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Design and Synthesis of Optically Active Esters of γ-Amino-β-oxo Acids as Precursors for the Synthesis of Tetramic Acids Derived from L-Serine, L-Tyrosine, and L-Threonine

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Tetramic acids bearing a hydroxyalkyl or hydroxybenzyl group at C-5 of the heterocyclic ring were successfully prepared. α-Amino acids appropriately protected and activated were used as acylating agents for the C-acylation of active methylene compounds. These novel synthesized intermediates, substituted γ-amino acids, were isolated in excellent yields and enantiomeric purities. Cyclization under basic conditions afforded the desired products in high yields and enantiomeric purity.

Introduction

Tetramic acid derivatives constitute an important class of nitrogen heterocycles containing the pyrrolidine-2,4-dione ring system. They are commonly found in many natural products exhibiting distinct pharmaceutical and biological activities, including antibiotic, antifungal, cytotoxic, and anti-HIV.[1] Over 100 natural products containing the tetramic acid moiety have been isolated to date from a variety of marine and terrestrial species such as sponges, cyanobacteria, bacteria, and fungi. The natural products tenuazonic acid,[2] melophlins,[3] and reutericyclin[4] are representative examples of the structurally diverse family of acyltetramic acids.

Recently, peptide analogues incorporating the pyrrolidine-2,4-dione ring have been prepared.[5] This motif is found in many natural products displaying interesting biological activities such as dolastatin 15[6] and althiomycin.[7] Many natural products such as equisetin[8] and trichosetin,[9] paecilosetin[10] and virgineone[11] (Figure 1) include the tetramic acid structural unit derived from L-serine, L-tyrosine, and L-threonine.[12] Equisetin was first isolated in 1974 from the white mould *Fusarium equiseti* and shows remarkable antibiotic and HIV inhibitory activities, cytotoxicity, phytotoxicity, and mammalian DNA binding. Both trichosetin and paecilosetin, structurally related to equisetin, are well known for exhibiting antimicrobial activity, whereas virgineone possesses antifungal activity. Recently, it was discovered that the Gram-negative bacterium *Pseudomonas aeruginosa*, produces the antibiotic (*S*)-3-(1-hydroxydecylidene)-5-(2-hydroxyethyl)pyrrolidine-2,4-dione derived from a Claisen-like condensation reaction from one of the quorum sensing molecules.[13]

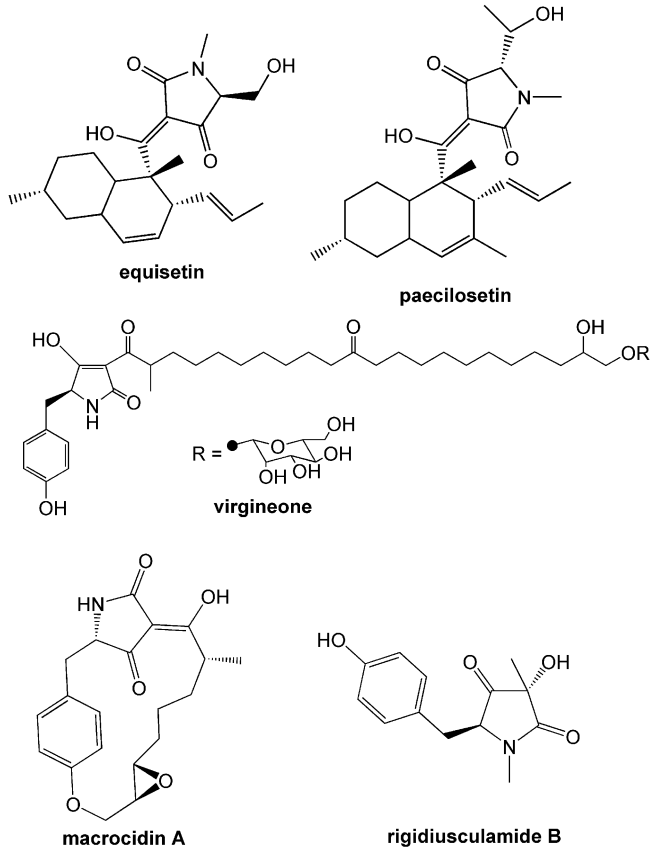

Figure 1. Naturally occurring tetramic acids.

Although much information concerning the synthesis of tetramic acids and congeners is available in the litera-

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ture,[14,3b,4b] the generation of functionalized tetramic acids containing a polar substituent at the 5-position is still a challenging problem. Our research group has contributed noteworthy to the synthesis and study of many heterocyclic compounds in solution[15] and in the solid phase,[16] including functionalized tetramic acids.[17] In the present study, we describe the synthesis of optically active tetramic acids bearing a hydrophilic group (hydroxyalkyl or hydroxybenzyl) in the side arm attached to the C-5 position of the pyrrolidine-2,4-dione moiety by using suitably protected *O*-benzyl-L-serine, L-tyrosine, and L-threonine as scaffolds.

Of note is the isolation in excellent purity, yields, and *ee* values of the intermediate γ-amino-β-oxopentanoates **1**, attractive precursors of β-hydroxy-γ-amino acids. The latter are found in several natural products as relevant statin substructures.[18] Moreover, in two recent studies,[19] they have been reported as important intermediates to the synthesis of a novel peptide lactone melleumin A and its seco acid methyl ester melleumin B, natural products isolated from cultured plasmodium of the myxomycete Physarium melleum.[20]

Results and Discussion

The synthetic course for tetramic acids **3a**–**f** is outlined in Scheme 1. The *N*-Boc-protected tetramic acids were prepared in just three steps from the appropriate commercially available *N*-hydroxy succinimide esters[21] of *O*-benzyl-protected *N*-Boc amino acids. Benzyl protection of the hydroxy group was chosen because of the mild conditions involved in its removal by catalytic hydrogenolysis and for the compatibility with the Boc protecting group attached to the amine at the deprotection step.[22] Moreover, etherification of the starting material made the final products and the intermediates easier to handle. It is well known that the high polarity of tetramic acids make them difficult to handle, and the fact that they exist in various tautomeric forms (Figure 2) makes the interpretation of their spectra a challenge.

