Some Studies on the Uses of 2-Bromoethyl and 2-Iodoethyl Ester Blocking Groups in Peptide Synthesis: Samarium Diiodide-Mediated Deprotection

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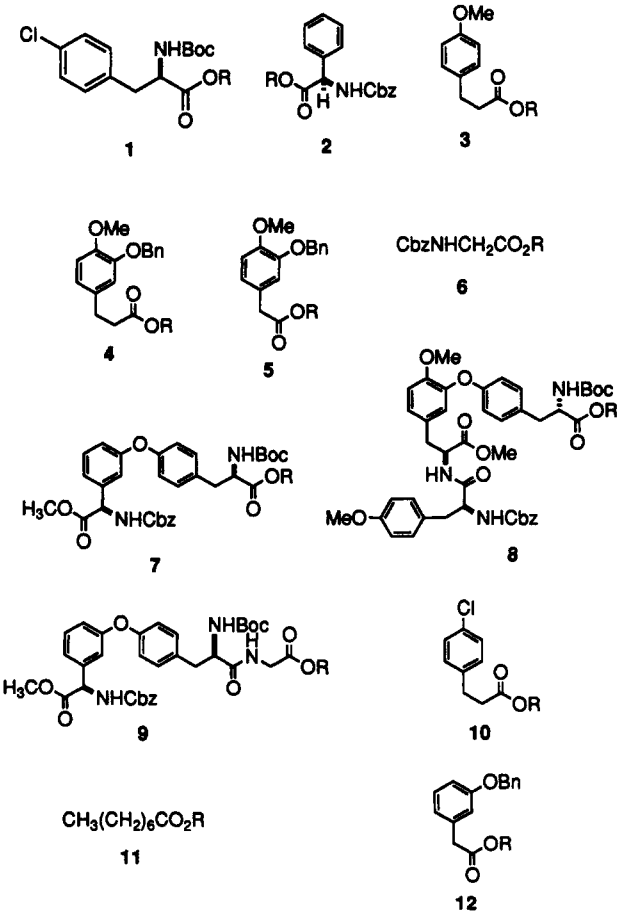
Introduction

In connection with studies, currently underway in our laboratory, that are directed toward the synthesis of compounds related to the glycopeptide antibiotics ristocetin and vancomycin,[1] we required a carboxylate blocking group that is sufficiently robust to withstand a number of synthetic operations elsewhere in the molecule, yet can be removed under mild neutral conditions. The latter restriction is due to the fact that the target molecules contain a number of arylglycine residues that are prone to racemization under mildly basic conditions, and that *tert*-butoxycarbonyl and/or benzyloxycarbonyl groups were projected for amine protection during their assembly. A potentially useful candidate for our purposes is the 2-bromoethyl ester, which has been reported to be removable under a variety of nonbasic reaction conditions.[2] We were soon to learn, however, that this deprotection is highly problematic. In almost every case that we have studied, the 2-bromoethyl ester was converted to a 2-hydroxyethyl ester, probably via a classical neighboring group participation involving the carboxyl oxygen, which facilitates hydrolysis of the bromide.[3] It has been reported that the 2-bromoethyl ester can be converted, via Finkelstein reaction, to a 2-iodoethyl ester.[2c] The latter is somewhat easier to cleave reductively (Zn powder) and both two-step and one-pot procedures have been described for unmasking the carboxylate group.[2c,4] In our hands, this tactic has also led to formation of 2-hydroxyethyl esters, either exclusively or as the major product.[3] Magnus and co-workers have described similar difficulties during the deprotection of 2-chloroethyl carbamates, a problem that was solved by using samarium diiodide as the reducing agent.[5] This paper reports on the use of SmI_2 for the deprotection of 2-iodoethyl esters under anhydrous conditions, which are compatible with the presence of arylglycines as well as a number of amine blocking groups, leading to the carboxylic acids in reproducibly excellent yields.

Results and Discussion

A number of 2-bromoethyl esters were prepared from the corresponding acids by following the standard method using 2-bromoethanol/(DCC, pyridine) (Table 1). Direct deprotection of these esters by using SmI_2 was found to be extremely slow and inefficient, and so they were converted to 2-iodoethyl esters via Finkelstein reaction using NaI (5.0 equiv) in dry acetone for 7 h under nitrogen. This halide conversion was easily confirmed by ^1H and ^{13}C NMR. Several 2-iodoethyl esters were also prepared directly from reaction of the carboxylic acid with 2-iodoethanol in the presence of DCC.

In the initial studies of deprotection by using SmI_2, *N*-Boc-*p*-chloro-D-phenylalanine 2-iodoethyl ester (**1b**) was used to determine the optimum reaction conditions. The reasons for choosing **1b** as model compound are that it has a relatively sensitive protecting group (*N*-Boc) and it is a chiral amino acid which is very closely related to intermediates that are currently being employed in our studies on vancomycin and ristocetin A. After reaction of **1b** with SmI_2 (7.0 equiv) at rt under deoxygenated, dry argon for 1 day, 75% was deprotected (^1H NMR); prolonged stirring (2 days) with excess of SmI_2 (10.0 equiv) did not lead to complete deprotection. At slightly higher temperature (35 °C, 7.0 equiv of SmI_2) the reaction was determined to be complete after 10 h from the ^1H NMR of crude product; at 40 °C, several products were observed, presumably due to instability of the *N*-Boc protecting group. For a comparison of *N*-Cbz and *N*-Boc, we investigated the deprotection of **2**, which showed that *N*-Cbz is stable toward SmI_2 at 40 °C. The optimized reaction conditions



