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Synthesis of GABOB and GABOB-Based Chiral Units Possessing Distinct Protecting Groups

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In addition to the varied biological activity of GABOB (4-amino-3-hydroxybutanoic acid), the structure of its protected derivatives makes them interesting chiral intermediates for the synthesis of more complex compounds. A stereoselective route to GABOB derivatives with three different protecting groups is presented, using anhydride desymmetrization as a chirality-inducing step. Selective removal of the protecting groups gave compounds with a free carboxylic acid or hydroxy group. Removal of all of the protecting groups allowed GABOB to be isolated in good yield and with excellent *ee*.

Introduction

As a metabolic derivative of the neurotransmitter γ-aminobutanoic acid, GABOB (4-amino-3-hydroxybutanoic acid; Figure 1)[1a] has various biological activities and may, among other uses, be used in the treatment of personality disorder conditions such as epilepsy and schizophrenia.[2,3] In addition, due to its specific structure, it has recently been recognized as an interesting chiral segment that could be useful in the synthesis of other biologically active natural products, such as carnitine (vitamin B_t), negamycin[4] (an antibiotic), or microsclerodermin E[5] (an antitumor cyclic peptide).

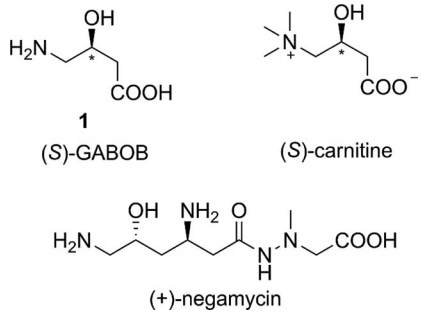

Figure 1. GABOB and structurally related natural products.

As research into γ-amino acids is an area of intense study,[1b] due to both their pharmacological properties and their use as building blocks for the synthesis of other biologically active compounds, different ways to synthesize GABOB are known. Racemic GABOB is, for example, available from allyl cyanide in four steps: preparation of the epoxide, opening with azide, hydrogenation, and hydrolysis.[6] As regards the optically pure compound, syntheses of (*R*)-GABOB have been described starting from chiral materials such as ascorbic acid,[7] malic acid,[8] hydroxyproline esters,[9] or 4-chloro-3-hydroxybutanoic acid.[10]

The asymmetric synthesis of enantiopure compounds starting from achiral materials is a focus of current research. Thus, several asymmetric routes to **1** and its analogues have been reported,[1] including enzymatic methods,[11–13] the addition of organometallic reagents to lactones,[14] or osmium-catalysed asymmetric aminohydroxylation.[15]

To address the need for metal-free catalytic methods suitable for the production of both enantiomers, we report in this paper a stereoselective route to GABOB and its derivatives with distinct protecting groups, using the organocatalytic opening of anhydrides for the introduction of chirality.

Results and Discussion

While planning the synthesis, the stable and easily removable benzyl ether (Bn) seemed to be a reasonable choice for a hydroxy protecting group (PG^1). However, *O*-alkylation of diethyl 3-hydroxyglutarate (**2**) proved to be quite challenging. While esters and silyl ethers[16] of **2** are readily available, to the best of our knowledge, alkyl ethers of **2** have not been described in the literature.

With diethyl 3-hydroxyglutarate, our initial attempts met with little success. Alkylation with silver oxide and benzyl bromide, or via a trichloroacetimidate intermediate, proceeded in poor yields (Table 1, entries 2 and 3). Under

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Williamson conditions (NaH, benzyl bromide), the desired product was not observed at all.

Table 1. *O*-Protection of diethyl 3-hydroxyglutarate (**2**).

Entry	PG^1	Conditions	Yield [%]
1	Bn	NaH, BnBr	–
2	Bn	Ag_2O, BnBr	30
3	Bn	$BnOC(NH)CCl_3$, TfOH[a]	35
4	Bn	1. TMSCl, imidazole 2. $FeCl_3$, Et_3SiH, PhCHO	76
5	Cinn	1. TMSCl, imidazole 2. $FeCl_3$, Et_3SiH, cinnamaldehyde	41
6	BOM	BOM-Cl, DIPEA, TBAI	85
7	TBDMS	TBDMS-Cl, imidazole	99

[a] Trifluoromethanesulfonic acid.

Tamborini et al. have reported a similar problem in the synthesis of the structurally related 3-hydroxyglutamate.[17] While the Ag_2O-catalysed alkylation with benzyl bromide proceeded smoothly in their synthesis of the 4-hydroxy analogue, no reaction took place with the 3-hydroxy analogue, which forced them to move on to another route. Thus, it became clear that the standard methods for ether synthesis are not appropriate here. Consequently, we decided to investigate the known conversion of readily available silyl ethers into alkyl ethers by reductive etherification.[18]

The reaction of a silyl ether, an aldehyde, and triethylsilane is known to proceed in the presence of Lewis acids, such as trityl perchlorate,[19] $BiBr_3$,[20,21] or $FeCl_3$.[22] In addition, Bourdreux et al. have reported several other iron catalysts to be suitable for the alkylation of silyl protected glucopyranosides.[23] In general, better results are obtained if polar aprotic solvents, such as nitromethane or acetonitrile, are used.[22]

Under the conditions described above, benzyl ether protection was introduced onto the hydroxy group in 76% yield starting from diethyl 3-hydroxyglutarate (**2**; Table 1, entry 4). The reaction was run overnight due to lower reactivity of the parent protected secondary alcohol. When we attempted to make the cinnamyl ether (Cinn) under the same conditions (Table 1, entry 5), lower yields were obtained, and the majority of the cinnamaldehyde remained unreacted.

Alternatively, a benzyloxymethyl ether (BOM) was produced in a somewhat higher yield than the benzyl ether, and silyl derivatives such as the trimethylsilyl ether (TMS) or the more stable *tert*-butyldimethylsilyl ether (TBDMS) were isolated almost quantitatively. Thus Bn, BOM, and TBDMS (Figure 2) were chosen to be PG^1 in the continuation of the synthesis.