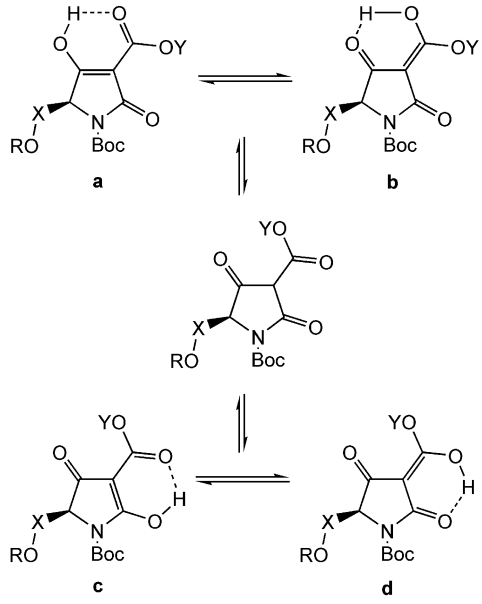
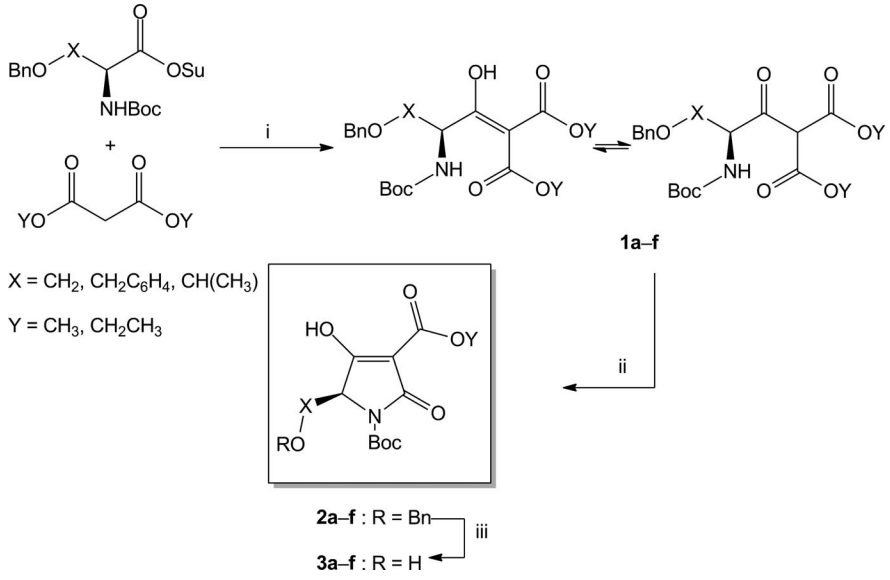


Figure 2. Enol–enol tautomers of the tetramic acids.

Coupling of the active methylene compound with the free hydroxy *N*-Boc-protected L-serine or L-tyrosine under the reaction conditions was unsuccessful and did not provide the desired products. The C-acylation reaction of an active methylene compound with the activated amino acids provided intermediates **1a**–**f** in almost quantitative yield (93–99%) and high purities. Formation of **1a**–**f** was best achieved when 1 equiv. of the active methylene compound



Scheme 1. Synthetic protocol methodology. Reagents and conditions: (i) NaH, dry THF, 1 h, 0 °C → r.t, 10% HCl; (ii) 2 N NaOH, MeOH or EtOH, 2 h, r.t., 10% HCl; (iii) H_2, Pd/C (10%), 1 h, r.t., 1 atm.

was treated with 1 equiv. of the amino acid ester in the presence of an excess amount (2 equiv.) of NaH in THF for 1 h. The resulting salt after careful acidification with 10% hydrochloric acid gave the pure γ-amino-β-oxopentanoates as solids or colorless oils without the need for further purification.

Cyclization of **1a**–**f** under basic conditions gave the *O*-benzyl-protected tetramic acids. Hydrogenolytic removal of the benzyl group of the tetramic acid was accomplished over 10% Pd/C and led to the formation of the *N*-protected tetramic acids in an overall yield of up to 92% over three steps.

Table 1 shows the resulting yields for the synthesized tetramic acids and the intermediates. All the products are newly synthesized and fully characterized by ^{1}H and ^{13}C NMR spectroscopy, melting point, specific rotation, FTIR spectroscopy, and HRMS. The target molecules could be approached in a two-step synthesis, apart from the deprotection step. Our procedure enables us to obtain tetramic acids bearing a hydrophilic group in the C-5 position in very good yields, with mild reaction conditions, short reaction times, and great purities without the need for chromatography or recrystallization as no side products are formed. The activation of the chiral α-amino acids as the *N*-hydroxysuccinimide esters as building blocks is beneficial for the maintenance of the stereochemical integrity of the corresponding molecules.

Table 1. Synthesized γ-amino-β-oxopentanoates and tetramic acids.

Entry	X	Y	Yield [%]		
			1	**2**	**3**
a	CH_2	Me	96	82	99
b	CH_2	Et	94	98	92
c	$CH_2C_6H_4$	Me	96	90	96
d	$CH_2C_6H_4$	Et	99	99	94
e	$CH(CH_3)$	Me	93	89	86
f	$CH(CH_3)$	Et	94	80	82

The ^{1}H NMR spectra of the deprotected tetramic acids showed in the case of serine and threonine derivatives abnormal broadening in [D$_6$]DMSO, whereas in nonpolar solvents ($CDCl_3$) it was not possible to obtain satisfactory spectra. Moreover, the ^{13}C NMR spectra showed weak signals for the carbonyl moieties. This phenomenon is probably due to a dynamic tautomerization that occurs at room temperature.[8b,10]

Intermediates **1a**–**f** exist as keto/enol tautomers (Figure 3) as observed by ^{1}H NMR spectroscopy in $CDCl_3$ (keto/enol, 80:20) and in [D$_6$]DMSO (keto/enol, 40:60). The tetramic acids, similarly, exist in two enolic tautomers (80:20) in chloroform (Figure 2), as no peaks assignable to H-3 or methine C-3 (keto form) were detected, whereas in DMSO only one form is observable. The NMR spectroscopic data are in full accordance with the structural investigations that have been previously published.[23] The products derived from L-threonine, thus having two asymmetric carbon atoms, were diastereomerically pure as determined by ^{1}H NMR spectroscopy.