For all structures: (a) R = CH_2CH_2Br; (b) R = CH_2CH_2I; (c) R = H

thus obtained (A: SmI_2 (6.0 equiv), 40 °C, 8 h; B: SmI_2 (7.0 equiv), 35 °C, 10 h) were used with several different

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Table 1. Yields for the Preparation and Deprotection of 2-Iodoethyl Esters[a]

entry	substrate	yield of b (%)	yield for b → c (%)
1	1[b]	75	82
2	2	87	88
3	3	86	93
4	4	91	91
5	5	89	94
6	6	86	89
7	7	83	76
8	8[c]	95	70
9	9[d]	82	38
10	10[b]	80	90
11	11[b]	75	93
12	12[b]	73	88

[a] Methods and spectroscopic data are given in the Experimental Section; for all structures: (a) R = CH_2CH_2Br; (b) R = CH_2CH_2I; (c) R = H. [b] These iodoethyl esters were prepared directly from the corresponding acid (RCO_2H/iodoethanol/DCC), as described for compound **1b**. [c] The preparation of this compound is described in ref 8. [d] The preparations of **7a** and **9a** are described in refs 1 and 3.

compounds, and the results are summarized in Table 1. For simple 2-iodoethyl ester derivatives, reaction conditions A worked well and gave products of high purity in excellent yields. For amino acid derivatives, reaction conditions A (for *N*-Cbz) or B (for *N*-Boc) gave good to excellent yields. We next turned our attention to the possibility of racemization during the deprotection reaction. For this investigation, the racemization-prone phenylglycine derivative **2** was chosen as a model compound. Conversion of **2c** ($[\alpha]^{22}_D$ = −121.2°, *c* 0.58, EtOAc) to **2a** (2-bromoethanol, DCC, HOBT, DMF, CH_2Cl_2, 0 °C, 17 h, 86%) then to **2b** (NaI, acetone, Δ), followed by deprotection of **2b**, returned **2c** without change in optical rotation ($[\alpha]^{22}_D$ = −121.0°, *c* 0.48, EtOAc), showing that no racemization occurs during the entire protection/halide exchange/deprotection sequence.

Conclusions

The 2-iodoethyl ester protecting group is removed successfully with SmI_2 under mild conditions. Theoretically, 2.0 equiv of SmI_2 is sufficient for this deprotection reaction, and the requirement for a large excess of this reagent may be due to its instability. In this context it may be noted that the deprotection does not proceed to completion unless oxygen is rigorously excluded, owing to competing oxidation of the samarium reagent. A two-step sequence (Finkelstein reaction, followed by deprotection with SmI_2) provides useful methodology for the deprotection of 2-bromoethyl esters. The latter protecting group is more stable than iodoethyl toward various reaction conditions, but its direct removal is problematic.

Experimental Section

SmI_2 (0.1 M in THF) was purchased from Aldrich Co. and used directly. All reactions using SmI_2 were performed under dry oxygen-free argon. All spectroscopic and general procedures were as described previously.[1]

General Procedure for the Preparation of 2-Bromoethyl Esters and Direct Preparation of 2-Iodoethyl esters. See the preparation of **6a** and **1b**, respectively.

General Procedure for Finkelstein Reaction. See the preparation of **9b**.

General Procedure for the Deprotection of Iodoethyl Esters Using SmI_2. See the preparation of **2c** and **7c**.

***N*-[(1,1-Dimethylethoxy)carbonyl]-4-chloro-D-phenylalanine 2-Iodoethyl Ester (1b).** To a precooled (0 °C), stirred solution of *N*-Boc-4-chloro-D-phenylalanine (556 mg, 1.86 mmol) in 20 mL of CH_2Cl_2 under N_2 were added 174 μL (1.2 equiv) of 2-iodoethanol followed by 301 μL of pyridine (2.0 equiv) by syringe. The mixture was stirred for 10 min at 0 °C and then 422 mg of DCC (1.1 equiv) was added in one portion. The resulting mixture was stirred for 16 h at 0 °C under N_2 in the dark. The reaction was quenced by the addition of 25 mg (0.15 equiv) of oxalic acid in 0.5 mL of THF and then it was allowed to come to rt and stirred for 30 min. The solid was filtered off and the filter cake was washed well with CH_2Cl_2 (10 mL × 3). The combined organic extracts were washed with 0.1 N HCl and brine and dried over $MgSO_4$, and the solvent was removed *in vacuo* to give a solid residue. Purification by flash chromatography on silica gel (Hex/EtOAc, 7/3) gave 629 mg (75%) of **1b** as a white solid: mp 80.5–81.5 °C; R_f 0.37 (Hex/EtOAc, 7/3); IR ($CHCl_3$) 3438, 3026, 2982, 2934, 1744, 1711, 1493 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, 2 H, *J* = 8.3 Hz), 7.11 (d, 2 H, *J* = 8.3 Hz), 4.96 (d, 1 H, *J* = 7.2 Hz), 4.59–4.57 (m, 1 H), 4.39–4.34 (m, 2 H), 3.28–3.00 (m, 4 H, $CO_2CH_2CH_2I$ overlapping with ArC*H*HCH, ArCH*H*CH), 1.42 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 155.0, 134.4, 133.0, 130.7, 128.7, 80.2, 65.4, 54.2, 37.7, 28.3, −0.6; HRMS calcd for $C_{16}H_{21}NO_2ClI$ 453.0206, found 453.0213.