Hydrolysis of diesters **4**–**6** gave the corresponding diacids. For benzyloxymethyl-protected compound **5**, *O*-deprotection also occurred to some extent under the harsh conditions. The 50% yield obtained using 1.5 M KOH improved to 81% when 0.3 M LiOH was used instead. The silyl protected diacid was not isolated, due to its instability to strong acids[24] (which would normally be added prior to the extraction). Instead, the crude mixture was used directly

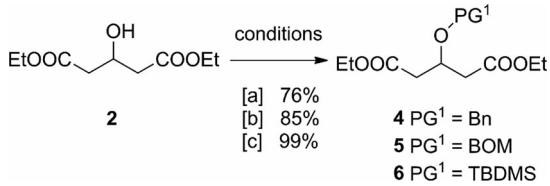

Figure 2. Protection of the hydroxy group in diethyl 3-hydroxyglutarate. Conditions: [a] 1. Trimethylsilyl chloride, imidazole, CH_2Cl_2; 2. Benzaldehyde, triethylsilane, $FeCl_3$, acetonitrile; [b] benzyloxymethyl chloride, diisopropylamine (DIPEA), tetra-*n*-butylammonium iodide (TBAI), CH_2Cl_2; [c] *tert*-butyldimethylsilyl chloride, imidazole, CH_2Cl_2.

in the following step, as described in the literature.[16] Dehydratation of the diacids in acetic anhydride yielded *meso* glutaric anhydrides **9**–**11** in 64–81% overall yield (Figure 3).

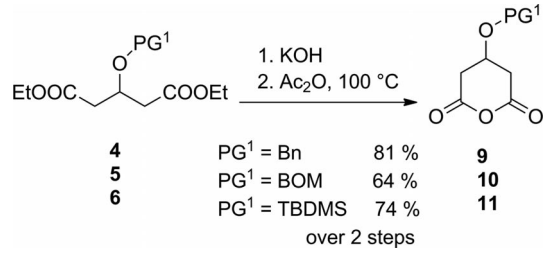

Figure 3. Preparation of *O*-protected 3-hydroxyglutaric anhydrides.

The enantioselective desymmetrization of the cyclic *meso* anhydrides[25,26] has already been identified as a convenient method for stereochemical induction in the total syntheses of biologically active substances,[27–29] including Pregabalin,[30] Biotin,[31] Baclofen,[32] Rolipram,[33] etc. The reaction works with a wide range of nuclephiles, so a variety of carboxy-protecting groups may be introduced in the chiral-centre formation step (Figure 4).

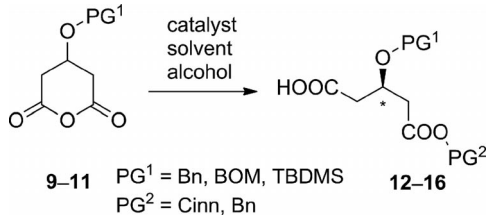

Figure 4. Opening of cyclic anhydrides.

The procedure using stoichiometric quantities of natural cinchona alkaloids at low temperatures was developed by Bolm and co-workers for the opening of succinic anhydrides.[34] However, with the more challenging glutaric anhydrides, worse results are typically obtained under these conditions. In addition, some authors have quite recently shown that the opposite enantiomer of the product may be produced at room temperature simply by using an organic acid additive.[35,36] Thus, using unmodified cinchona alkaloids, the same chiral catalyst can be used to form both enantiomers in moderate to good *ee*, which can subsequently be increased to the desired level by crystallization.[33]

On the other hand, the use of modified alkaloids, including ethers,[37] ureas or thioureas,[38] and sulfonamides,[39] in catalytic amounts, has also been studied. Of these modified compounds, sulfonamides (Figure 5) have a slightly better overall performance.

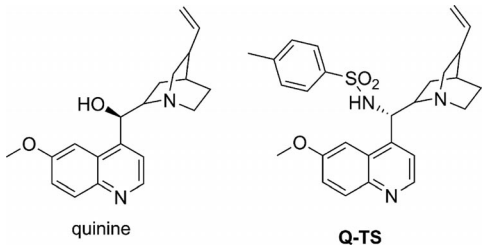

Figure 5. Quinine and sulfonamide catalyst **Q-TS**.

The use of alcohols as nucleophiles in the enantioselective opening of *O*-protected anhydrides **9**–**11** introduces an ester protecting group (PG^2) to one of the carboxylic acids, as well as introducing the chiral centre. The other carboxylic acid remains free for further reaction to continue the synthesis.

Initial screening of conditions for the desymmetrization of the anhydrides was performed using anhydride **11** as the substrate. In general, slightly better *ee* values were obtained when the anhydride was opened with benzyl alcohol rather than with cinnamyl alcohol. When natural alkaloids were used as sources of chirality, both enantiomers could be produced in 55–63% *ee* (Table 2, entries 1–3), and the stereochemistry of the product was controlled either by the inclusion of an acid additive or by the right choice of alkaloid. Thus, following this route, the final product and all of the intermediates are available in both enantiomeric forms using the same reaction steps. On the other hand, when a sulfonamide derivative (**Q-TS**) was used in toluene, the (*R*)-configured enantiomer was produced under both stoichiometric and catalytic conditions, although some improvement in the enantioselectivity was observed (Table 2, entries 5–7). With methyl *tert*-butyl ether (MTBE) as the solvent, the *ee* of the product was somewhat higher (up to 92%) than in toluene. The difference between catalytic and stoichiometric conditions was minimal here, showing that 0.1 equiv. of the catalyst was sufficient. Under these conditions, *O*-protected anhydride substrates **9**–**11** were all opened on a gram scale with good to excellent *ee*'s (Table 3). The highest selectivities were achieved for the opening of anhydride **11** with benzyl alcohol (Table 3, entry 1). The absolute configuration of monoesters **12**–**16** was initially assigned by analogy, since the direction of opening is highly predictable under the reaction conditions used, and it was later confirmed by comparing the sign of optical rotation of the final product (i.e., **1**) with literature values.

After the anhydride desymmetrization, a Curtius rearrangement can be used to transform the free carboxylic acid into an amine protected by an *N*-protecting group (PG^3; Figure 6). Various *N*-protected unnatural amino acids[28,30,40] are available starting from succinic or glutaric acid monoesters by a one-pot sequence involving a Curtius rearrangement. The initially formed azide rearranges thermally into an unstable isocyanate intermediate, which reacts with a nucleophile to give *N*-protected amino esters.[41]

Table 2. Screening of conditions for anhydride desymmetrization.[a]

Entry	Product	ROH	Solvent	Catalyst (equiv.)	*t* [d]	Yield [%][b]	*ee* [%]
1	**12**	BnOH	toluene	quinine (1.1)[c]	8	58	63
2	**12**	BnOH	toluene	quinidine (0.1) X9A[d] (0.2)	3	67	62
3	*ent*-**12**	BnOH	toluene	quinine (0.1) X9A[d] (0.2)	3	64	55[e]
4	*ent*-**13**	CinnOH	toluene	quinine (0.1) X9A[d] (0.2)	3	57	50[e]
5	**12**	BnOH	toluene	Q-TS (0.1)	2	61	77
6	**12**	BnOH	toluene	Q-TS (1)	1	58	87
7	**13**	CinnOH	toluene	Q-TS (0.1)	2	56	70
8	**13**	CinnOH	MTBE	Q-TS (0.1)	2	70	83
9	**13**	CinnOH	MTBE	Q-TS (1)	1	77	86
10	**12**	BnOH	MTBE	Q-TS (0.1)	2	63	90
11	**12**	BnOH	MTBE	Q-TS (1)	1	63	92

[a] All reactions were performed at room temperature with anhydride **11** (0.1 g) in 0.1 M solution for the time indicated. [b] Isolated yield. [c] Reaction was performed at –30 °C. [d] Xanthene-9-carboxylic acid. [e] (*S*)-configured product.