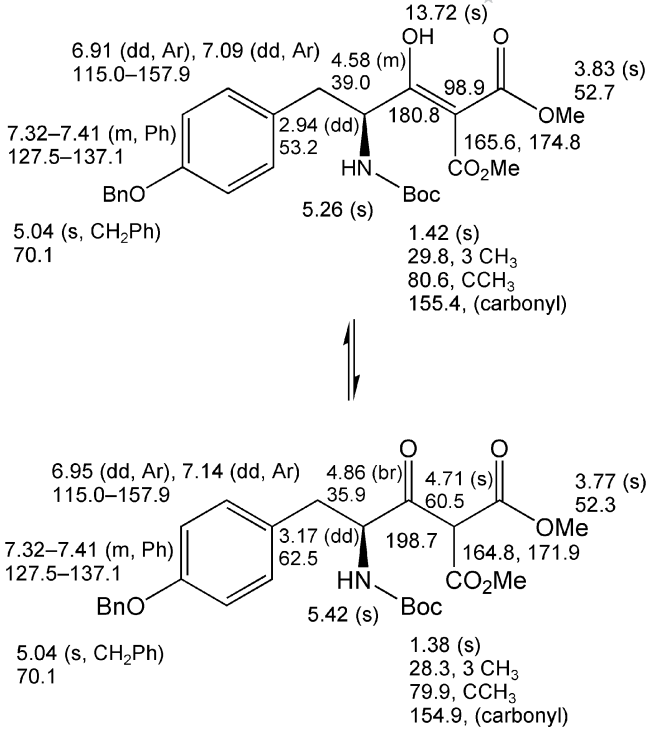


Figure 3. ^{1}H and ^{13}C NMR chemical shifts (ppm) and multiplicities for compound **3c** as observed for the two tautomeric forms existing in $CDCl_3$ solution at 26 °C.

The IR spectra of the prepared compounds further support their suggested molecular structures. Intermediate esters **1** are characterized mainly by bands at 1734–1718 cm^{-1} corresponding to the β-dicarbonyl system.[24] Cyclized tetramic acids **2** are characterized by the appearance of the absorption band at 1649–1645 cm^{-1}, indicating a lactam carbonyl moiety. The appearance of the bands at 2996–2948 cm^{-1}, characteristic of a free hydroxy group, strongly verifies the deprotection of the hydroxy group at C-5.

The enantiomeric excess of some representative derivatives were determined by chiral HPLC and were found to be over 98% for the intermediate pentanoates and 95% in the case of the final products.

Conclusions

In summary, we have demonstrated that the *O*-protected activated esters of L-serine, L-tyrosine, and L-threonine may be transformed into γ-amino-β-oxopentanoates, important statin precursors, in high yields and enantiopurities. These products may be cyclized and deprotected to afford 5-hydroxyalkyl and 5-hydroxybenzyl tetramic acids. The key step of our proposed work was the use of a benzyl group for protection of the hydroxy group of the amino acids. This protection, apart from blocking the reactive hydroxy group thus preventing unwanted reactions, lowered the polarity of the products. Therefore, we were able to adapt these challenging target molecules to the methodology developed from our group.

The synthesis of more complex molecules with polar groups on the side arm of the tetramic acid skeleton, from different amino acid analogues as precursors, and the possibility of the application of this methodology to natural products containing the pyrrolidine-2,4-dione nucleus with specific side chain arms is part of our future plans.

Experimental Section

General: All reagents were purchased from Aldrich, Fluka, and Acros and used without further purification. Dry THF was distilled from Na/Ph_2CO. Flash column chromatography was carried out on silica gel Macherey–Nagel 0.063-0.2 mm/70-230 mesh. Melting points were determined with a Gallenkamp MFB-595 melting point apparatus. HRMS were carried out in the department of Chemistry & Biochemistry of the University of Notre Dame, IN, USA, with an ESI instrument. NMR spectra were recorded with a Varian Gemini-2000 300 MHz spectrometer operating at 300 MHz (^{1}H) and 75 MHz (^{13}C). Chemical shifts are reported in ppm relative to [D_6]DMSO (^{1}H: δ = 2.50 ppm, ^{13}C: δ = 39.52 ppm) and $CDCl_3$ (^{1}H: δ = 7.26 ppm, ^{13}C: δ = 77.16 ppm). HPLC separations were performed by using a DAICEL CHIRALPAK AS (4.6×250 mm) column incorporated in an HPLC system consisting of a Varian 2510 HPLC pump, Varian 2510 variable λ detector, and a SRI Model 203 Peaksimple chromatography data system using *n*-hexane/ethanol as eluent. Optical rotations were measured with a Perkin–Elmer 241 polarimeter.

Typical Procedure for the Synthesis of Compounds 1a–f: To a suspension of NaH (60% in mineral oil, 20 mg, 0.50 mmol) in dry THF (1.5 mL) at 0 °C and under an atmosphere of argon was added dropwise dimethyl malonate (33 mg, 0.25 mmol). After stirring for 30 min, the hydroxysuccinimide ester of the appropriate Boc-*O*-benzyl-L-amino acid was added (0.25 mmol), and the reaction mixture was stirred for 1 h at room temperature. The mixture was concentrated, and the residue was diluted with water (0.5 mL). The suspension was washed with diethyl ether and acidified with 10% hydrochloric acid. The precipitated solid was filtered, washed with water (2×) and dried to afford the desired product as white solid or colorless oil.

(*S*)-Methyl 5-Benzyloxy-4-*tert*-butoxycarbonylamino-2-methoxycarbonyl-3-oxopentanoate (1a): Colorless oil; yield 98 mg, 96%. $[\alpha]_D^{20}$ = +1.0 (*c* = 1.8, $CHCl_3$); R_f = 0.46 (petroleum ether/AcOEt, 8:2). ^{1}H NMR (300 MHz, $CDCl_3$; keto/enol, 80:20): δ = 1.44 (s, 9 H, 3 CH_3), 3.64 (dd, *J* = 4.8, 9.9 Hz, 0.8 H, CH_2CH, keto), 3.70 (d, 0.4 H, CH_2CH, enol), 3.75 (s, 4.8 H, CO_2CH_3, keto), 3.83 (s, 1.2 H, CO_2CH_3, enol), 3.94 (dd, *J* = 3.6, 9.6 Hz, 0.8 H, CH_2CH, keto), 4.50 (s, 1.6 H, CH_2Ph, keto), 4.54 (s, 0.4 H, CH_2Ph, enol), 4.60 (m, 0.8 H, CH_2CH, keto), 4.88 [s, 0.8 H, CH(CO_2CH_3)$_2$, keto], 5.06 (m, 0.2 H, CH_2CH, enol), 5.25 (d, 0.2 H, NH, enol), 5.42 (d, 0.8 H, NH, keto), 7.27- 7.37 (m, 5 H, Ph), 13.8 (s, 0.2 H, OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.3, 29.7, 52.4, 52.7, 53.2, 53.8, 59.5, 62.5, 69.3, 69.9, 70.6, 73.1, 73.5, 80.1, 80.6, 99.4, 127.6, 127.8, 127.8, 127.9, 128.0, 128.4, 128.5, 137.3, 137.7, 155.2, 155.7, 164.7, 165.6, 171.8, 173.6, 179.8, 197.9 ppm. IR (ATR): $\tilde{\nu}$= 3648–3837 (m), 1718 (s, CO-CH-CO, ester), 1689 (s, urethane), 1508 (s, aromatics), 1454, 1367 (CO_2Me), 1250 (s, *t*Bu) cm^{-1}. HRMS: calcd. for $C_{20}H_{28}NO_8$ 410.1809; found 410.1798.

