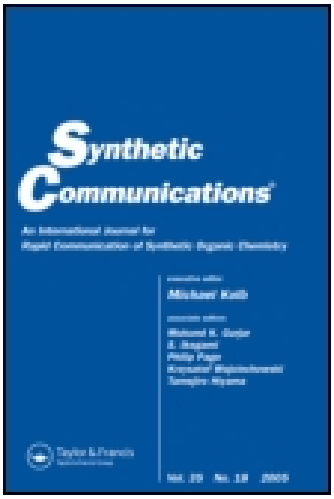

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Improved Synthesis of Cyclic α-Hydrazino Acids of Five- to Nine-Membered Rings and Optical Resolution of 5,6,7-Membered Ring Hydrazino Acids

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IMPROVED SYNTHESIS OF CYCLIC α-HYDRAZINO ACIDS OF FIVE- TO NINE-MEMBERED RINGS AND OPTICAL RESOLUTION OF 5,6,7-MEMBERED RING HYDRAZINO ACIDS

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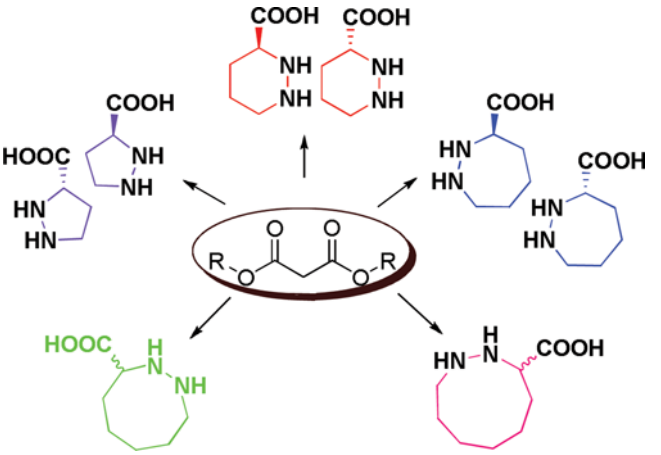
Department of Organic Chemistry, Indian Association for the Cultivation of Science, Kolkata, India

GRAPHICAL ABSTRACT



Abstract *Synthesis of cyclic α-hydrazino acids of five- to nine-membered rings has been described. Di-*tert*-butyl or dibenzyl malonate was used as starting materials instead of diethyl malonate, which was used in our first report. Deprotection of* tert*-butyl or benzyl ester of the final compounds was much easier than that of ethyl or methyl esters. Overall yield of these acids were 39, 50, 47, 52, and 51%, respectively. These acids were then converted to the diastereomers either via the formation of peptides with L-phenylalanine methyl ester or via the formation of esters (for five- to seven-membered rings) with L-2--phenylalaninol. All diastereomers were separated except the nine-membered ring by flash chromatography. Hydrolysis of diastereomeric esters generated the optically pure five-, six- and seven-membered cyclic α-hydrazino acids. In this process, both the*

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enantiomers have been isolated and the chiral auxiliary L-2-phenylalaninol was recovered. Absolute stereochemistry was determined from x-ray crystallographic analysis.

Keywords Cyclic α-hydrazino acids; malonates; (*S*)/(*R*)-δ-aza proline; (*S*)/(*R*)-1, 2-diazepane-3-carboxylic acid; (*S*)/(*R*)-piperazic acid

INTRODUCTION

In our efforts toward the synthesis of cyclic α-hydrazino acids (Fig. 1) from diethyl malonate as one of the starting materials, we encountered problems associated with the hydrolysis of methyl or ethyl esters of eight- and nine-membered rings to generate free acids, which was eventually achieved under harsh conditions using BBr_3.[1] Though there are several methods reported on the synthesis of piperazic acid,[2] there are only few synthetic routes to delta aza-proline **1**[3] or substituted aza-prolines[4] and no reports on the synthesis of eight- and nine-membered rings. Rutjes et al.[5] has reported the synthesis of cyclic α-hydrazino acid derivatives, where mostly five- and six-membered rings along with one example of seven-membered ring having a chloro group at the 5-position has been discussed. However, no reports described the synthesis of unsubstituted seven-membered cyclic amino acid **3**. As a part of our chemical biology program, we require cyclic α-hydrazino acids, which will be used to prepare peptide inhibitors, and the presence of N and N′ will help us to design them accordingly.