Table 3. Opening of anhydrides **9**–**11**.[a]

Entry	Product	PG^1	ROH	Catalyst (equiv.)	*t* [d]	Yield [%][b]	*ee* [%]
1	**12**	TBDMS	BnOH	Q-TS (0.1)	2	79	90
2	**14**	Bn	CinnOH	quinine (1.1)	2	40	66[c]
3	**14**	Bn	CinnOH	Q-TS (0.1)	1	79	85
4	**14**	Bn	CinnOH	Q-TS (0.2)	1	84	88
5	**15**	BOM	BnOH	Q-TS (0.1)	1	73	88
6	**15**	BOM	BnOH	Q-TS (0.3)	1	79	89
7	**16**	BOM	CinnOH	Q-TS (0.2)	1	79	86

[a] All reactions were performed in MTBE on a gram scale (see Exp. Sect.). [b] Isolated yield. [c] Reaction was performed at –20 °C.

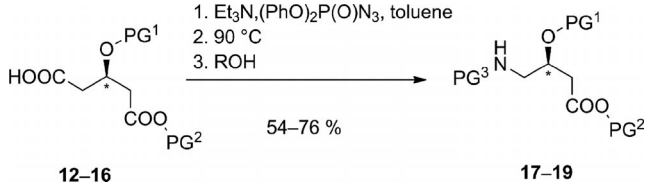

Figure 6. Curtius rearrangement of monoesters to give triprotected derivatives of GABOB (**1**).

The choice of PG^3 is made so that it is orthogonal to the protecting groups already present in the molecule for easier selective manipulation during the deprotection. Selected results are presented in Table 4.

Table 4. Curtius rearrangement of selected monoesters.

Entry	Product	PG^1	PG^2	PG^3	Yield [%]
1	**17**	Bn	Cinn	Bn-OC(O)–	76
2	**18**	BOM	Cinn	Bn-OC(O)–	59
3	**19**	TBDMS	Bn	Cinn-OC(O)–	54

The deprotection of the GABOB derivatives with three distinct protecting groups may be performed in several ways. Attempts were made to produce a diprotected compound with a free amino group. However, thermal deprotection of similar compounds is known to result in lactam formation by spontaneous cyclization of the amino ester formed,[33] and transallylation would not proceed at room temperature. Thus, the preferred order of steps in this route would be to remove the protection of the carboxy group prior to that of the amine group. By this method, GABOB itself and the protected intermediates may be isolated, as demonstrated below.

The cinnamyl ester protecting group of the carboxyl moiety in compounds **17** and **18** was selectively removed by transallylation of morpholine with a palladium catalyst. On the other hand, glutaric acid monoesters tend to be unstable under alkaline conditions, slowly hydrolysing in dilute carbonate solution.[33,42] Thus, although the reaction was slower, the carboxylic functionality could be deprotected with KOH (0.1 M in water/methanol), as demonstrated for compound **19**, where the cinnamyl group was protecting the amine moiety (Figure 7). To avoid the decomposition of the silyl protection during work-up, pH 5.4 buffer was used in place of strong acid during the extraction.

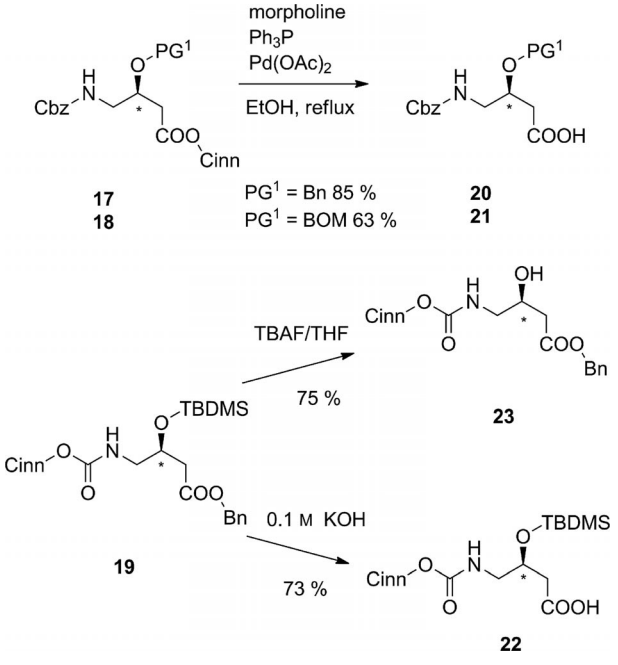

Figure 7. Selective deprotection of triprotected GABOB derivatives **17**–**19**.

As determined by HPLC, no racemization occurred under these conditions, as the product (i.e., **22**) was isolated without any loss of enantiopurity. From the same precursor (i.e., **19**), diprotected hydroxy derivative **23** was obtained after treatment with tetrabutylammonium fluoride (TBAF) in THF to remove the TBDMS protecting group.

Selective deprotection of **20** was achieved by controlling the hydrogen pressure (Figure 8). Thus, monoprotected amino acid **24** was isolated after hydrogenation of diprotected amino acid **20** at atmospheric pressure. The procedure was then repeated at a higher hydrogen pressure (15 bar) to obtain pure 4-amino-3-hydroxyglutaric acid (**1**). In addition, spontaneous enrichment of the product occurred, therefore GABOB was isolated in 66% yield with 97% *ee* (the *ee* of starting monoester **14** was 88%). A single recrystallization from ethanol allowed the product to be isolated with 99% *ee*.

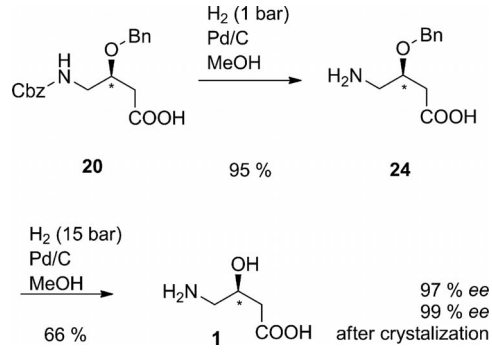

Figure 8. Stepwise deprotection of **20**.