(*S*)-Ethyl 5-Benzyloxy-4-*tert*-butoxycarbonylamino-2-ethoxycarbonyl-3-oxopentanoate (1b): Colorless oil; yield 103 mg, 94%. $[\alpha]_D^{20}$ = +8.0 (*c* = 1.8, $CHCl_3$); R_f = 0.47 (petroleum ether/AcOEt, 8:2). ^{1}H NMR (300 MHz, $CDCl_3$; keto/enol, 75:25): δ = 1.24–1.32 (m, 3 H, $CO_2CH_2CH_3$), 1.44 (s, 9 H, 3 CH_3), 3.65 (dd, *J* = 4.8, 9.9 Hz, 1.5 H, CH_2CH, keto), 3.75 (d, 0.5 H, CH_2CH, enol), 3.94 (dd, *J* = 4.2, 9.6 Hz, 0.75 H, CH_2CH, keto), 4.17-4.27 (m, 4 H, $CO_2CH_2CH_3$), 4.51 (s, 1.5 H, CH_2Ph, keto), 4.54 (s, 0.5 H, CH_2Ph, enol), 4.62 (m, 0.75 H, CH_2CH, keto), 4.83 [s, 0.75 H, CH($CO_2CH_2CH_3$)$_2$, keto], 5.07 (m, 0.25 H, CH_2CH, enol), 5.26 (d, 0.25 H, NH, enol), 5.42 (d, 0.75 H, NH, keto), 7.28-7.34 (m, 5 H, Ph), 13.86 (s, 0.25 H, OH, enol) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 13.9, 14.0, 14.0, 28.2, 29.6, 53.6, 59.3, 61.1, 61.4, 61.7, 62.3, 62.7, 69.1, 69.8, 72.9, 73.2, 80.0, 80.4, 99.8, 127.5, 127.7, 128.3, 137.2, 137.4, 155.2, 155.5, 164.1, 165.1, 171.3, 173.5, 179.1, 197.9 ppm. IR (ATR): $\tilde{\nu}$= 3648–3846 (m), 1718 (s, CO-CH-CO, ester), 1686 (s, urethane), 1508 (s, aromatics), 1457, 1364 (CO_2Et), 1250 (s, *t*Bu) cm^{-1}. HRMS: calcd. for $C_{22}H_{32}NO_8$ 438.2122; found 438.2101.

(*S*)-Methyl 5-[4-(Benzyloxy)phenyl]-4-*tert*-butoxycarbonylamino-2-met-hoxycarbonyl-3-oxopentanoate (1c): White solid; yield 116 mg, 96%; m.p. 94–95 °C (ether). $[\alpha]_D^{20}$ = +4.2 (*c* = 1.6, $CHCl_3$). R_f = 0.24 (petroleum ether/AcOEt, 8:2). ^{1}H NMR (300 MHz, $CDCl_3$; keto/enol, 80:20): δ = 1.38 (s, 7.2 H, 3 CH_3, keto), 1.42 (s. 1.8 H, 3 CH_3, enol), 2.90 (m, 1 H, CH_2CH), 3.16 (dd, *J* = 13.5, 4.8 Hz, 1 H, CH_2CH), 3.77 (s, 4.8 H, 2 CO_2CH_3, keto), 3.83 (s, 1.2 H, 2 CO_2CH_3, enol), 4.58 (m, 0.2 H, CH_2CH, enol), 4.71 [s, 0.8 H, CH(CO_2Me)$_2$, keto], 4.86 (br., 0.8 H, CH_2CH, keto), 5.04 (s, 2 H, OCH_2Ph), 6.91 (d, *J* = 8.1 Hz, 2 H, $CHCH_2C_6H_4$), 7.09 (d, *J* = 8.1 Hz, 2 H, $CHCH_2C_6H_4$), 7.32–7.41 (m, 5 H, Ph), 13.72 (s, 0.2 H, OH, enol) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.3, 29.8, 35.9, 39.0, 52.3, 52.7, 53.2, 60.5, 62.5, 70.1, 79.9, 80.6, 98.9, 115.0, 127.5, 128.0, 128.6, 130.4, 130.5, 137.1, 154.9, 155.4, 157.9, 164.8, 165.6, 171.9, 174.8, 180.8, 198.7 ppm. IR (ATR): $\tilde{\nu}$ = 3648–3847 (m), 1734 (s, CO-CH-CO, ester), 1685 (s, urethane), 1510 (s, aromatics), 1456, 1369 (s, CO_2Me), 1248 (s, *t*Bu) cm^{-1}. HPLC (*n*-hexane/ethanol/TFA, 65:35:0.1; flow rate: 1.00 mL/min; 254 nm): t_R = 5.13 (99%; *S*, major enantiomer), 6.77 min (1%; *R*, minor enantiomer). HRMS: calcd. for $C_{26}H_{32}NO_8$ 486.2122; found 486.2097.