***N*-[(1,1-Dimethylethoxy)carbonyl]-4-chloro-D-phenylalanine (1c):** yield 82%; mp 106.5–108.5 °C; $[\alpha]^{22}_D$ −28.7° (*c* 0.2, EtOAc); R_f 0.35 (EtOAc/MeOH, 9/1); IR ($CHCl_3$) 3438, 3026, 2982, 1719, 1653, 1493, 1221 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 12.62 (bs, 1 H), 7.32–7.24 (m, 4 H), 7.10 (d, 1 H, *J* = 8.8 Hz), 4.11–4.04 (m, 1 H), 3.00 (dd, 1 H, *J* = 13.7, 3.8 Hz), 2.80 (dd, 1 H, *J* = 13.7, 10.9 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.4, 155.4, 137.1, 131.0, 128.0, 78.1, 55.0, 35.8, 28.1.

***N*-[(Phenylmethoxy)carbonyl]-D-phenylglycine 2-bromoethyl ester (2a):** yield 86%; mp 62–64 °C; $[\alpha]^{22}_D$ −50.1° (*c* 0.74, EtOAc); R_f 0.30 (Hex/EtOAc, 7/3); IR ($CHCl_3$) 3435, 3036, 2946, 1723, 1500, 1216 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.25 (m, 10 H), 5.78 (d, 1 H, *J* = 7.3 Hz, $PhCH_2OCONHCH$), 5.41 (d, 1 H, *J* = 7.3 Hz, $PhCH_2OCONHCH$), 5.13 (d, 1 H, *J* = 12.2 Hz, PhC*H*HOCO), 5.08 (d, 1 H, *J* = 12.2 Hz, PhCH*H*OCO), 4.40 (m, 2 H, $CO_2CH_2CH_2Br$), 3.41 (m, 2 H, $CO_2CH_2CH_2Br$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 155.3, 136.0, 129.0, 128.7, 128.5, 128.2, 127.2, 67.2, 64.8, 58.0, 27.7; HRMS calcd for $C_{18}H_{18}NO_4Br$ 391.0420, found 391.0408.

***N*-[(Phenylmethoxy)carbonyl]-D-phenylglycine 2-iodoethyl ester (2b):** yield 87%; mp 68.5–70.5 °C; $[\alpha]^{25}_D$ −55.3° (*c* 0.6, $CHCl_3$); R_f 0.36 (Hex/EtOAc, 7/3); IR ($CHCl_3$) 3435, 3014, 2967, 1742, 1723, 1602, 1517 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 7.37–7.26 (m, 10 H), 5.78 (d, 1 H, *J* = 7.1 Hz), 5.39 (d, 1 H, *J* = 7.1 Hz), 5.13 (d, 1 H, *J* = 12.1 Hz), 5.08 (d, 1 H, *J* = 12.1 Hz), 4.40–4.33 (m, 2 H), 3.49–3.17 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 155.3, 136.1, 136.0, 129.0, 128.7, 128.5, 128.2, 127.2, 67.2, 65.6, 58.0, −0.9; HRMS calcd for $C_{18}H_{18}NO_4I$ 439.0282, found 439.0283.

***N*-[(Phenylmethoxy)carbonyl]-D-phenylglycine (2c).** To a stirred, precooled (0 °C) solution of 2-iodoethyl ester (**2b**, 10 mg, 0.18 mmol) in 10 mL of THF was added 10.9 mL (6.0 equiv, 0.1 M in THF) of SmI_2 by syringe. The resulting mixture was warmed to 40 °C and stirred for 8 h under deoxygenated argon. The mixture was cooled to rt, diluted with 30 mL of EtOAc, and quenched by the addition of 10 mL of 0.1 N HCl. The organic layer was separated and the aqueous layer was washed with EtOAc (10 mL × 2). The combined organic extracts were washed with 10 mL of 0.2 M sodium thiosulfate and brine and dried over $MgSO_4$, and the solvent was removed *in vacuo* to give a yellow residue. Purification by short column chromatography on silica gel (1 × 15 cm, EtOAc/MeOH, 95/5) afforded 46 mg (88%) of **2c** as a white solid: mp 127.5–129.5 °C; $[\alpha]^{24}_D$ −121.0° (*c* 0.48, EtOAc); R_f 0.21 (EtOAc/MeOH, 9/1); IR ($CHCl_3$) 3436, 3026, 1725, 1667, 1497 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 12.86 (bs, 1 H, $PhCHCO_2H$), 8.11 (d, 1 H, *J* = 8.1 Hz, $PhCH_2OCONH$), 7.41–7.30 (m, 10 H), 5.16 (d, 1 H, *J* = 8.1 Hz, $PhCHCO_2H$), 5.04 (s, 2 H, $PhCH_2OCONH$); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.0, 155.8, 137.1, 136.9, 128.4, 127.7, 65.6, 58.0; HRMS calcd for $C_{16}H_{15}NO_4$ 285.1001, found 285.1001.