Conclusions

A stereoselective route to GABOB is presented, using anhydride desymmetrization as a step for the introduction of chirality. Intermediate GABOB derivatives with three different protecting groups were selectively deprotected to produce diprotected derivatives with a free carboxylic acid or hydroxy group. After all of the protecting groups were removed, (*S*)-GABOB was isolated in good yield and with excellent *ee*.

Experimental Section

General Methods: All reactions were carried out under an argon atmosphere. Anhydride **11**[16] and catalyst **Q-TS**[39] were prepared according to literature procedures. Buffer pH 5.4 was prepared by dissolving NaH_2PO_4 dihydrate (17.78 g) and citric acid monohydrate (7.78 g) in 1 L of water. All other reagents and solvents were purchased from commercial suppliers, and were used without purification. ^1H and ^{13}C NMR spectra were recorded with a Bruker AV 300 spectrometer. Chemical shifts (δ_H and δ_C) are quoted in parts per million (ppm), and were referenced to tetramethylsilane. High-resolution mass spectrometry (HRMS) was carried out with a 4800 Plus MALDI TOF/TOF Analyzer. Optical rotations were measured with an Optical Activity AA-10 automatic polarimeter. Melting points were determined with an Electrothermal 9100 apparatus in open capillaries. For the determination of purity and monitoring the progress of reactions, a Nucleosil 100–5 C18 column was used.

Diethyl 3-(Trimethylsilyloxy)glutarate (3): Diethyl 3-hydroxyglutarate (95% w/w; 5 g, 23.2 mmol) was dissolved in dry CH_2Cl_2 (40 mL), and then trimethylsilyl chloride (4.40 mL, 34.8 mmol,

1.5 equiv.) and imidazole (3.17 g, 46.4 mmol, 2 equiv.) were added. The reaction mixture was stirred overnight at room temperature, then it was diluted with diethyl ether (100 mL), and washed with H_2O (2 × 50 mL) and brine (50 mL). The organic phase was dried with Na_2SO_4, filtered, and concentrated under reduced pressure to give compound **3** (6.40 g, 99%) as a colourless viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.13 (s, 9 H), 1.29 (t, J = 7.1 Hz, 6 H), 2.54 (d, J = 6.3 Hz, 4 H), 4.08–4.24 (m, 4 H), 4.54–4.63 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –0.01, 14.13, 42.68, 60.37, 66.30, 170.87 ppm.

Diethyl 3-(Benzyloxy)glutarate (4): Diethyl 3-(trimethylsilyloxy)-glutarate (**3**; 6.4 g, 23.2 mmol) was dissolved in dry acetonitrile (100 mL). Triethylsilane (4.45 mL, 27.8 mmol, 1.2 equiv.) was added, followed by $FeCl_3$ (0.75 g, 4.64 mmol, 0.2 equiv.). The mixture was stirred for 15 min, and then benzaldehyde (2.83 mL, 27.8 mmol, 1.2 equiv.) was added. The mixture was stirred overnight. The solvent was removed under reduced pressure, and the residue was partitioned between water (100 mL) and CH_2Cl_2 (100 mL). The organic phase was washed with brine (50 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/diethyl ether, 9:1, to hexane/diethyl ether, 1:1) to give compound **4** (5.22 g, 77%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24 (t, J = 7.1 Hz, 6 H), 2.55–2.71 (m, 4 H), 4.13 (q, J = 7.1 Hz, 4 H), 4.29–4.37 (m, 1 H), 4.59 (s, 2 H), 7.22–7.34 (m, 5 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.14, 39.79, 60.54, 72.11, 72.91, 127.62, 127.71, 128.28, 138.11, 170.88 ppm.

Diethyl 3-(Benzyloxymethoxy)glutarate (5): Diethyl 3-hydroxyglutarate (95% w/w; 5 g, 23.2 mmol) was dissolved in dry CH_2Cl_2 (80 mL), and then benzyl chloromethyl ether (60% w/w; 7.53 mL, 32.5 mmol, 1.4 equiv.), *N*-ethyldiisopropylamine (7.9 mL, 46.4 mmol, 2 equiv.), and tetrabutylammonium iodide (0.86 g, 2.32 mmol, 0.1 equiv.) were added. The reaction mixture was stirred overnight at room temperature. Ammonium chloride (saturated aq.; 30 mL) was added. The phases were separated. The organic phase was washed again with ammonium chloride (saturated aq.; 30 mL) and with brine (30 mL), then it was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/diethyl ether, 1:1) to give compound **5** (6.37 g, 85%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (t, J = 7.15 Hz, 6 H), 2.62–2.77 (m, 4 H), 4.16 (q, J = 7.15 Hz, 4 H), 4.47–4.53 (m, 1 H), 4.63 (s, 2 H), 4.85 (s, 2 H), 7.30–7.39 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.14, 39.97, 60.53, 69.71, 71.63, 94.50, 127.66, 127.84, 128.37, 137.69, 170.72 ppm.

3-(Benzyloxy)glutaric Acid (7): Diethyl 3-(benzyloxy)glutarate (**4**; 3.67 g, 12.5 mmol) was dissolved in methanol (60 mL). A solution of lithium hydroxide monohydrate (1.57 g, 37.5 mmol, 3 equiv.) in water (60 mL) was added. The reaction mixture was stirred for 4 h at room temperature. The solvent was removed under reduced pressure, and the residue was partitioned between water (80 mL) and CH_2Cl_2 (80 mL). The aqueous phase was separated, acidified with concd. HCl, and extracted with diethyl ether (3 × 50 mL). The combined ether phases were washed with brine (30 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure to give compound **7** (2.83 g, 95%) as a white solid, m.p. 144.9–145.9 °C. ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 2.52 (d, J = 6.1 Hz, 4 H), 4.13–4.21 (m, 1 H), 4.53 (s, 2 H), 7.23–7.34 (m, 5 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 39.61, 71.21, 73.39, 127.79, 127.89, 128.56, 139.01, 172.77 ppm. HRMS (MALDI): calcd. for $C_{11}H_{14}O_5K$ [M + K]$^+$ 277.0473; found 277.0475.

3-(Benzyloxymethoxy)glutaric Acid (8): Diethyl 3-(benzyloxymethoxy)glutarate (**5**; 4.9 g, 15.2 mmol) was dissolved in methanol (70 mL). A solution of lithium hydroxide monohydrate (1.91 g, 45.6 mmol, 3 equiv.) in water (50 mL) was added. The reaction mixture was stirred for 4 h at room temperature. The solvent was removed under reduced pressure, and the residue was partitioned between water (50 mL) and CH_2Cl_2 (50 mL). The aqueous phase was acidified with concd. HCl, and extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were washed with brine (30 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure to give compound **8** (3.3 g, 81%) as a viscous yellow oil. ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 2.49–2.62 (m, 4 H), 4.27–4.35 (m, 1 H), 4.54 (s, 2 H), 4.75 (s, 2 H), 7.28–7.35 (m, 5 H), 12.32 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 39.83, 69.36, 71.11, 93.62, 127.93, 128.27, 128.68, 138.44, 172.61 ppm.