In this article, we report an improved procedure for the synthesis of cyclic α-hydrazino acids of five- to nine-membered rings. Diastereomeric separation of five- to eight-membered rings after the formation of peptides with L-phenylalanine methyl ester and optical resolution of five- to seven-memebered ring hydrazino acids via the hydrolysis of their diastereomeric esters using L-2-phenylalaninol as a chiral auxiliary have been reported.

RESULTS AND DISCUSSION

To address the problem of ester hydrolysis at the last step and to improve the yields of five- to nine-membered cyclic hydrazino acids, we used di-*tert*-butyl or dibenzyl malonate as one of the starting materials. The retrosynthetic route is shown in Scheme 1.

The synthesis of five- (**1**), six- (**2**), and seven- (**3**) membered rings proceeded as expected following our previously reported protocol[1] from common intermediate **7**. The experimental details are provided in the supporting information.

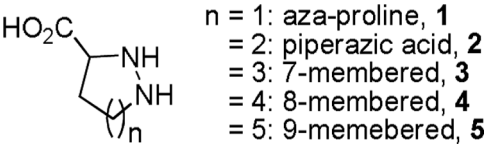
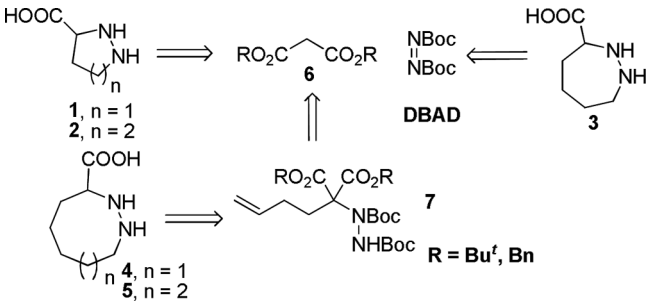


Figure 1. Cyclic α-hydrazino acids.



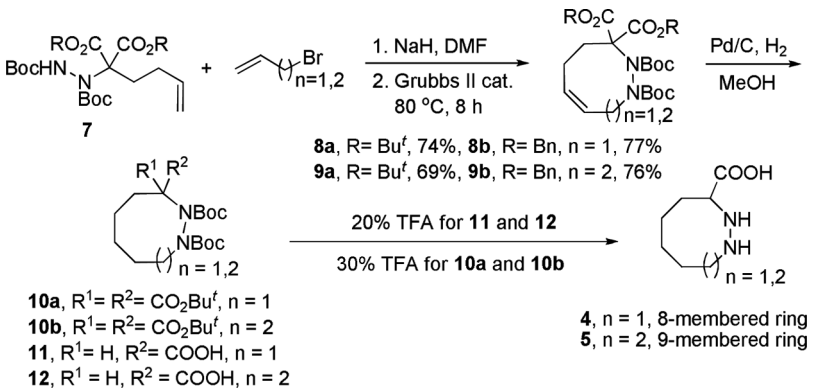
Scheme 1. Retrosynthetic analysis.