(*S*)-Ethyl 5-[4-(Benzyloxy)phenyl]-4-*tert*-butoxycarbonylamino-2-ethoxycarbonyl-3-oxopentanoate (1d): White solid; yield 127 mg, 99%; m.p. 95–98 °C. $[\alpha]_D^{20}$ = +1.2 (*c* = 0.9, $CHCl_3$). R_f = 0.45 (petroleum ether/AcOEt, 90:10). ^{1}H NMR (300 MHz, $CDCl_3$; keto/enol, 75:25): δ = 1.24–1.35 (m, 3 H, $CO_2CH_2CH_3$), 1.38 (s, 9 H, 3 CH_3), 2.93 (dd, *J* = 7.8, 14.1 Hz, 1 H, CH_2CH), 3.18 (dd, *J* = 6.0, 13.8 Hz, 1 H, 1 H, CH_2CH), 4.18–4.30 (m, 4 H, $CO_2CH_2CH_3$), 4.62 (m, 0.2 H, CH_2CH, enol), 4.67 [s, 0.8 H, CH($CO_2CH_2CH_3$)$_2$, keto], 4.92 (m, 0.8 H, CH_2CH, keto), 5.04 (s, 2 H, OCH_2Ph), 6.90 (d, *J* = 8.4 Hz, 2 H, $CHCH_2C_6H_4$), 7.10 (d, *J* = 8.4 Hz, 2 H, $CHCH_2C_6H_4$), 7.31–7.43 (m, 5 H, Ph), 13.70 (s, 0.2 H, OH, enol) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 14.2, 28.3, 29.8, 36.0, 39.1, 60.5, 61.3, 61.8, 62.5, 62.9, 70.1, 80.5, 99.0, 115.0, 115.1, 127.5, 128.1, 128.6, 128.7, 130.5, 137.1, 153.9, 155.3, 157.9, 158.0, 164.5, 164.6, 171.5, 174.8, 198.9 ppm. IR (ATR): $\tilde{\nu}$ = 3648–3837 (m), 1734 (s, CO-CH-CO, ester), 1689 (s, urethane), 1516 (s, aromatics), 1456, 1367 (s, CO_2Et), 1244 (s, *t*Bu) cm^{-1}. HRMS: calcd. for $C_{28}H_{36}NO_8$ 514.2435; found 514.2416.

(3*S*,4*R*)-Methyl 5-Benzyloxy-4-*tert*-butoxycarbonylamino-2-methoxy-carbonyl-3-oxohexanoate(1e): Colorless oil after column chromatography (petroleum ether/AcOEt, 8:2); yield 98 mg, 93%. $[\alpha]_D^{20}$ = –0.4 (*c* = 1.8, $CHCl_3$). R_f = 0.53 (petroleum ether/AcOEt, 8:2). ^{1}H NMR (300 MHz, $CDCl_3$; keto/enol, 80:20): δ = 1.19 (d, *J* = 6.3 Hz, 3 H, CH_3CH), 1.27 (dd, *J* = 3.0, 6.3 Hz, 3 H, CH_3CH), 1.45 (s, 9 H, 3 CH_3), 3.75 (s, 4.8 H, CO_2CH_3, keto), 3.83 (s, 1.2 H, CO_2CH_3, enol), 3.99 (m, 0.2 H, CH_3CHCH, enol), 4.18 (m, 0.2 H, CH_3CHCH, enol), 4.26 (pseudoq, 0.8 H, CH_3CHCH, keto), 4.38

(br., 0.2 H, CH_3CHCH), 4.47 (m, 0.8 H, CH_3CHCH), 4.58 (dd, J = 11.7, 7.2 Hz, 2 H, CH_2Ph), 4.83 (m, 0.2 H, CH_3CHCH), 4.90 [s, 0.8 H, $CH(CO_2CH_3)_2$, keto], 5.33 (d, J = 8.7 Hz, 0.2 H, NH, enol), 5.41 (d, J = 8.7 Hz, 0.8 H, NH, keto), 7.29-7.36 (m, 5 H, Ph), 14.03 (s, 0.2 H, OH, enol) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.1, 16.2, 17.2, 28.4, 29.8, 41.2, 52.3, 52.6, 53.2, 56.6, 57.8, 63.0, 63.8, 71.4, 71.7, 74.1, 74.6, 76.1, 77.1, 80.0, 80.2, 80.6, 98.9, 127.7, 127.8, 128.0, 128.4, 128.5, 137.7, 138.1, 155.8, 156.3, 164.5, 164.9, 165.8, 167.1, 174.0, 180.8, 198.9 ppm. IR (ATR): $\tilde{\nu}$ = 3648–3846 (m), 1723 (s, CO-CH-CO, ester), 1686 (s, urethane), 1508 (s, aromatics), 1457, 1366 (CO_2Me), 1250 (s, tBu) cm^{-1}. HRMS: calcd. for $C_{21}H_{30}NO_8$ 424.1966; found 424.1948.

(3*S*,4*R*)-Ethyl 5-Benzyloxy-4-*tert*-butoxycarbonylamino-2-ethoxycarbo-nyl-3-oxohexanoate (1f): Colorless oil after column chromatography (petroleum ether/AcOEt, 8:2); yield 106 mg, 94%. $[\alpha]_D^{20}$ = –6.5 (c = 1.8, $CHCl_3$). R_f = 0.49 (petroleum ether/AcOEt, 8:2). ^{1}H NMR (300 MHz, $CDCl_3$; keto/enol, 80:20): δ = 1.18 (t, J = 6.6 Hz, 3 H, CH_3), 1.24 (t, J = 6.9 Hz, 6 H, $CO_2CH_2CH_3$), 1.43 (s, 9 H, 3 CH_3), 4.20 (q, J = 6.9 Hz, 4 H, $CO_2CH_2CH_3$), 4.44–4.57 (m, 3 H, CH_3CHCH, CH_2Ph), 4.66 (s, 1 H, CH_2Ph), 4.83 (m, 0.2 H, CH_3CHCH, enol), 4.85 [s, 0.8 H, $CH(CO_2CH_2CH_3)_2$, keto], 5.33 (d, J = 9.3 Hz, 0.2 H, NH, keto), 5.42 (d, J = 9.3 Hz, 0.8 H, NH, keto) 7.26-7.33 (m, 5 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 14.1, 16.1, 17.1, 28.2, 29.7, 58.0, 61.1, 61.6, 61.8, 62.3, 63.3, 63.7, 71.3, 71.5, 74.1, 74.7, 80.2, 80.4, 99.3, 127.7, 127.8, 127.9, 128.0, 128.1, 128.3, 128.4, 137.8, 138.2, 155.8, 156.3, 164.2, 164.5, 174.4, 176.1, 181.4, 198.9 ppm. IR (ATR): $\tilde{\nu}$ = 3648–3847 (m), 1724 (s, CO-CH-CO, ester), 1690 (s, urethane), 1510 (s, aromatics), 1457, 1366 (CO_2Et), 1247 (s, tBu) cm^{-1}. HRMS: calcd. for $C_{23}H_{34}NO_8$ 452.2279; found 452.2264.

Typical Procedure for the Synthesis of Compounds 2a–f: To a solution of **1** (≈0.25 mmol) in MeOH or EtOH (0.5 mL) was dropwise added a sodium hydroxide solution (0.4 mL, 2 N). The resulting suspension was stirred for 3 h. ROH was evaporated at room temperature, and the aqueous suspension was carefully acidified with 10% hydrochloric acid at 0 °C. The precipitated solid was filtered, washed with water (2×) and petroleum ether (3×) and dried to afford the desired product as white solid.