3-(Benzyloxy)glutaric Anhydride (9): 3-(Benzyloxy)glutaric acid (**7**; 3.26 g, 13.7 mmol) was dissolved in acetic anhydride (6.5 mL, 68 mmol, 5 equiv.). The mixture was stirred for 90 min at 100 °C. The mixture was allowed to cool, and then the solvent was removed under reduced pressure. The product was recrystallized from chloroform/hexane to give anhydride **9** (2.54 g, 84%) as a white solid, m.p. 84.3–84.9 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.76 (dd, J = 16.6, J = 2.9 Hz, 2 H), 3.13 (dd, J = 16.6, J = 3.8 Hz, 2 H), 4.08–4.12 (m, 1 H), 4.60 (s, 2 H), 7.29–7.42 (m, 5 H) ppm. ^{13}C NMR (150 MHz, [D_6]DMSO): δ = 35.80, 66.89, 70.90, 127.67, 128.27, 128.65, 136.53, 164.71 ppm.

3-(Benzyloxymethoxy)glutaric Anhydride (10): 3-(Benzyloxymethoxy)glutaric acid (**8**; 3.3 g, 12.3 mmol) was dissolved in acetic anhydride (11.7 mL, 123 mmol, 10 equiv.). The mixture was stirred for 90 min at 100 °C. The mixture was allowed to cool, and then the solvent was removed under reduced pressure to give anhydride **10** (2.44, 79%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.69–2.76 (m, 2 H), 3.04–3.12 (m, 2 H), 4.26–4.31 (m, 1 H), 4.59 (s, 2 H), 4.82 (s, 2 H), 7.28–7.40 (m, 5 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 35.93, 65.83, 70.07, 93.19, 127.52, 127.60, 128.09, 136.49, 165.32 ppm.

3-(*tert*-Butyldimethylsilyloxy)glutaric Anhydride (11): Compound **11** was prepared according to a literature procedure.[16] ^{1}H NMR (600 MHz, $CDCl_3$): δ = –0.01 (s, 6 H), 0.75 (s, 9 H), 2.63–2.68 (m, 2 H), 2.78–2.83 (m, 2 H), 4.27–4.31 (m, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = –5.02, 17.79, 25.45, 39.14, 61.92, 165.03 ppm.

General Procedure for the Desymmetrization of Anhydrides: The catalyst and the alcohol were added to a 0.1 M solution of the anhydride, according to Table 3. The reaction mixture was stirred until >90% conversion was reached (see Table 3), and then the reaction was stopped by the addition of HCl (5%). The organic phase was washed with HCl (5%), and the solvents were evaporated. The oily residue was dissolved in K_2CO_3 (2% aq.), and then this solution was washed with EtOAc. The aqueous solution was acidified with HCl to pH 2, and then it was extracted with EtOAc unless noted otherwise. The organic extracts were dried with Na_2SO_4 and evaporated in vacuo.

(*R*)-Monobenzyl 3-(*tert*-Butyldimethylsilyloxy)glutarate (12): Starting from 3-(*tert*-butyldimethylsilyloxy)glutaric acid anhydride (**11**; 2 g, 8.20 mmol), benzyl alcohol (1.26 mL, 12.30 mmol, 1.5 equiv.), and catalyst **Q-TS** (0.39 g, 0.82 mmol, 0.1 equiv.) in MTBE (80 mL), following the general procedure, compound **12** (2.28 g, 79%) was obtained as a yellow oil. During the extraction work-up, buffer pH 5.4 was used for the acidification instead of hydrochloric acid. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.09 (s, 3 H), 0.11 (s, 3 H), 0.88 (s, 9 H), 2.49–2.71 (m, 4 H), 4.54–4.64 (m, 1 H), 5.08–5.18 (m,

2 H) 7.31–7.42 (m, 5 H), 8–11 (br. s, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = –4.97, –4.91, 17.85, 25.62, 42.21, 42.33, 66.08, 66.43, 127.00, 128.26, 128.54, 135.69, 170.69, 176.76 ppm. *ee* = 90% (Chiralcel OD; 210 nm; flow = 1 mL/min; *n*-hexane/EtOH, 96:4). $[\alpha]_D^{25}$ = –2.24 (*c* = 0.894, CH_2Cl_2). HRMS (MALDI): calcd. for $C_{18}H_{28}O_5SiNa$ $[M + Na]^+$ 375.1598; found 375.1588.

(*R*)-Mono(3-phenylallyl) 3-(Benzyloxy)glutarate (14): Starting from 3-(benzyloxy)glutaric acid anhydride (**9**; 1.47 g, 6.70 mmol), cinnamyl alcohol (1.04 mL, 8.04 mmol, 1.2 equiv.), and catalyst **2** (0.64 g, 1.34 mmol, 0.2 equiv.) in MTBE (70 mL), following the general procedure, compound **14** (2.0 g, 84%) was obtained as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.63–2.79 (m, 4 H), 4.30–4.38 (m, 1 H), 4.60 (s, 2 H), 4.74 (d, *J* = 6.4 Hz, 2 H), 6.25 (dt, *J* = 6.4, *J* = 15.9 Hz, 1 H), 6.64 (d, *J* = 15.9 Hz, 1 H), 7.22–7.37 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 39.27, 39.54, 65.34, 72.26, 74.45, 122.87, 126.65, 127.80, 127.83, 128.11, 128.39, 128.60, 134.53, 136.14, 137.73, 170.60, 176.04 ppm. *ee* = 88% (Chiralcel OD; 254 nm; flow = 1 mL/min; *n*-hexane/EtOH/TFA (trifluoroacetic acid), 95:5:0.1). $[\alpha]_D^{25}$ = +1.47 (*c* = 4.08, CH_2Cl_2). HRMS (MALDI): calcd. for $C_{21}H_{22}O_5Na$ $[M + Na]^+$ 377.1359; found 377.1356.