Synthesis of Eight- and Nine-Membered Cyclic α-Hydrazino Acids

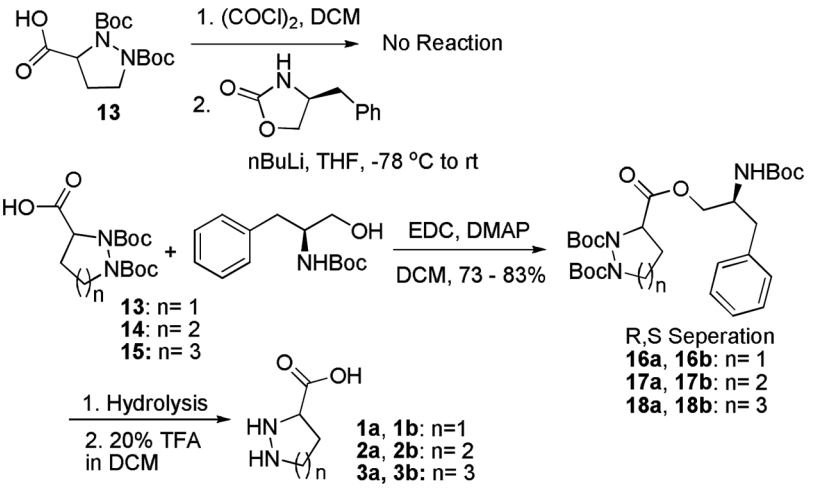
The intermediate **7** was subjected to N-allylation/homoallylation followed by RCM with Grubbs's second-generation catalyst[6] in toluene to obtain the eight- and nine-membered rings **8a**/**b** and **9a**/**b**, respectively. The protected compounds were then subjected to hydrogenation condition during which the reduction of the double bond of **8/9** and debenzylation of the esters **8b** and **9b** occurred smoothly. The free acids **4** and **5** were generated in quantitative yields from **10a**/**b, 11,** and **12** on treatment with trifluoroacetic acid (TFA) in dichloromethane (DCM) (Scheme 2).

Chiral Resolution

The amino acids need to be enantiopure to be used as building blocks for the synthesis of bioactive peptides. Accordingly, we tried to separate the enantiomers through the formation of diastereomers with Evans's chiral auxiliary; unfortunately, the acid coupling reaction with the auxiliary did not take place under various conditions (acid chloride, $AgCN/C_6H_6$, LDA/THF, BuLi/THF). We then had to employ a different strategy using a chiral auxiliary with different functionality, a rather primitive form of chiral auxiliary (Scheme 3).



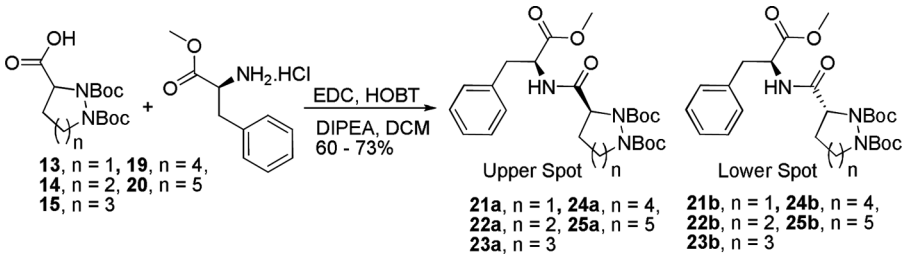
Scheme 2. Synthesis of eight- and nine-membered α-hydrazino acids.



Scheme 3. Chiral resolution.