(*S*)-*N*-*tert*-Butoxycarbonyl-5-benzyloxymethyl-3-methoxycarbonyltetramic Acid (2a): White solid; yield 74 mg, 82%; m.p. 114 °C. $[\alpha]_D^{20}$ = +38.5 (c = 0.8, $CHCl_3$). R_f = 0.24 (DCM/MeOH/AcOH, 95:5:0.1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (s, 2.25 H, 3 CH_3), 1.50 (s, 6.75 H, 3 CH_3), 3.56 (dd, J = 3.0, 9.3 Hz, 0.25 H, CH_2CH), 3.71 (dd, J = 3.0, 9.3 Hz, 1 H, CH_2CH), 3.91 (s, 3 H, CO_2CH_3), 4.08 (dd, J = 3.0, 9.3 Hz, 0.75 H, CH_2CH), 4.49 (s, 1.5 H, CH_2Ph), 4.53 (s, 0.25 H, CH_2Ph), 4.57 (dd, 1 H, CH_2CH), 7.21–7.33 (m, 5 H, Ph), 9.80 (br., 1 H, OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.2, 29.8, 52.4, 59.5, 65.8, 69, 9, 73.5, 73.6, 80.3, 83.4, 99.7, 127.6, 127.7, 127.9, 128.1, 128.5, 137.5, 149.8, 155.8, 163.2, 167.5, 173.9, 185.9 ppm. IR (ATR): $\tilde{\nu}$ = 3648–3837 (m), 1753 (s, ester), 1699 (s, urethane), 1649 (s, C-2), 1521 (s, aromatics), 1460, 1354 (s, CO_2Me), 1253 (s, tBu) cm^{-1}. HRMS: calcd. for $C_{19}H_{24}NO_7$ 378.1547; found 378.1532.

(*S*)-*N*-*tert*-Butoxycarbonyl-5-benzyloxymethyl-3-ethoxycarbonyltetramic Acid (2b): White solid; yield 90 mg, 98%; m.p. 114–116 °C. $[\alpha]_D^{20}$ = +24.1 (c = 1.1, $CHCl_3$). R_f = 0.54 (DCM/MeOH, 95:5). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (t, J = 6.9 Hz, 3 H, $CO_2CH_2CH_3$), 1.29 (s, 2.25 H, 3 CH_3), 1.35 (s, 6.75 H, 3 CH_3), 3.56 (dd, J = 3.0, 9.6 Hz, 0.25 H, CH_2CH), 3.74 (dd, J = 1.8, 10.2 Hz, 1 H, CH_2CH), 3.92 (dd, J = 3.0, 9.6 Hz, 0.75 H, CH_2CH), 4.23 (q, J = 6.9 Hz, 2 H, $CO_2CH_2CH_3$), 4.34 (s, 2.5 H, CH_2Ph, $CHCH_2$), 4.38 (s, 0.5 H, CH_2Ph), 7.06–7.20 (m, 5 H, Ph), 7.80 (br., 1 H, OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 28.0, 29.6, 59.3, 61.6, 65.5, 69.8, 73.3, 73.4, 80.0, 83.2, 99.6, 126.9, 127.4, 127.5, 127.7, 127.9, 128.1, 128.3, 128.3, 137.3, 137.4, 149.7, 155.6, 162.8, 167.1, 173.5, 185.7 ppm. IR (ATR): $\tilde{\nu}$ = 3648–3837 (m), 1731 (s, ester), 1676 (s, urethane), 1645 (s, C-2), 1571 (s, aromatics), 1456, 1365 (s, CO_2Et), 1255 (s, tBu) cm^{-1}. HRMS: calcd. for $C_{20}H_{26}NO_7$ 392.1704; found 392.1687.

(*S*)-*N*-*tert*-Butoxycarbonyl-5-[4-(benzyloxy)benzyl]-3-methoxycarbonyltetramicAcid (2c): White solid; yield 95 mg, 90%, m.p. 188–191 °C. $[\alpha]_D^{20}$ = +3.2 (c = 0.7, $CHCl_3$). R_f = 0.47 (DCM/MeOH/AcOH, 95:5:0.5). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.46 (s, 3 H, 3 CH_3), 3.09 (br. dd, 2 H, CH_2CH), 3.50 (s, 3 H, CO_2CH_3), 4.00 (s, 1 H, CH_2CH), 4.96 (s, 2 H, CH_2Ph), 6.76 (d, J = 8.1 Hz, 2 H, $CHCH_2C_6H_4$), 6.91 (d, J = 8.1 Hz, 2 H, $CHCH_2C_6H_4$), 7.30–7.42 (m, 5 H, OCH_2Ph) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 27.9, 34.2, 49.7, 61.9, 69.1, 79.7, 90.3, 113.9, 127.5, 127.8, 128.3, 128.5, 130.6, 134.5, 137.2, 150.0, 156.8, 164.9, 169.4, 189.0 ppm. IR (ATR): $\tilde{\nu}$ = 3648–3847 (m), 1754 (s, ester), 1694 (s, urethane), 1649 (s, C-2), 1522 (s, aromatics), 1460, 1362 (s, CO_2Me), 1253 (s, tBu) cm^{-1}. HRMS: calcd. for $C_{25}H_{28}NO_7$ 454.1860; found 454.1838.

(*S*)-*N*-*tert*-Butoxycarbonyl-5-[4-(benzyloxy)benzyl]-3-ethoxycarbonyltetramicAcid (2d): White solid; yield 114 mg, 99%; m.p. 101–102 °C. $[\alpha]_D^{20}$ = +22.7 (c = 0.3, $CHCl_3$). R_f = 0.50 (DCM/MeOH/AcOH, 95:5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (br., 3 H, $CO_2CH_2CH_3$), 1.40 (s, 2.25 H, 3 CH_3), 1.53 (s, 6.75 H, 3 CH_3), 3.17 (d, J = 12.3 Hz, 1 H, CH_2CH), 3.30 (br., 1 H, CH_2CH), 4.27 (br., 2 H, $CO_2CH_2CH_3$), 4.50 (br., 1 H, CH_2CH), 4.96 (s, 1.5 H, CH_2Ph), 5.03 (s, 0.5 H, CH_2Ph), 6.78 (d, J = 7.8 Hz, 1.5 H, C_6H_4), 6.85 (d, J = 7.8 Hz, 0.5 H, C_6H_4), 6.97 (d, J = 7.8 Hz, 1.5 H, C_6H_4), 7.07 (d, J = 7.8 Hz, 0.25 H, C_6H_4), 7.32-7.38 (m, 5 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4, 28.3, 29.8, 34.7, 61.1, 70.1, 83.1, 89.0, 100.3, 114.8, 115.0, 127.6, 128.0, 128.7, 130.6, 130.8, 137.2, 150.4, 156.8, 158.0, 166.7, 174.0, 182.8 ppm. IR (ATR): $\tilde{\nu}$ = 3648–3846 (m), 1753 (s, ester), 1701 (s, urethane), 1646 (s, C-2), 1521 (s, aromatics), 1460, 1358 (s, CO_2Et), 1256 (s, tBu) cm^{-1}. HRMS: calcd. for $C_{26}H_{30}NO_7$ 468.2017; found 468.1993.