(*R*)-Monobenzyl 3-(Benzyloxymethoxy)glutarate (15): Starting from 3-(benzyloxymethoxy)glutaric acid anhydride (**10**; 7.61 g, 30 mmol), benzyl alcohol (4.72 mL, 45 mmol, 1.5 equiv.), and catalyst **2** (1.4 g, 3 mmol, 0.1 equiv.) in MTBE (300 mL), following the general procedure, compound **15** (7.97 g, 73%) was obtained as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.67–2.79 (m, 4 H), 4.46–4.50 (m, 1 H), 4.57 (d, *J* = 1.1 Hz, 1 H), 4.79 (s, 2 H), 5.11 (d, *J* = 2.1 Hz, 1 H), 7.25–7.36 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 39.58, 39.76, 66.51, 69.87, 71.31, 94.55, 127.72, 127.87, 128.28, 128.29, 128.40, 128.56, 135.66, 137.53, 169.98, 176.31 ppm. $[\alpha]_D^{25}$ = +1.07 (*c* = 3.72, $CHCl_3$). *ee* = 88% (Chiralcel OJ; 215 nm; flow = 1 mL/min; *n*-hexane/EtOH/TFA, 50:50:0.2). $[\alpha]_D^{25}$ = +1.07 (*c* = 3.72, $CHCl_3$). HRMS (MALDI): calcd. for $C_{20}H_{22}O_6Na$ $[M + Na]^+$ 381.1305; found 381.1314.

(*R*)-Mono(3-phenylallyl) 3-(Benzyloxymethoxy)glutarate (16): Starting from 3-(benzyloxymethoxy)glutaric acid anhydride (**10**; 1.76 g, 7.00 mmol), cinnamyl alcohol (1.13 g, 8.4 mmol, 1.2 equiv.), and catalyst **2** (0.67 g, 0.2 equiv.) in MTBE (70 mL), following the general procedure, compound **16** (2.13 g, 79%) was obtained as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.65–2.81 (m, 4 H), 4.46–4.54 (m, 1 H), 4.59 (s, 2 H), 4.73 (dd, *J* = 6.4, *J* = 1.4 Hz, 2 H), 4.82 (s, 2 H), 6.24 (dt, *J* = 6.4, *J* = 15.9 Hz, 1 H), 6.63 (d, *J* = 15.9 Hz, 1 H), 7.22–7.42 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 39.58, 39.75, 65.31, 69.86, 71.25, 94.51, 122.80, 126.61, 127.73, 127.87, 128.09, 128.41, 128.58, 134.45, 136.08, 137.49, 170.48, 176.47 ppm. *ee* = 86% (Chiralpak AD; 254 nm; flow = 1 mL/min; *n*-hexane/EtOH/TFA, 90:10:0.1). $[\alpha]_D^{25}$ = +1.77 (*c* = 1.13, $CHCl_3$). HRMS (MALDI): calcd. for $C_{22}H_{24}O_6$ $[M + H]^+$ 385.1645; found 385.1630.

(*S*)-3-Phenylallyl 3-(Benzyloxy)-4-(benzyloxycarbonylamino)butyrate (17): Diphenylphosphoryl azide (0.47 mL, 2.17 mmol, 1.2 equiv.) was added to a dry toluene solution (50 mL) of mono-(3-phenylallyl) 3-(benzyloxy)glutarate (**14**; 0.64 g, 1.81 mmol, 1 equiv.) and triethylamine (0.31 mL, 2.17 mmol, 1.2 equiv.) at 20 °C. The reaction mixture was stirred for 30 min, and then it was slowly warmed to 90 °C. When the evolution of nitrogen ceased (30–45 min), benzyl alcohol (0.22 mL, 2.17 mmol, 1.2 equiv.) was added, and the mixture was heated at reflux overnight. The reaction mixture was washed with $NaNO_2$ (1% aq.; 2× 100 mL), then with $NaHCO_3$ (1.5% aq.; 2× 100 mL), and with H_2O (100 mL). The organic phase was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (CH_2Cl_2/EtOAc, 95:5) to give compound **17** (0.63 g, 76%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.61 (dd, *J* = 5.4, *J* = 15.5 Hz, 1 H), 2.71 (dd, *J* = 7.0, *J* = 15.5 Hz, 1 H), 3.35–3.55 (m, 2 H), 4.00–4.14 (m, 1 H), 4.55–4.66 (m, 2 H), 4.78 (d, *J* = 6.2 Hz, 2 H), 5.02–5.13 (m, 1 H), 5.13 (br. s, 2 H), 6.29 (dt, *J* = 6.5, *J* = 15.8 Hz, 1 H), 6.68 (d, *J* = 15.8 Hz, 1 H), 7.25–7.52 (m, 15 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.68, 43.81, 65.34, 66.83, 70.04, 74.76, 122.94, 126.66, 127.80, 127.85, 128.11, 128.12, 128.47, 128.52, 128.61, 134.50, 136.17, 136.50, 137.86, 156.50, 170.74 ppm. $[\alpha]_D^{25}$ = +5.46 (*c* = 1.83, $CHCl_3$). HRMS (MALDI): calcd. for $C_{28}H_{29}NO_5Na$ $[M + Na]^+$ 482.0938; found 482.0939.

(*S*)-3-Phenylallyl 4-(Benzyloxycarbonylamino)-3-(benzyloxymethoxy)butyrate (18): Diphenylphosphoryl azide (0.58 mL, 2.68 mmol, 1.2 equiv.) was added to a dry toluene solution (60 mL) of mono-(3-phenylallyl) 3-(benzyloxymethoxy)glutarate (**15**; 0.86 g, 2.24 mmol, 1 equiv.) and triethylamine (0.37 mL, 2.68 mmol, 1.2 equiv.) at 20 °C. The reaction mixture was stirred for 30 min, and then it was slowly warmed to 90 °C. When the evolution of nitrogen ceased (30–45 min), benzyl alcohol (0.28 mL, 2.68 mmol, 1.2 equiv.) was added, and the mixture was heated at reflux overnight. The reaction mixture was washed with $NaNO_2$ (1% aq.; 2× 100 mL), then with $NaHCO_3$ (1.5% aq.; 2× 100 mL) and with H_2O (100 mL). The organic phase was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (CH_2Cl_2/EtOAc, 95:5) to give compound **18** (0.65 g, 59%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.53–2.70 (m, 2 H), 3.29–3.54 (m, 2 H), 4.13–4.23 (m, 1 H), 4.59 (m, 2 H), 4.72 (d, *J* = 6.5 Hz, 2 H), 4.81 (s, 2 H), 5.08 (s, 2 H), 5.23–5.28 (m, 1 H), 6.23 (dt, *J* = 6.5, *J* = 15.8 Hz, 1 H), 6.63 (d, *J* = 15.8 Hz, 1 H), 7.25–7.45 (m, 15 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 38.18, 44.54, 65.31, 66.81, 70.08, 74.73, 94.79, 122.90, 126.63, 127.83, 128.09, 128.46, 128.50, 128.60, 134.45, 136.16, 136.51, 137.38, 156.51, 170.52 ppm. $[\alpha]_D^{25}$ = +10.09 (*c* = 1.09, CH_2Cl_2). HRMS (MALDI): calcd. for $C_{29}H_{31}NO_6Na$ $[M + Na]^+$ 512.2043; found 512.2048.