The five-, six-, and seven-membered NBoc protected cyclic α-hydrazino acids underwent 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) coupling[7a] with 2-amino-3-phenylpropan-1-ol (L-2-phenylalaninol, chiral auxiliary) to form diastereomeric esters (**16, 17,** and **18**), which were then separated by flash chromatography. The separated esters were hydrolyzed (K_2CO_3 in $MeOH/H_2O$) back to the respective free NBoc-protected acids and the chiral auxiliary was recovered. TFA-mediated deprotection of the NBoc protected acids yielded the pure enantiomeric mono-TFA salts[2a] of five-, six-, and seven-membered cyclic α-hydrazino acids. The eight- and nine-membered NBoc-protected cyclic α-hydrazino acids were avoided because of the inability of the ester bonds to undergo hydrolysis under usual conditions.[1] The efficacy of the method was justified by comparing the specific rotation values (−10.9 and +10.5) of piperazic acid **2,** with the literature reports (−10.5 and +11.1) for the *R* and *S* enantiomers, respectively.[2c,d] This is the fourth asymmetric synthesis of δ-aza proline and first asymmetric synthesis of seven-membered cyclic hydrazino acids. In the case of piperazic acid, few syntheses have been reported. Among these syntheses, the Evans auxiliary-mediated synthesis was widely used by several groups during the piperazic acid–containing natural product synthesis. Though fewer number of steps were involved in their syntheses, yields were variable, strong organometallic reagents (nBuLi, LDA) were involved, and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) was used in excess amount (26 equivalent) to minimize the formation of side products. Hale et al.[2i] then standardized the reaction conditions where DMPU was used as 16.5 equivalents and also reported a better method using alternative oxazolidinone. In their method 3*R* isomer was obtained in 96% *ee* whereas 3*S*-isomer was obtained in 90% *ee*.

After the successful separation of diastereomeric esters, we then became interested to see their separation through peptide coupling with a standard amino acid, L-phenylalanine. Accordingly, the NBoc-protected cyclic α-hydrazino acids (**13** to **20**) were subjected to an EDC coupling[7b] with L-phenylalanine methyl ester to obtain a diasteriomeric mixture of dipeptides (Scheme 4). The dipeptides were separated by flash chromatography.



Scheme 4. Peptide coupling.

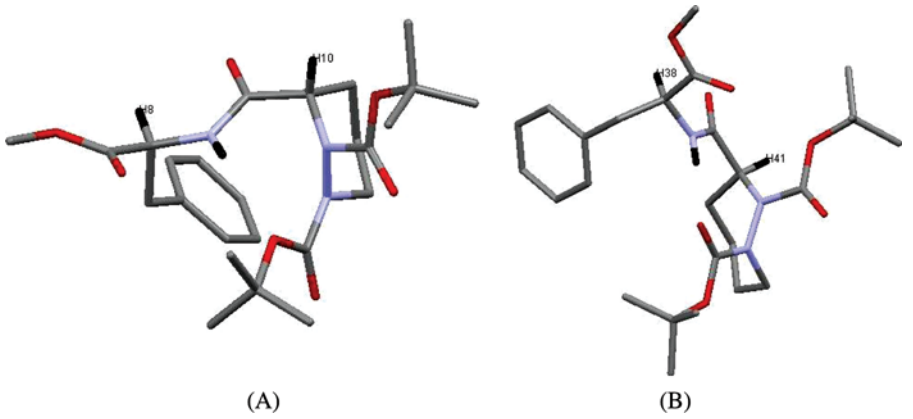


Figure 2. (A) X-ray crystal structure of **22a.** (B) X-ray crystal structure of **23a** (thermal ellipsoids are drawn at the 30% probablity level).[8]

Assigning the absolute stereochemistry of the diastereomers poised itself as a major challenge but fortunately the compounds **22a** and **23a** could be crystallized. The crystal structure (Fig. 2) revealed that the upper spots (in TLC) corresponds to the L-isomer as the (hydrogen marked in black) chiral centers are both (*S*) and accordingly the lower spot corresponds to D isomer of the α-hydrazoic acids in both the cases and hence by analogy we may conclude that the same is true for **21a, 24a, 25a** and **21b, 24b, 25b** in five-, eight-, and nine-membered rings, respectively.