(*S*)-*N*-*tert*-Butoxycarbonyl-5-[(*R*)-1-(benzyloxy)ethyl]-3-methoxycarbonyltetramic Acid (2e): White solid; yield 81 mg, 89%; m.p. 175–177 °C. $[\alpha]_D^{20}$ = +46.4 (c = 0.1, $CHCl_3$). R_f = (DCM/MeOH/AcOH, 95:5:1). ^{1}H NMR (300 MHz, [D$_6$]DMSO; keto/enol, 80:20): δ = 1.09 (d, J = 6.3 Hz, 3 H, CH_3CH), 1.41 (s, 9 H, 3 CH_3), 3.54 (s, 3 H, CO_2CH_3), 3.92 (br., 1 H, CH_3CH), 4.08 (br., 1 H, CH_3CHCH), 4.48 (s, 2 H, CH_2Ph), 7.28 (br., 5 H, Ph), 14.00 (s, 1 H, OH, enol) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 16.6, 27.8, 49.4, 63.2, 70.5, 74.7, 78.5, 78.9, 79.2, 79.4, 80.3, 127.0, 127.1, 127.3, 128.0, 138.8, 150.0, 168.7 ppm. IR (ATR): $\tilde{\nu}$ = 3648–3837 (m), 1759 (s, ester), 1699 (s, urethane), 1649 (s, C-2), 1521 (s, aromatics), 1458, 1354 (s, CO_2Me), 1253 (s, tBu) cm^{-1}. HRMS: calcd. for $C_{20}H_{26}NO_7$ 392.1704; found 392.1697.

(*S*)-*N*-*tert*-Butoxycarbonyl-5-[(*R*)-1-(benzyloxy)ethyl]-3-ethoxycarbonyltetramic Acid (2f): White solid; yield 76 mg, 80%; m.p. 182–184 °C. $[\alpha]_D^{20}$ = +13.1 (c = 0.8, $CHCl_3$). R_f = 0.44 (DCM/MeOH, 95:5). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (d, J = 6.3 Hz, 3 H, CH_3CH), 1.28 (t, J = 7.2 Hz, 3 H, $CO_2CH_2CH_3$), 1.46 (s, 9 H, 3 CH_3), 4.21 (q, J = 7.2 Hz, 2 H, $CO_2CH_2CH_3$), 4.37 (br. d, J = 8.7 Hz, 1 H, CH_3CHCH), 4.52 (dd, J = 11.7, 42.6 Hz, 2 H, CH_2Ph), 5.33 (br. d, J = 8.7 Hz, 1 H, CH_3CHCH), 7.27-7.31 (m, 5 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 16.2, 28.4, 34.7, 58.0, 61.7, 71.4, 74.5, 80.4, 127.9, 128.1, 128.6, 137.6, 153.9, 156.3, 166.8, 175.1 ppm. IR (ATR): $\tilde{\nu}$ = 3648–3847 (m), 1747 (s, ester), 1699 (s, urethane), 1649 (s, C-2), 1602 (s, aromatics), 1452,

1363 (s, CO_2Et), 1219 (s, *t*Bu) cm^{-1}. HRMS: calcd. for $C_{21}H_{28}NO_7$ 406.1860; found 406.1854.

Typical Procedure for the Synthesis of Compounds 3a–f: To a solution of **2** (0.25 mmol) in dry THF (15 mL) was carefully added 10% Pd/C (210 mg, 0.20 mmol). The reaction mixture was placed under a H_2 atmosphere (doubled balloon) and stirred for 1 h. The reaction was monitored by TLC (DCM/MeOH, 90:10–95:5). The reaction mixture was then filtered through Celite 545, and washed with THF (3×), and the filtrate was evaporated in vacuo at room temperature to give Boc-tetramic acid **3c**. For analytical purposes, the crude product was purified by column chromatography (DCM/MeOH/AcOH, 95:5:1).

(*S*)-*N*-*tert*-Butoxycarbonyl-5-hydroxymethyl-3-methoxycarbonyltetramic Acid (3a): White solid; yield 71 mg, 99%; m.p. >300 °C. $[\alpha]_D^{20}$ = –4.7 (*c* = 0.55, MeOH). R_f = 0.29 before column chromatography, 0.14 after column chromatography (DCM/MeOH/AcOH, 90:10:1). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.44 (s, 3 H, 3 CH_3), 3.57 (s, 3 H, CO_2CH_3), 3.75 (br., 3 H, CHCH_2) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 27.9, 50.1, 59.4, 63.9, 79.0, 83.6, 145.3, 169.4, 191.1, 211.6 ppm. IR (ATR): $\tilde{\nu}$ = 3648–3847 (m), 2996 (br., OH), 1744 (s, ester), 1699 (s, urethane), 1647 (s, C-2), 1442, 1361 (s, CO_2Me), 1220 (s, *t*Bu) cm^{-1}. HPLC (*n*-hexane/ethanol/TFA, 70:30:0.1; flow rate: 0.60 mL/min; 254 nm): t_R = 6.32 (97.5%; *S*, major enantiomer), 6.90 min (2.5%; *R*, minor enantiomer). HRMS: calcd. for $C_{12}H_{18}NO_7$ 288.1078; found 288.1094.