(*S*)-Benzyl 3-(*tert*-Butyldimethylsilyloxy)-4-[(3-phenylallyloxy)carbonylamino]butyrate (19): Diphenylphosphoryl azide (1.14 mL, 5.28 mmol, 1 equiv.) was added to a dry toluene solution (40 mL) of mono-benzyl 3-(*tert*-butyldimethylsilyloxy)glutarate (**12**; 1.86 g, 5.28 mmol, 1 equiv.) and triethylamine (0.81 mL, 5.80 mmol, 1.1 equiv.) at 20 °C. The reaction mixture was stirred for 30 min, and then it was slowly warmed to 90 °C. When the evolution of nitrogen ceased (30–45 min), cinnamyl alcohol (0.85 g, 6.33 mmol, 1.2 equiv.) in dry toluene (20 mL) was added, and the mixture was heated at reflux overnight. The reaction mixture was washed with $NaNO_2$ (1% aq.; 2× 100 mL), then with $NaHCO_3$ (1.5% aq.; 2× 100 mL), and with H_2O (100 mL). The organic phase was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 5:1) to give compound **19** (1.37 g, 54%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.08 (s, 3 H), 0.12 (s, 3 H), 0.90 (s, 9 H), 2.55–2.60 (m, 2 H), 3.22–3.48 (m, 2 H), 4.25–4.38 (m, 1 H), 4.70–4.80 (d, *J* = 6.38 Hz, 2 H), 4.95–5.07 (br. s, 1 H), 5.09–5.21 (m, 2 H), 6.25–6.38 (m, 1 H), 6.61–6.73 (d, *J* = 15.8 Hz, 1 H), 7.24–7.46 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.96, –4.93, 17.93, 25.71, 40.21, 46.48, 65.53, 66.46, 68.20, 123.90, 126.61, 127.95, 128.12, 128.26, 128.29, 128.56, 133.71, 135.72, 136.36, 156.40, 170.85 ppm. *ee* = 90% (Chiralcel OJ; 254 nm; flow = 0.6 mL/min; EtOH). $[\alpha]_D^{25}$ = –9.20 (*c* = 0.87, CH_2Cl_2). HRMS (MALDI): calcd. for $C_{27}H_{37}NO_5SiNa$ $[M + Na]^+$ 506.2333; found 506.2327.

(*S*)-3-(Benzyloxy)-4-(benzyloxycarbonylamino)butyric Acid (20): Morpholine (0.19 mL, 2.26 mmol, 2 equiv.) was added a solution of 3-phenyl-allyl 4-(benzyloxycarbonylamino)-3-(benzyloxy)butyrate (**17**; 0.52 g, 1.13 mmol, 1 equiv.) in absolute EtOH (10 mL), followed by triphenylphosphine (47 mg, 0.18 mmol) and $Pd(OAc)_2$ (2 mg, 0.008 mmol). The reaction mixture was heated at reflux for 3 h, and then it was cooled to room temperature. The solvent was evaporated. Na_2CO_3 (2% aq.; 100 mL) was added. The mixture was stirred for 15 min, and then it was washed with EtOAc (2× 50 mL). The aqueous phase was acidified with concd. HCl, then it was extracted with diethyl ether (3× 50 mL). The combined organic phases were washed with brine (30 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure to give compound **20** (0.33 g, 85%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.55 (dd, J = 5.8, J = 15.8 Hz, 1 H), 2.65 (dd, J = 6.5, J = 15.8 Hz, 1 H), 3.30–3.50 (m, 2 H), 3.94–4.04 (m, 1 H), 4.48–4.65 (m, 2 H), 5.02–5.19 (m, 3 H), 7.20–7.40 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.13, 43.58, 66.95, 71.96, 74.39, 127.85, 127.92, 128.09, 128.18, 128.47, 128.51, 136.29, 137.59, 156.69, 175.66 ppm. $[\alpha]_D^{25}$ = +6.36 (c = 1.10, $CHCl_3$). HRMS (MALDI): calcd. for $C_{19}H_{21}NO_5K$ $[M + K]^+$ 382.1051; found 382.1052.

(*S*)-4-(Benzyloxycarbonylamino)-3-(benzyloxymethoxy)butyric Acid (21): Morpholine (0.38 mL, 4.36 mmol, 2 equiv.) was added to a solution of 3-phenyl-allyl 4-(benzyloxycarbonylamino)-3-(benzyloxymethoxy)butyrate (**18**; 1.06 g, 2.18 mmol, 1 equiv.) in absolute EtOH (30 mL), followed by triphenylphosphine (47 mg, 0.18 mmol) and $Pd(OAc)_2$ (1 mg, 0.004 mmol). The reaction mixture was heated at reflux for 3 h, and then it was cooled to room temperature. The solvent was evaporated. Na_2CO_3 (2% aq.; 100 mL) was added. The mixture was stirred for 15 min, and then it was washed with EtOAc (2× 50 mL). The aqueous phase was acidified with HCl (concd.) and extracted with diethyl ether (3× 50 mL). The combined organic phases were washed with brine (30 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (CH_2Cl_2/EtOAc/CH_3OH, 8:2:1) to give compound **21** (0.51 g, 63%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.52–2.65 (m, 2 H), 3.31–3.47 (m, 2 H), 4.04–4.11 (m, 1 H), 4.56–4.61 (m, 2 H), 4.80 (s, 2 H), 5.08 (s, 2 H), 5.29 (br. s, 1 H), 7.24–7.35 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.72, 44.40, 66.93, 70.15, 74.45, 94.73, 127.04, 128.09, 128.13, 128.46, 128.51, 136.39, 137.32, 156.71, 175.32 ppm. $[\alpha]_D^{25}$ = +6.78 (c = 2.80, CH_2Cl_2). HRMS (MALDI): calcd. for $C_{20}H_{23}NO_6Na$ $[M + H]^+$ 396.1417; found 396.1427.