CONCLUSION

We have developed a simple method for the synthesis of cyclic α-hydrazino acids from easily available starting materials and reagents. Overall yields of five- to nine-membered rings have been improved from 26, 16, 34, 13.5, and 13.33% to 39, 50, 47, 52, and 51%, respectively, by changing diethylmalonate to di-*tert*-butyl or dibenzyl malonates. Reactions were very clean, isolated the products in very pure form without any contamination of reagents or starting materials. The optical resolution of both the enantiomers of five-, six-, and seven-membered rings were achieved using phenylalaninol as a simple chiral auxiliary and obtained both the isomers in

100% optically pure form. Chiral auxiliary was recovered just by simple acid/base workup method. Absolute configuration was determined by x-ray crystallographic analysis.

EXPERIMENTAL

All reagents were purchased from commercial sources and used without further purification, unless otherwise stated. Petroleum ether (PE) refers to the fraction of petroleum boiling between 60 and 80 °C. THF is the abbreviation for tetrahydrofuran, TFA for trifluoroacetic acid, and EA stands for ethyl acetate. All reactions were carried out in oven-dried glassware under an argon atmosphere using anhydrous solvents, standard syringe, and septum techniques unless otherwise indicated. Organic extracts were dried over anhydrous Na_2SO_4 and then filtered prior to removal of all volatiles under reduced pressure on rotary evaporator. Chromatographic purification of products was accomplished using column chromatography on silica gels (mesh 100–200). Thin-layer chromatography (TLC) was carried out on aluminum sheets, silica gel 60 F254 (Merck; layer thickness 0.25 mm). Visualization of the developed chromatogram was performed by ceric ammonium molybdate (CAM) stains. ^1H and ^{13}C NMR spectra were recorded at 300 or 500 MHz and 75 or 125 MHz, respectively, using $CDCl_3$ or CD_3OD as solvent. Chemical shifts (δ) are given in parts per million relative to the solvent residual peak or TMS as internal standard. The following abbreviations are used for multiplicity of NMR signals: s = singlet, d = doublet, t = triplet, m = multiplet, and br = broad. DBAD indicates di-*tert*-butylazodicarboxylate. The presence of extra signals in ^{13}C of compounds **11, 17, 18, 24, 25,** and **29** can be attributed to the presence of multiple conformers of the hydrazino rings.

General Procedure for N-Allylation and RCM (8a): 1,2-Di-*tert*-buty-l-3,3-di-*tert*-butyl-1,2-diazocane-1,2,3,3-tetracarboxylate, 8a

NaH (67 mg, 2.79 mmol) was added to a solution of **7c** (0.583 g, 1.16 mmol) in dry DMF (10 ml) at 0 °C under argon atmosphere and stirred for 10 min, after which allyl bromide (0.28 mg, 2.79 mmol, 0.2 ml) was added. The reaction mixture was then allowed to stir for 30 min. Aqueous saturated NH_4Cl solution (1 ml) was added to the reaction mixture followed by removal of DMF under reduced pressure; it was then extracted with EtOAc (30 ml) and washed with water (3 × 10 ml) and brine. The organic layer was dried over anhydrous Na_2SO_4. Removal of organic solvent in vacuo quantitatively yielded the N-allylated product as a colorless oil.

Grubbs's second-generation catalyst (47 mg, 0.055 mmol, 5 mol%) was added to a solution of the previous compound in 90 ml dry toluene. The mixture was then heated at 80 °C for 4 h followed by the addition of another 47 mg (0.055 mmol, 5 mol%) of the catalyst, and stirring continued for another 2 h. After completion of the reaction (as indicated by TLC), toluene was removed in vacuo. The crude product was column purified (15% EA in PE) to obtain the product in 74% (0.44 g, 0.86 mmol, 2 steps) yield.