3-(4-Methoxyphenyl)propionic acid 2-bromoethyl ester (3a): yield 72%; R_f 0.56 (Hex/EtOAc, 6/4); IR ($CHCl_3$) 3014, 1734, 1514 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.11 (d, 2 H, *J* = 8.6 Hz), 6.82 (d, 2 H, *J* = 8.6 Hz), 4.35 (t, 2 H, *J* = 6.1 Hz, $CO_2CH_2CH_2Br$), 3.76 (s, 3 H, OCH_3), 3.45 (t, 2 H, *J* = 6.1 Hz, OCH_2CH_2-

Br), 2.90 (t, 2 H, J = 7.7 Hz, ArCH_2CH$_2$CO$_2$), 2.63 (t, 2 H, J = 7.7 Hz, ArCH$_2$CH_2CO$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 158.0, 132.1, 129.1, 113.8, 63.6, 55.1, 35.8, 29.9, 28.6; HRMS calcd for $C_{12}H_{15}O_3Br$ 286.0205, found 286.0203.

3-(4-Methoxyphenyl)propionic acid 2-iodoethyl ester (3b): yield 86%; R_f 0.49 (Hex/EtOAc, 7/3); IR ($CHCl_3$) 3020, 1734, 1514 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, J = 8.6 Hz, 2 H), 6.83 (d, J = 8.6 Hz, 2 H), 4.32 (t, J = 6.9 Hz, 2 H, OCH_2CH$_2$I), 3.78 (s, 3 H), 3.25 (t, J = 6.9 Hz, 2 H, OCH$_2$CH_2I), 2.91 (t, J = 7.7 Hz, 2 H, ArCH_2CH$_2$CO$_2$), 2.63 (t, J = 7.7 Hz, 2 H, ArCH$_2$CH_2-CO$_2$); ^{13}NMR (75 MHz, $CDCl_3$) δ 172.3, 158.1, 132.3, 129.2, 113.9, 64.5, 55.3, 36.0, 30.0, 0.3; HRMS calcd for $C_{12}H_{15}O_3I$ 334.0068, found 334.0067.

3-(4-Methoxyphenyl)propionic acid (3c): yield 93%; mp 102.5–104.0 °C (Aldrich catalogue: 98–100 °C); R_f 0.56 (Hex/EtOAc, 2/8); IR ($CHCl_3$) 3011, 2957, 1711, 1612, 1514, 1248 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.98 (bs, 1 H), 7.12 (d, 2 H, J = 8.0 Hz), 6.83 (d, 2 H, J = 8.0 Hz), 3.79 (s, 3 H), 2.90 (t, 2 H, J = 7.7 Hz), 2.65 (t, 2 H, J = 7.7 Hz).

3-[3-(Benzyloxy)-4-methoxyphenyl]propionic acid 2-bromoethyl ester (4a): yield 83%; mp 44.0–45.5 °C; R_f 0.35 (Hex/EtOAc, 8/2); IR ($CHCl_3$) 3016, 1737, 1515 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.27 (m, 5 H), 6.84–6.74 (m, 3 H), 5.13 (s, 2 H, OCH_2Ph), 4.34 (t, 2 H, J = 6.2 Hz), 3.86 (s, 3 H), 3.45 (t, 2 H, J = 6.2 Hz), 2.86 (t, 2 H, J = 7.7 Hz), 2.60 (t, 2 H, J = 7.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 148.3, 148.1, 137.1, 132.8, 128.5, 127.8, 127.3, 120.8, 114.5, 111.9, 71.0, 63.7, 56.1, 35.8, 30.3, 28.7; HRMS calcd for $C_{19}H_{21}O_4Br$ 392.0624, found 392.0629.

3-[3-(Benzyloxy)-4-methoxyphenyl]propionic acid 2-iodoethyl ester (4b): yield 91%; mp 52.5–54.0 °C; R_f 0.55 (Hex/EtOAc, 8/2); IR ($CHCl_3$) 3016, 1737, 1515 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–7.26 (m, 5 H), 6.84–6.74 (m, 3 H), 5.13 (s, 2 H), 4.29 (t, 2 H, J = 6.8 Hz), 3.86 (s, 3 H) 3.23 (t, 2 H, J = 6.8 Hz), 2.86 (t, 2 H, J = 7.7 Hz), 2.59 (t, 2 H, J = 7.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 148.3, 148.1, 137.1, 132.8, 128.5, 127.8, 127.3, 120.8, 114.5, 111.9, 71.0, 64.4, 56.1, 35.9, 30.4, 0.4; HRMS calcd for $C_{19}H_{21}O_4I$ 440.0486, found 440.0487.

3-[3-(Benzyloxy)-4-methoxyphenyl]propionic acid (4c): yield 91%; mp 122.5–124.5 °C; R_f 0.41 (Hex/EtOAc, 2/8); IR ($CHCl_3$) 3522, 3017, 2935, 1710, 1591, 1515, 1256, 1211 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.26 (m, 5 H), 6.84–6.74 (m, 3 H), 5.13 (s, 2 H), 3.86 (s, 3 H), 2.85 (t, 2 H, J = 7.7 Hz), 2.60 (t, 2 H, J = 7.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.0, 148.2, 148.0, 137.1, 132.6, 128.5, 127.8, 127.3, 120.7, 114.5, 111.9, 71.0, 56.0, 35.7, 30.0; HRMS calcd for $C_{17}H_{18}O_4$ 286.1205, found 286.1210.