(*S*)-3-(*tert*-Butyldimethylsilyloxy)-4-[(3-phenylallyloxy)carbonylamino]butyric Acid (22): A solution of KOH (166 mg, 2.96 mmol, 4 equiv.) in water (5 mL) was added to a solution of benzyl 3-(*tert*-butyldimethylsilyloxy)-4-[(3-phenylallyloxy)carbonylamino]butyrate (**19**; 357 mg, 0.74 mmol, 1 equiv.) in methanol (25 mL). The reaction mixture was stirred until the starting material had disappeared (2 d, monitored by TLC). Water (5 mL) was added, and the methanol was removed under reduced pressure. The mixture was washed with EtOAc (2× 10 mL), and then buffer pH 5.4 (30 mL) and phosphoric acid (0.5 mL) were added. The mixture was extracted with EtOAc (2× 10 mL). The combined organic extracts were dried with Na_2SO_4 and evaporated in vacuo to give compound **22** (201 mg, 73%) as a yellowish oil. Further purification was performed by column chromatography on silica gel (CH_2Cl_2/MeOH, 20:1). ^{1}H NMR (300 MHz, [D$_4$]methanol): δ = 0.06 (s, 3 H), 0.11 (s, 3 H), 0.86 (s, 9 H), 2.40–2.60 (m, 2 H), 3.20–3.42 (m, 2 H), 4.15–4.32 (m, 1 H), 4.65–4.80 (m, 2 H), 4.98–5.08 (br. s, 1 H), 6.21–6.34 (m, 1 H), 6.60–6.68 (d, J = 15.8 Hz, 1 H), 7.20–7.42 (m, 5 H), 8.0–10.0 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.95, –4.79, 17.93, 25.70, 39.92, 46.35, 65.68, 68.06, 123.78, 126.61, 127.97, 128.56, 133.83, 136.33, 156.60, 175.88 ppm. *ee* = 90% (Chiralcel OD; 254 nm; flow = 1 mL/min; hexane/EtOH, 93:7). $[\alpha]_D^{25}$ = –7.08 (c = 1.13, MeOH). HRMS (MALDI): calcd. for $C_{20}H_{31}NO_5SiNa$ $[M + Na]^+$ 416.1864; found 416.1853.

(*S*)-Benzyl 3-Hydroxy-4-[(3-phenylallyloxy)carbonylamino]butyrate (23): Tetrabutylammonium fluoride (1 M in THF; 1.1 mL, 1.2 equiv.) was added to a solution of benzyl 3-(*tert*-butyldimethylsilyloxy)-4-[(3-phenylallyloxy)carbonylamino]butyrate (**19**; 388 mg, 0.80 mmol, 1 equiv.) in THF (3 mL). The reaction mixture was stirred overnight, and then water (5 mL) was added. The mixture was extracted with EtOAc (2× 10 mL). The combined organic extracts were dried with Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 20:1) to give compound **23** (221 mg, 75%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.53–2.63 (m, 2 H), 3.12–3.30 (m, 2 H), 3.10–3.29 (m, 1 H), 3.32–3.49 (m, 1 H), 3.43 (s, 1 H), 4.08–4.24 (m, 1 H), 4.66–4.79 (d, J = 6.34 Hz, 2 H), 5.12–5.18 (s, 2 H), 5.24 (br. s, 1 H), 6.20–6.36 (m, 1 H), 6.58–6.69 (d, J = 15.8 Hz, 1 H), 7.14–7.47 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 38.54, 45.78, 65.65, 66.70, 67.43, 123.68, 126.58, 127.96, 128.25, 128.43, 128.55, 128.62, 133.73, 135.36, 136.24, 156.85, 172.26 ppm. $[\alpha]_D^{25}$ = –2.98 (c = 1.006, CH_2Cl_2). HRMS (MALDI): calcd. for $C_{11}H_{23}NO_5SiNa$ $[M + Na]^+$ 392.1469; found 392.1464.

(*S*)-4-Amino-3-(benzyloxy)butyric Acid (24): 3-(Benzyloxy)-4-(benzyloxycarbonylamino)butyric acid (**20**; 300 mg, 0.87 mmol) was dissolved in methanol (30 mL). Pd/C (10%; 30 mg) was added, and the mixture was hydrogenated under atmospheric pressure at room temperature for 6 h. Water (1 mL) was added, and the mixture was filtered. The filtrate was concentrated under reduced pressure, and the residue was recrystallized from ethanol to give compound **24** (174 mg, 95%) as a white powder, m.p. 160.2–161.2 °C. ^{1}H NMR (300 MHz, D_2O): δ = 2.37 (dd, J = 6.9, J = 14.9 Hz, 1 H), 2.62 (dd, J = 5.8, J = 14.9 Hz, 1 H), 3.02 (dd, J = 8.3, J = 13.4 Hz, 1 H), 3.20 (dd, J = 3.5, J = 13.4 Hz, 1 H), 4.05–4.14 (m, 1 H), 4.60 (d, J = 11.0 Hz, 1 H), 4.67 (d, J = 11.0 Hz, 1 H, partial overlap with D_2O), 7.31–7.52 (m, 5 H) ppm. ^{13}C NMR (75 MHz, D_2O): δ = 40.29, 42.62, 71.41, 73.19, 128.49, 128.69, 128.84, 137.19, 178.23 ppm. $[\alpha]_D^{25}$ = +28.0 (c = 1, H_2O). HRMS (MALDI): calcd. for $C_{11}H_{15}NO_3Na$ $[M + Na]^+$ 323.0944; found 323.0952.

(*S*)-4-Amino-3-hydroxybutyric Acid (1): (*S*)-4-Amino-3-(benzyloxy)butyric acid (**24**; 140 mg, 0.67 mmol) was dissolved in methanol (30 mL). Pd/C (10%; 80 mg) was added, and the mixture was hydrogenated overnight at room temperature under hydrogen pressure (15 bar). Water (1 mL) was added, and the mixture was filtered. The filtrate was concentrated under reduced pressure, and then the residue was crystallized from EtOH to give compound **1** (58 mg, 73%) as a white powder. ^{1}H NMR (300 MHz, D_2O): δ = 2.41 (d, J = 6.5 Hz, 2 H), 2.94 (dd, J = 9.3, J = 13.1 Hz, 1 H), 3.15 (dd, J = 3.2, J = 13.1 Hz, 1 H), 4.13–4.23 (m, 1 H) ppm. ^{13}C NMR (75 MHz, D_2O): δ = 42.44, 44.26, 65.65, 178.65 ppm. *ee* = 97%, determined from optical rotation. $[\alpha]_D^{25}$ = +20.0 (c = 1.25, H_2O) {ref.[14] $[\alpha]_D^{25}$ = +20.7 (c = 1.9, H_2O)}. Recrystallization from 78% EtOH further increased the optical purity of the title compound to *ee* = 99%. $[\alpha]_D^{25}$ = +20.56 (c = 1.41, H_2O). HRMS (MALDI): calcd. for $C_4H_9NO_3K$ $[M + K]^+$ 158.0214; found 158.0208.

Supporting Information (see footnote on the first page of this article): NMR spectra.

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