(*S*)-*N*-*tert*-Butoxycarbonyl-3-ethoxycarbonyl-5-hydroxymethyltetramic Acid (3b): White solid; yield 69 mg, 92%; m.p. 122–125 °C. $[\alpha]_D^{20}$ = +1.3 (*c* = 0.3, MeOH). R_f = 0.15 (AcOEt/MeOH, 90:10). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.17 (br., 3 H, $CO_2CH_2CH_3$), 1.38, 1.44 (s, 9 H, 3 CH_3), 3.60 (CH_2OH), 3.75 (CHCH$_2$), 4.06 (br., 2 H, $CO_2CH_2CH_3$), 6.30 (OH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 14.6, 28.2, 57.7, 62.1, 63.7, 77.8, 84.0, 146.1, 168.9, 192.1 ppm. IR (ATR): $\tilde{\nu}$ = 3648–3843 (m), 2966 (br., OH), 1751 (s, ester), 1690 (s, urethane), 1647 (s, C-2), 1442, 1348 (s, CO_2Et), 1220 (s, *t*Bu) cm^{-1}. HRMS: calcd. for $C_{13}H_{20}NO_7$ 302.1234; found 302.1256.

(*S*)-*N*-*tert*-Butoxycarbonyl-5-(4-hydroxybenzyl)-3-methoxycarbonyltetramic Acid (3c): White solid; yield 87 mg, 96%; m.p. 230 °C (dec.). $[\alpha]_D^{20}$ = –28.4 (*c* = 0.3, EtOH). R_f = 0.69 before column chromatography, 0.26 after column chromatography (DCM/MeOH/AcOH, 9:1:0.05). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.47 (s, 3 H, 3 CH_3), 3.03 (pseudoq, 2 H, CH_2CH), 3.51 (s, 3 H, CO_2CH_3), 3.95 (s, 1 H, C-5), 6.54 (d, *J* = 8.1 Hz, 2 H, Ar), 6.79 (d, *J* = 8.1 Hz, 2 H, Ar), 9.10 (br., 1 H, ArOH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 27.9, 34.2, 49.7, 62.1, 80.5, 91.0, 114.7, 125.8, 130.5, 149.9, 155.7, 166.2, 190.6, 204.0 ppm. IR (ATR): $\tilde{\nu}$ = 3648–3847 (m), 2956 (br., OH), 1744 (s, ester), 1679 (s, urethane), 1645 (s, C-2), 1564 (s, aromatics), 1442, 1356 (s, CO_2Me), 1223 (s, *t*Bu) cm^{-1}. HRMS: calcd. for $C_{18}H_{22}NO_7$ 364.1391; found 364.1389.

(*S*)-*N*-*tert*-Butoxycarbonyl-3-ethoxycarbonyl-5-(4-hydroxybenzyl)-tetramic Acid (3d): White solid; yield 89 mg, 94%; m.p. > 250 °C (dec.). $[\alpha]_D^{20}$ = –16.1 (*c* = 0.5, MeOH). R_f = 0.64 before column chromatography, 0.18 after column chromatography (AcOEt/MeOH, 95:5). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.13 (br., 3 H, $CO_2CH_2CH_3$); 1.46 (s, 9 H, 3 CH_3); 3.01 (br. dd, 2 H, CH_2CH), 3.92 (s, 1 H, C-5), 4.01 (br., 2 H, $CO_2CH_2CH_3$), 6.53 (pseudod, 2 H, Ar), 6.78 (pseudod, 2 H, Ar), 9.10 (s, 1 H, ArO*H*) ppm. ^{13}C NMR (75 MHz,[D$_6$]DMSO): δ = 14.6, 27.9, 34.3, 57.7, 62.0, 80.2, 91.0, 114.6, 126.1, 127.5, 127.8, 130.5, 150.0, 155.6, 165.7, 190.5 ppm. IR (ATR): $\tilde{\nu}$ = 3648–3844 (m), 2972 (br., OH), 1752 (s, ester), 1687 (s, urethane), 1647 (s, C-2), 1566 (s, aromatics), 1444, 1366 (s, CO_2Et), 1228 (s, *t*Bu) cm^{-1}. HRMS: calcd. for $C_{19}H_{24}NO_7$ 378.1547; found 378.1546.

(*S*)-*N*-*tert*-Butoxycarbonyl-5-[(*R*)-1-hydroxyethyl]-3-methoxycarbonyltetramic Acid (3e): White solid; yield 65 mg, 86%; m.p. > 200 °C (dec.). $[\alpha]_D^{20}$ = +5.6 (*c* = 0.8, MeOH). R_f = 0.35 before column chromatography, 0.31 after column chromatography (DCM/MeOH/AcOEt, 95:5:1). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 0.93 (br., 3 H, CH_3CH), 1.43 (s, 9 H, 3 CH_3), 3.55 (s, 3 H, CO_2CH_3), 3.84 [br., 1 H, CHCH(CH$_3$)OH], 4.12 [br., 1 H, CHCH(CH$_3$)OH], 5.00 (br., 1 H, OH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 18.1, 27.8, 49.6, 63.4, 66.4, 80.8, 91.1, 150.0, 165.5, 190.9, 207.2 ppm. IR (ATR): $\tilde{\nu}$ = 3648–3847 (m), 2948 (br., OH), 1755 (s, ester), 1694 (s, urethane), 1646 (s, C-2), 1442, 1361 (s, CO_2Me), 1219 (s, *t*Bu) cm^{-1}. HRMS: calcd. for $C_{13}H_{20}NO_7$ 302.1234; found 302.1248.

(*S*)-*N*-*tert*-Butoxycarbonyl-3-ethoxycarbonyl-5-[(*R*)-1-hydroxyethyl]tetramic Acid (3f): White solid; yield 65 mg, 82%; m.p. > 250 °C. $[\alpha]_D^{20}$ = +7.3 (*c* = 0.4, MeOH). R_f = 0.56 (DCM/MeOH/AcOEt, 95:5:1). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 0.92 (d, *J* = 6.3 Hz, 3 H, CH_3CH), 1.16 (t, *J* = 6.9 Hz, 3 H, $CO_2CH_2CH_3$), 1.43 (s, 9 H, 3 CH_3), 4.01 (q, *J* = 6.9 Hz, 2 H, $CO_2CH_2CH_3$), 3.77 [d, 1 H, CHCH(CH$_3$)OH], 4.13 [br., 1 H, CHCH(CH$_3$)OH], 5.04 (br., 1 H, OH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 14.4, 18.1, 27.9, 57.9, 64.0, 66.7, 79.9, 86.2, 149.8, 167.7, 191.0, 207.4 ppm. IR (ATR): $\tilde{\nu}$ = 3648–3847 (m), 2956 (br., OH), 1749 (s, ester), 1699 (s, urethane), 1647 (s, C-2), 1442, 1361 (s, CO_2Et), 1223 (s, *t*Bu) cm^{-1}. HRMS: calcd. for $C_{14}H_{22}NO_7$ 316.1391; found 364.1407.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of compounds **1**–**3b**, **1**–**3c**, and **1**–**3e**.

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