^1H NMR (500 MHz, $CDCl_3$) δ 5.72–5.74 (m, 0.32H), 5.59–5.64 (m, 0.68H), 5.44–5.46 (m, 0.29H), 5.38–5.40 (d, 0.71H), 4.63 (d, 0.71H, $J = 17.5$ Hz), 4.34

(brm, 0.29H), 3.80 (dd, 0.29H, $J = 16.5,5$ Hz), 3.72 (dd, 0.71H, $J = 17.5$, 4 Hz), 2.46–2.60 (m, 2H), 2.28–2.33 (m, 1H), 2.13–2.21 (m, 1H), 1.20–1.51 (m, 36H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 167.2, 166.8, 166.6, 155.6, 153.7, 153.1, 129.4, 127.4, 127.0, 82.1, 82.0, 81.8, 81.6, 81.1, 80.9, 80.1, 49.0, 47.9, 32.2, 32.0, 29.8, 29.4, 28.7, 28.5, 28.4, 28.1, 27.9, 22.1; HRMS (ESI) $(M + Na)^+$ calculated for $C_{26}H_{44}N_2O_8Na^+ = 535.2995$ found 535.2993.

General Procedure for Hydrogenolysis (10a): Tetra-*tert*-butyl 1,2-Diazocane-1,2,3,3-tetracarboxylate, 10a

To a solution of **8a** (0.41 g, 0.8 mmol) in methanol (10 ml), 10% Pd/C (20 mg) was added, and the resulting mixture was then stirred under hydrogen atmosphere (1 atm) for 4 h. The reaction was monitored by TLC. Methanol was removed followed by celite filtration with DCM provided the pure compound (0.407 g, 0.79 mmol) in almost quantitative yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.98 (br s, 0.50H), 3.70–3.78 (br m, 0.50H), 3.08–3.30 (br m, 1H), 2.26–2.29 (m, 1H), 1.88–2.02 (m, 1H), 1.62–1.71 (m, 5H), 1.25–1.67 (m, 43H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.7, 167.2, 166.7, 155.3, 153.3, 82.2, 82.0, 81.4, 81.1, 80.6, 73.5, 50.6, 48.6, 34.4, 33.1, 28.4, 28.4, 28.3, 28.3, 28.2, 28.0, 26.5, 25.8, 25.4, 25.1; HRMS (ESI) $(M + Na)^+$ calculated for $C_{26}H_{46}N_2O_8Na^+$ 537.3152; found 537.3152.

General Procedure for *tert*-Butyl Group Deprotection (4): 1,2-Diazocane-3-carboxylic Acid, 4[1]

A solution of **10a** (0.35 g, 0.68 mmol) in 30% TFA in DCM (8 ml) was stirred at 0 °C for 6 h. Removal of TFA and DCM gave eight-membered free acid **4** (0.257 g, 0.66 mmol) in 97% yield.

^{1}H NMR (500 MHz, CD_3OD) δ 3.702–3.734 (q, 1H, $J = 6.5$), 3.053–3.112 (m, 2H), 2.187 (s, 1H), 1.893–1.957 (brm, 3H), 1.812 (brs, 2H), 1.643 (s, 2H), 1.264–1.313 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 174.6, 59.4, 49.4, 48.1, 48.0, 47.8, 47.6, 47.5, 47.3, 47.1, 26.1, 24.9, 24.4, 22.2 ; HRMS (ESI) $(M + H)^+$ calculated for $C_7H_{15}N_2O_2^+$ 159.1134; found 159.1127.

General Procedure for Diasterioisomer Formation (Esterification with L-Phenylalaninol) (16)

(2-(*tert*-Butoxycarbonylamino)-3-phenylpropyl)-1,2-di-*tert*-butyl-pyrazolidine-1,2,3-tricarboxylate, 16. A mixture of **13** (0.03 g, 0.095 mmol), NBoc-L-phenylalaninol (0.026 g, 0.10 mmol), EDC (0.02 g, 0.10 mmol), and DMAP (2 mg, 0.01 mmol) in dry DCM (3 ml) was stirred for 4 h at 4 °C. The resulting dicyclohexylurea was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography to separate the two diastereoisomers **16a** and **16b** (overall yield 87%, 6.7 mg, 0.007 mmol, mixture). Compound **16a**: Yield 38% (0.02 g, 0.036 mmol of **16a**) from 0.03 g, 0.09 mmol of **13**.