3-(Benzyloxy)-4-methoxyphenylacetic acid 2-bromoethyl ester (5a): yield 71%; mp 54.0–55.5 °C; R_f 0.32 (Hex/EtOAc, 8/2); IR ($CHCl_3$) 3019, 2944, 1736, 1515 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–7.25 (m, 5 H), 6.86–6.82 (m, 3 H), 5.15 (s, 2 H), 4.35 (t, 2 H), 3.87 (s, 3 H), 3.54 (s, 2 H), 3.44 (t, 2 H, J = 6.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 148.9, 148.1, 137.0, 128.5, 127.8, 127.3, 125.9, 122.0, 115.0, 111.8, 70.9, 64.0, 56.0, 40.6, 28.6; HRMS calcd for $C_{18}H_{19}O_4Br$ 378.0467, found 378.0464.

3-(Benzyloxy)-4-methoxyphenylacetic acid 2-iodoethyl ester (5b): yield 89%; mp 59.5–61.5 °C; R_f 0.35 (Hex/EtOAc, 7/3); IR ($CHCl_3$) 3019, 2936, 1734, 1515 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.25 (m, 5 H), 6.86–6.84 (m, 3 H), 5.16 (s, 2 H), 4.28 (t, 2 H, J = 6.8 Hz), 3.86 (s, 2 H), 3.53 (s, 2 H), 3.20 (t, 2 H, J = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 148.9, 148.1, 137.0, 128.5, 127.8, 127.2, 125.9, 122.0, 115.0, 111.8, 70.9, 64.7, 56.0, 40.6, 0.2; HRMS calcd for $C_{18}H_{19}O_4I$ 426.0330, found 426.0319.

3-(Benzyloxy)-4-methoxyphenylacetic acid (5c): yield 94%; mp 122.0–123.5 °C (lit.[6] 123.0–125.0 °C); R_f 0.47 ($CHCl_3$/MeOH, 10/1); IR ($CHCl_3$) 3020, 2936, 1711, 1515, 1443 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.25 (m, 5 H), 6.85 (s, 3 H), 5.13 (s, 2 H), 3.87 (s, 3 H), 3.55 (s, 2 H).

***N*-[(Phenylmethoxy)carbonyl]glycine 2-bromoethyl ester (6a).** To a stirred, precooled (0 °C) solution of *N*-Cbz-glycine (1.00 g, 4.78 mmol) in 40 mL of dry CH_2Cl_2 were added 407 μL (1.2 equiv) of 2-bromoethanol, followed by 773 μL (2.0 equiv) of pyridine by syringe. The mixture was stirred for 10 min at 0 °C, 1.09 g (1.1 equiv) of DCC was added in one portion, and the resulting mixture was stirred for 16 h at 0 °C under N_2. The reaction was quenched with 143 μL (0.15 equiv) of 5 M oxalic acid in THF, allowed to come to rt, and stirred further for 30 min. The mixture was filtered and the filter cake was washed well with CH_2Cl_2 (10 mL × 3). The combined organic extracts were washed with dilute HCl (0.1 N, 20 mL) and brine and dried over $MgSO_4$. After removal of solvent *in vacuo*, the crude product was flash-chromatographed (silica gel, Hex/EtOAc, 7/3) to give 1.27 g (84%) of pure product **6a** as a pale yellow solid: mp 59.0–60.0 °C; R_f 0.21 (Hex/EtOAc, 7/3); IR ($CHCl_3$) 3452, 3020, 1752, 1724, 1517, 1220 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.29 (m, 5 H), 5.26 (bs, 1 H, PhCH$_2$OCON*H*), 5.14 (s, 2 H, PhCH_2-OCONH), 4.46 (t, 2 H, J = 6.1 Hz, CO$_2$CH_2CH$_2$Br), 4.04 (d, 2 H, J = 5.6 Hz, NHCH_2CO$_2$), 3.51 (t, 2 H, J = 6.1 Hz, CO$_2$CH$_2$CH_2-Br); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 156.2, 136.1, 128.5, 128.2, 128.1, 67.1, 64.5, 42.6, 28.1; HRMS calcd for $C_{12}H_{14}NO_4Br$ 315.0107, found 315.0104.

***N*-[(Phenylmethoxy)carbonyl]glycine 2-iodoethyl ester (6b):** yield 86%; mp 85.5–87.0 °C; R_f 0.26 (Hex/EtOAc, 7/3); IR ($CHCl_3$) 3447, 3021, 1751, 1724, 1517 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.26 (m, 5 H), 5.24 (bs, 1 H, PhCH$_2$OCON*H*), 5.14 (s, 2 H, PhCH_2OCO), 4.41 (t, 2 H, J = 6.8 Hz, CO$_2$CH_2CH$_2$I), 4.02 (d, 2 H, J = 5.7 Hz, NHCH_2CO$_2$), 3.29 (t, 2 H, J = 6.8 Hz, CO$_2$-CH$_2$CH_2I); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 156.2, 136.1, 128.5, 128.2, 128.1, 67.2, 65.3, 42.7, –0.5; HRMS calcd for $C_{12}H_{14}NO_4I$ 362.9969, found 362.9967.

***N*-[(Phenylmethoxy)carbony]glycine (6c):** yield 89%; mp 116.5–118.5 °C (lit.[7] 118–119 °C); R_f 0.25 (EtOAc/MeOH, 9/1); IR ($CHCl_3$) 3451, 3018, 1726, 1517 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.24 (m, 5 H), 5.23 (bs, 1 H, OCON*H*CH$_2$), 5.14 (s, 2 H, ArCH_2OCO), 4.06 (d, 2 H, J = 6.7 Hz, NHCH_2CO$_2$H).