$[\alpha]_D^{25}$ − 4.13 (*c* 0.96, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.18–7.31 (m, 5H), 5.39–5.41 (m, 1H), 4.74 (dd, 1H, $J = 8.1$, 6.9 Hz), 4.02–4.16 (m, 4H), 3.19–3.28 (m, 1H), 2.80–2.95 (m, 2H), 2.37–2.48 (m, 1H), 2.19–2.31 (m, 1H), 1.39–1.50 (m, 27H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 156.1, 155.6, 154.6, 137.8, 129.5, 128.6, 126.6, 82.1, 81.8, 79.4, 65.8, 59.2, 51.3, 47.2, 37.8, 30.6, 28.5, 28.3; HRMS (ESI) $(M + Na)^+$ calculated for $C_{28}H_{43}N_3O_8Na^+$ 572.2948; found 572.2947.

2-(*tert*-Butoxycarbonylamino)-3-phenylpropyl)-1,2-di-*tert*-butylpyrazolidine-1,2,3-tricarboxylate 16b. Yield 36% (0.019 g, 0.034 mmol of **16b**) from 0.03 g, 0.095 mmol of **13**.

$[\alpha]_D^{25}$ − 1.42 (*c* 0.84, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.18–7.31 (m, 5H), 5.17 (brs, 1H), 4.67–4.72 (m, 1H), 4.08–4.16 (m, 4H), 3.19–3.29 (m, 1H), 2.75–2.92 (m, 2H), 2.38–2.47 (m, 1H), 2.18–2.30 (m, 1H), 1.39–1.50 (m, 27H); ^{13}C (75 MHz, $CDCl_3$) δ 170.9, 156.0, 155.5, 154.9, 137.5, 129.6, 129.5, 128.7, 126.7, 82.1, 81.8, 79.5, 65.6, 59.5, 50.9, 46.9, 38.0, 30.7, 28.5, 28.3, 28.3; HRMS (ESI) $(M + Na)^+$ calculated for $C_{28}H_{43}N_3O_8Na^+$ 572.2948; found 572.2946.

General Procedure for Preparation of Chiral α-Hydrazino Acid (1)

Pyrazolidine-3-carboxylic acid mono-TFA salt, 1a. K_2CO_3 (0.02 g, 0.14 mmol) was added to a solution of **16a** (0.02 g, 0.036 mmol) in 2 ml MeOH/H_2O (2:1) and the mixture was stirred for 2 h followed by removal of MeOH in vacuo. The reaction mixture was then washed with diethylether (3 × 2 ml) to recover the chiral auxiliary. The residue was acidified with cold 1 N HCl and extracted with EtOAc (10 ml). The organic layer was washed with water and brine. Removal of the organic solvent furnished the free acid in 88% (10 mg, 0.032 mmol) yield.

The free acid was redissolved in 2 ml dry DCM. It was then cooled to 0 °C, followed by the addition of 0.4 ml TFA. The reaction mixture was then allowed to stir for 4 h. Removal of the organic solvent yielded the TFA salt of completely deprotected **1a** (6.87 mg, 0.03 mmol), $[\alpha]_D^{25}$1.46 (*c* 1.00, CH_3OH).

Pyrazolidine-3-carboxylic acid mono-TFA salt, 1b[1]. $[\alpha]_D^{25}$ − 1.42 (*c* 0.90, CH_3OH). Yield, 76% over two steps (5.73 mg, 0.025 mmol) from 0.018 g, 0.033 mmol of **16b**.