(*R*)-4-*O*-[3-[1-[[(Phenylmethoxy)carbonyl]amino]-1-(methoxycarbonyl)methyl]phenoxy]-*N*-[(1,1-dimethylethoxy)carbonyl]-D-tyrosine α-(2-Bromoethyl) Ester (7a). Obtained as an oily foam; $[\alpha]^{24}_D$ –9.2° (*c* 0.47, $CHCl_3$); R_f 0.50 (Hex/EtOAc, 6/4); IR ($CHCl_3$) 3434, 3020, 1742, 1718, 1506 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–6.88 (m, 13 H), 5.96 (d, 1 H, J = 7.2 Hz, PhCH$_2$OCON*H*CH), 5.36 (d, 1 H, J = 7.2 Hz, PhCH$_2$OCONHC*H*), 5.14–5.04 (m, 3 H, PhCH_2OCO overlapping with N*H*CO$_2$C(CH$_3$)$_3$), 4.61–4.57 (m, 1 H, ArCH$_2$C*H*CO$_2$), 4.42–4.36 (m, 2 H, CO$_2$CH_2-CH$_2$Br), 3.71 (s, 3 H, CO$_2$CH_3), 3.47–3.43 (m, 2 H, CO$_2$CH$_2$CH_2-Br), 3.14–3.00 (m, 2 H, ArCH_2CHCO$_2$), 1.42 (s, 9 H, NHCO$_2$C-(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 170.9, 157.5, 155.7, 155.3, 155.0, 138.4, 136.0, 131.0, 130.6, 130.1, 128.4, 128.1, 121.7, 119.0, 118.4, 117.5, 80.0, 67.1, 64.5, 57.5, 54.4, 52.8, 37.4, 28.2.

(*R*)-4-[3-[1-[[(Phenylmethoxy)carbonyl]amino]-1-(methoxycarbonyl)methyl]phenoxy]-*N*-[(1,1-dimethylethoxy)carbonyl]-D-tyrosine α-(2-Iodomoethyl) Ester (7b): yield 83%; oily foam; $[\alpha]^{25}_D$ –5.5° (*c* 0.55, $CHCl_3$); R_f 0.51 (Hex/EtOAc, 6/4); IR ($CHCl_3$) 3436, 3019, 1743, 1718, 1506 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–6.89 (m, 13 H), 5.89 (d, 1 H, J = 7.4 Hz), 5.36 (d, 1 H, J = 7.4 Hz), 5.11–5.00 (m, 3 H), 4.63–4.57 (m, 1 H), 4.39–4.34 (m, 2 H), 3.78 (s, 3 H), 3.27–3.22 (m, 2 H), 3.17–3.01 (m, 2 H), 1.42 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 170.9, 157.6, 155.8, 155.2, 155.0, 138.5, 136.0, 131.0, 130.7, 130.2, 128.5, 128.1, 121.8, 119.1, 118.5, 117.6, 80.1, 67.1, 65.3, 57.6, 54.4, 52.9, 37.6, 28.3, –0.4.

(*R*)-4-[3-[1-[[(Phenylmethoxy)carbonyl]amino]-1-(methoxycarbonyl)methyl]phenoxy]-*N*-[(1,1-dimethylethoxy)carbonyl]-D-tyrosine (7c). To a stirred, precooled (0 °C) solution of **7b** (84 mg, 0.11 mmol) in 10 mL of freshly distilled THF was added 8.1 mL (7.0 equiv) of SmI_2 (0.1 M in THF) by syringe, and the resulting mixture was warmed to 35 °C for 10 h under deoxygenated argon. The reaction mixture was cooled to rt, diluted with 20 mL of EtOAc, and quenched by the addition of 10 mL of 0.1 N HCl. The organic layer was separated and the aqueous layer was washed well with EtOAc (10 mL × 2). The combined organic extracts were washed with 10 mL of 0.2 M sodium thiosulfate solution, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a solid residue. Purification by short column chromatography on silica gel (1 × 15 cm, Hex/EtOAc, 2/8) gave 50 mg (76%) of pure acid **7c**: $[\alpha]^{26}_{Hg,365}$ –1.8° (*c* 0.5, CH_3CN); R_f 0.25 (EtOAc/MeOH, 9/1); IR ($CHCl_3$) 3433, 3028, 3012, 2982, 1750, 1716, 1590, 1506, 1223 cm^{-1}; ^{1}H NMR (300

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MHz, CD_3CN + $CDCl_3$) δ 7.36–6.90 (m, 13 H), 6.39 (d, 1 H, J = 7.2 Hz), 5.40 (d, 1 H, J = 7.2 Hz), 5.28 (d, 1 H, J = 7.7 Hz), 5.07 (s, 2 H), 4.35 (bs, 1 H), 3.68 (s, 3 H), 3.13 (dd, 1 H, J = 14.5, 4.3 Hz), 2.91 (dd, 1 H, J = 14.5, 8.3 Hz).