General Procedure for Peptide Coupling with Methyl Ester of L-Phenylalanine (21)

(*S*)-Di-*tert*-butyl-3-((*S*)-1-methoxy-1-oxo-3-phenylpropan-2-yl-carbamoyl) pyrazolidine-1,2-dicarboxylate, 21a. Diisopropylethylamine (0.45 g, 0.6 ml, 3.5 mmol) was added dropwise to a stirred suspension of L-phenylalanine methyl ester hydrochloride (0.35 g, 1.6 mmol) in dichloromethane (15 ml) at room temperature under an atmosphere of nitrogen. The solution was cooled to 0 °C and then **13** (0.551 g, 1.74 mmol) and 1-hydroxybenzotriazole (0.26 g, 1.9 mmol) were added successively, each in one portion. The suspension was stirred at 0 °C for a further 15 min and then EDC (0.37 g, 1.9 mmol) was added in one portion. The mixture was allowed to warm to room temperature over the course of 18 h. The reaction mixture was then evaporated in vacuo. The residue was taken up in EtOAc (100 ml) and washed with

0.1 N HCl, water, and brine. The organic layer was dried over anhydrous Na_2SO_4. Removal of organic solvent in vacuo followed by flash chromatography separated the diastereomers, and yields of **21a** and **21b** were 40% and 21%, respectively. Mixture of diastereomers was obtained in 12% yield (0.10 g, 0.21 mmol).

Yield 40% (0.33 g, 0.69 mmol of **21a**) from 0.551 g, 1.74 mmol, of **13**. $[\alpha]_D^{25}$ – 2.51 (*c* 8.19, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (brs, 1H), 7.13–7.31 (m, 5H), 4.82 (td, 1H, $J = 8.4$, 6 Hz), 4.52 (dd, 1H, $J = 8.7$, 6.6 Hz), 3.89 (ddd, 1H, $J = 11.1$, 8.4, 3 Hz), 3.69 (s, 3H), 3.12–3.23 (m, 2H), 2.89 (dd, 1H, $J = 10.8$, 8.7 Hz), 2.32–2.43 (m, 1H), 1.78–1.90 (m, 1H), 1.51 (s, 9H), 1.48 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.39, 170.31, 155.9, 154.9, 136.2, 129.2, 128.3, 126.9, 82.5, 82.3, 61.5, 53.1, 52.1, 46.7, 38.5, 31.2, 28.1, 28.0; HRMS (ESI) $(M + Na)^+$ calculated for $C_{24}H_{35}N_3O_7Na^+$ 500.2373; found 500.2372.

(*R*)-Di-*tert*-butyl-3-((*S*)-1-methoxy-1-oxo-3-phenylpropan-2-ylcarbam-oyl) pyrazolidine-1,2-dicarboxylate, 21b. Yield 21% (0.175 g, 0.37 mmol of **21b**) from 0.551 g, 1.74 mmol, of **13**.

$[\alpha]_D^{25}$12.51 (*c* 8.39, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (brs, 1H), 7.19–7.31 (m, 5H), 4.69–4.71 (brm, 1H), 4.57 (dd, 1H, $J = 9$, 5.7 Hz), 3.93 (ddd, 1H, $J = 15$, 8.4, 4.2 Hz), 3.66 (s, 3H), 3.13–3.28 (m, 2H), 2.92 (dd, 1H, $J = 8.3$, 5 Hz), 2.40–2.51 (m, 1H), 2.22–2.31 (m, 1H), 1.48 (s, 9H), 1.44 (s, 9H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 171.2, 156.7, 155.0, 136.2, 129.2, 129.1, 128.5, 126.9, 82.3, 61.3, 53.8, 52.1, 47.1, 47.1, 37.6, 31.3, 28.0; HRMS (ESI) $(M + Na)^+$ calculated for $C_{24}H_{35}N_3O_7Na^+$ 500.2373; found 500.2372.

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SUPPORTING INFORMATION

Supplemental data for this article can be accessed on the publisher's website.

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8. X-ray crystallographic data for compounds **22a** and **23a** have been deposited to the Cambridge Crystallographic Data Centre and assigned the deposition number CCDC 951986 (for **22a**) and 951987(for **23a**).