(*S*)-3-[4-[2-[[(1,1-Dimethylethoxy)carbonyl]amino]-3-oxo-3-(2-iodoethoxy)propyl]phenoxy]-*O*-methyl-*N*-[*O*-methyl-*N*-[(phenylmethoxy)carbonyl]-L-tyrosyl]-L-tyrosine α-Methyl Ester (8b). Details for the preparation of this compound are given elesewhere:[8] mp 63.5–65.5 °C; $[\alpha]^{26}_D$ +34.3° (*c* 0.58, $CHCl_3$); R_f 0.19 (Hex/EtOAc, 6/4); IR ($CHCl_3$) 3427, 3028, 2983, 1742, 1713, 1683, 1612, 1505, 1228 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–6.59 (m, 16 H), 6.27 (d, 1 H, J = 7.1 Hz), 5.33 (bs, 1 H), 5.12–5.04 (m, 3 H), 4.72–4.68 (m, 1 H), 4.56–4.54 (m, 1 H), 4.36–4.32 (m, 3 H), 3.77 (s, 3 H), 3.76 (s, 3 H), 3.60 (s, 3 H), 3.25–3.20 (m, 2 H), 3.11–2.85 (m, 6 H), 1.41 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 171.1, 170.4, 158.6, 157.1, 155.8, 155.1, 150.6, 144.4, 136.1, 130.4, 130.3, 129.7, 128.5, 128.4, 128.1, 127.9, 125.7, 122.1, 116.9, 114.0, 112.8, 80.0, 67.0, 65.2, 56.1, 55.9, 55.1, 54.4, 53.3, 52.3, 37.5, 37.3, 37.0, 28.2, –0.4. Anal. Calcd for $C_{45}H_{52}N_3O_{12}I$: C, 56.65; H, 5.50. Found: C, 56.56; H, 5.43.

(*S*)-3-[4-[2-Carboxy-2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]phenoxy]-*O*-methyl-*N*-[*O*-methyl-*N*-[(phenylmethoxy)carbonyl]-L-tyrosyl]-L-tyrosine α-Methyl Ester (8c): yield 70%; $[\alpha]^{23}_{Hg,365}$ +30.4° (*c* 0.38, MeOH, lit.[9] +27.6° (*c* 0.54, MeOH)); R_f 0.17 (EtOAc/MeOH, 9/1); IR ($CHCl_3$) 3412, 3054, 2985, 2939, 2865, 1741, 1715, 1684, 1612, 1513, 1262 cm^{-1}; ^1H NMR (300 MHz, $CD_3CN/CDCl_3$, 70:30) δ 7.34–6.72 (m, 17 H), 5.70 (bd, 1 H, J = 6.3 Hz), 5.33 (bd, 1 H, J = 7.0 Hz), 5.05 (d, 1 H, J = 12.6 Hz), 4.98 (d, 1 H, J = 12.6 Hz), 4.65–4.58 (m, 1 H), 4.40–4.24 (m, 2 H), 3.75 (s, 3 H), 3.74 (s, 3 H), 3.62 (s, 3 H), 3.08–2.73 (m, 6 H), 1.38 (s, 9 H).

(*R*)-3-[4-[2-[[(1,1-Dimethylethoxy)carbonyl]amino]-2-[[[[[(2-iodoethyl)oxy]carbonyl]methyl]amino]carbonyl]-ethyl]phenoxy]-*N*-[(phenylmethoxy)carbonyl]-D-phenylglycine α-Methyl Ester (9b). To a stirred solution of the corresponding bromide[1] (190 mg, 0.26 mmol) in 10 mL of dry acetone was added 192 mg (5.0 equiv) of NaI (anhydrous 99+%) and the resulting slurry was heated at reflux for 7 h under N_2. The reaction mixture was cooled to rt and filtered, and the filter cake was washed well with acetone (10 mL × 3). The combined organic extracts were evaporated to provide a solid residue which was dissolved in 50 mL of CH_2Cl_2, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was flash-chromatographed on silica gel (Hex/EtOAc, 6/4) to give 166 mg (82%) of **9b** as a white solid: mp 46.0–48.0 °C; $[\alpha]^{26}_D$ –1.8° (*c* 0.56, $CHCl_3$); R_f 0.28 (Hex/EtOAc, 6/4); IR ($CHCl_3$) 3430, 3019, 1734, 1718, 1685, 1507, 1220 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–6.89 (m, 13 H), 6.67–6.65 (m, 1 H, CONHCH$_2$CO$_2$), 5.97 (bs, 1 H, NHCO$_2$CH$_2$Ph), 5.36 (d, 1 H, J = 6.1 Hz, CHNHCO$_2$CH$_2$Ph), 5.19 (d, 1 H, J = 7.7 Hz, NHCO$_2$(CCH$_3$)$_3$), 5.12 (d, 1 H, J = 12.4 Hz, PhCHHOCONH), 5.07 (d, 1H, J = 12.4 Hz, PhCHHOCONH), 4.42–4.35 (m, 3 H, CHNHCO$_2$C(CH$_3$)$_3$ overlapping with CO$_2$CH$_2$CH$_2$I), 4.02–3.96 (m, 2 H, NHCH$_2$CO$_2$), 3.72 (s, 3 H, ArCHCO$_2$CH$_3$), 3.28–3.24 (m, 2 H, CO$_2$CO$_2$CH$_2$I), 3.14–2.98 (m, 2 H, ArCH$_2$CHCONH), 1.40 (s, 9 H, NHCO$_2$C(CH$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 170.9, 168.8, 157.7, 155.4, 155.3, 138.4, 136.0, 131.8, 130.7, 130.1, 128.4, 128.1, 121.6, 119.2, 118.2, 117.3, 80.2, 67.1, 65.2, 57.5, 55.6, 52.9, 41.1, 37.6, 28.2, –0.5. Anal. Calcd for $C_{35}H_{40}N_3O_{10}I$: C, 53.22; H, 5.11. Found: C, 52.82; H, 5.24.

(*R*)-3-[4-[2-[[(1,1-Dimethylethoxy)carbonyl]amino]-2-[[(carboxymethyl)amino]carbonyl]ethyl]phenoxy]-*N*-[(phenylmethoxy)carbonyl]-D-phenylglycine α-Methyl Ester (9c): yield 38%; $[\alpha]^{23}_{Hg,436}$ +2.4° (*c* 0.34, MeOH); IR ($CHCl_3$) 3426, 3020, 2961, 2927, 1724, 1675, 1507, 1217 cm^{-1}; ^1H NMR (300 MHz, CD_3CN + $CDCl_3$) δ 7.42–6.78 (m, 13 H), 6.37–6.32 (m, 1 H, CONHCH$_2$CO$_2$), 5.42–5.26 (m, 2 H, NHCO$_2$CH$_2$Ph overlapping with CHNHCO$_2$CH$_2$Ph), 5.11 (d, 1 H, J = 12.6 Hz, NHCO$_2$CHHPh), 5.03 (d, 1 H, J = 12.6 Hz, NHCO$_2$CHHPh), 4.38–4.28 (m, 2 H, NHBoc overlapping with CHNHBoc), 3.89–3.75 (m, 2 H, NHCH$_2$CO$_2$), 3.69 (s, 3 H, CO$_2$CH$_3$), 3.10–2.86 (m, 2 H, ArCH$_2$), 1.38 (s, 9 H, Boc).

3-(4-Chlorophenyl)propionic acid 2-Iodoethyl Ester (10b). Prepared as described for compound **1b**: yield 80%; R_f 0.49 (Hex/EtOAc, 8/2); IR ($CHCl_3$) 3019, 1735, 1493 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, 2 H, J = 8.3 Hz), 7.14 (d, 2 H, J = 8.3 Hz), 4.32 (t, 2 H, J = 6.8 Hz), 3.26 (t, 2 H, J = 6.8 Hz), 2.94 (t, 2 H, J = 7.6 Hz), 2.65 (t, 2 H, J = 7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 138.6, 132.0, 129.6, 128.5, 64.4, 35.3, 30.0, 0.4; HRMS calcd for $C_{11}H_{12}O_2ClI$ 337.9572, found 337.9573.

3-(4-Chlorophenyl)propionic acid (10c): yield 90%; mp 120.5–122.0 °C (lit.[10] 122–123 °C); R_f 0.45 (MeOH/$CHCl_3$, 1/9); IR ($CHCl_3$) 3019, 2949, 1712, 1493, 1409 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) d 7.27 (d, 2 H, J = 8.5 Hz), 7.14 (d, 2 H, J = 8.5 Hz), 2.93 (t, 2 H, J = 7.4 Hz), 2.67 (t, 2 H, J = 7.4 Hz).

***n*-Octanoic Acid 2-Iodoethyl Ester (11b).** Prepared as described for compound **1b**: yield 75%; R_f 0.47 (Hex/CH_2Cl_2, 1/1); IR ($CHCl_3$) 2955, 2930, 2857, 1734, 1602, 1468, 1220 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.33 (t, 2 H, J = 6.8 Hz), 3.30 (t, 2 H, J = 6.8 Hz), 2.34 (t, 2 H, J = 7.5 Hz), 1.66–1.62 (m, 2 H), 1.30–1.28 (m, 8 H), 0.88 (t, 3 H, J = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 64.2, 34.1, 31.6, 29.0, 28.8, 24.8, 22.5, 14.0, 0.5; HRMS calcd for $C_{10}H_{19}O_2I$ 298.0432, found 298.0434.

***n*-Octanoic acid (11c):** yield 93%; IR ($CHCl_3$) 2958, 2930, 1708 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.35 (t, 2 H, J = 7.5 Hz), 1.66–1.59 (m, 2 H), 1.31–1.28 (m, 8H), 0.88 (t, 3 H, J = 6.8 Hz).

3-(Benzyloxy)phenylacetic Acid 2-Iodoethyl Ester (12b). Prepared as described for compound **1b**: yield 73%; R_f 0.49 (Hex/EtOAc, 8/2); IR ($CHCl_3$) 3019, 1737, 1600, 1519 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45–7.22 (m, 5 H), 6.93–6.88 (m, 3 H), 5.06 (s, 2 H), 4.33 (t, 2 H, J = 6.9 Hz), 3.62 (s, 2 H), 3.26 (t, 2 H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 158.8, 136.8, 134.9, 129.5, 128.5, 127.9, 127.4, 121.8, 115.8, 113.6, 69.8, 64.8, 41.1, 0.2; HRMS calcd for $C_{17}H_{17}O_3I$ 396.0224, found 396.0226.

3-(Benzyloxy)phenylacetic acid (12c): yield 88%; mp 123.0–125.0 °C; R_f 0.52 (EtOAc/MeOH, 9/1); IR ($CHCl_3$) 3012, 2917, 1712, 1598 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42–7.18 (m, 5 H), 6.89–6.84 (m, 3 H), 5.02 (s, 2 H), 3.60 (s, 2 H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 177.6, 159.0, 136.8, 134.6, 129.7, 128.6, 128.0, 127.5, 122.0, 116.0, 113.7, 90.0, 41.0; HRMS calcd for $C_{15}H_{14}O_3$ 242.0943, found 242.0941.

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Supplementary Material Available: Copies of ^1H and ^{13}C NMR spectra of all compounds (54 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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