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A Practical Method for Selective Cleavage of a *tert*-Butoxycarbamoyl *N*-Protective Group from *N*,*N*-Diprotected α-Amino Acid Derivatives Using Montmorillonite K-10

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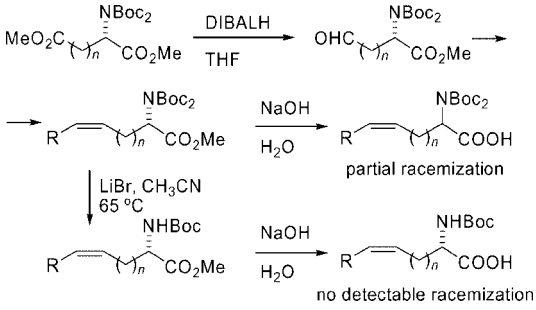
Dedicated to Professor Miguel Yus on the occasion of his 60th birthday

Keywords: α-Amino acids / Clays / Heterogeneous catalyst / Protecting groups / Lactones / Asymmetric synthesis

A new, practical, and mild procedure for the selective cleavage of a *tert*-butoxycarbonyl group (Boc) in *N*-Boc-*N*-acyl-diprotected amines is described. When applied to α-amino acids, complete integrity of the stereochemistry was observed. The use of *N*,*N*-di-Boc-α-amino-δ- and γ-hydroxy esters provided both δ- and γ-lactones in very good yields. The method is based on the use of Montmorillonite K-10 either in CH_2Cl_2 at room temperature or in toluene at 65 °C and is compatible with the presence of a large range of functional and other protecting groups in the substrates. In most cases virtually pure samples are obtained after filtration and removal of solvents.

Introduction

The *tert*-butoxycarbonyl group is one of the most useful amine-protecting groups in organic synthesis, thanks to its chemical stability over a large pH range and its ease of removal under specific conditions.[1] Although the protecting group is usually employed in the form of an *N*-Boc derivative, its use in diprotected *N*,*N*-Boc-acyl nitrogen derivatives is essential for the success of several reactions. Thus, di-*tert*-butyl imidodicarbonates and tosyl carbamates are very useful as phthalimide substitutes in Mitsunobu[1] and Gabriel-type processes.[1] The selective reduction of *N*,*N*-di-Boc-α-amino acid derivatives, obtained from natural α-amino acids (glutamic or aspartic acids) or the homologated compounds, produced ω-semialdehydes in very good yields and with complete integrity at the stereocenters.[4] Moreover, the introduction of the second *N*-Boc group produces several changes in the reactivity of the vicinal ester. For instance, whereas the alkaline hydrolysis of *N*-Boc-α-amino esters occurs without any racemization, the saponification of *N*,*N*-di-Boc-α-amino esters produces partial racemization[3b] (Scheme 1).[4] Many methods for the removal of Boc groups in *N*-protected amines can be found in the literature,[1] but only a few are suited for selective cleavage of the group in diprotected *N*-Boc-*N*-acyl amines.[5]



Scheme 1. Selectivity and modification in reactivity in *N*,*N*-di-Boc α-amino diesters.

On the other hand, the use of solid acidic materials such as Montmorillonite clays is very attractive since they can be easily recovered from reaction mixtures by simple filtration and can be reused after activation, thereby making the process economically viable and environmentally friendly. Montmorillonite K-10 has been reported to promote acid-dependent reactions.[6] Moreover, it has been used to cleave *N*-Boc groups selectively from aromatic amines.[7] We now report on a new and practical method for selective depro-

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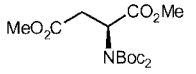
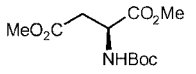
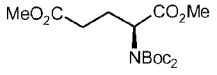
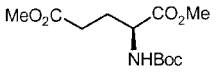
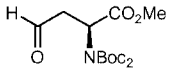
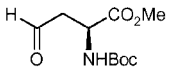
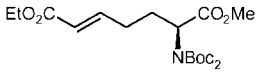
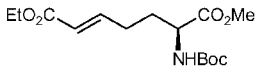
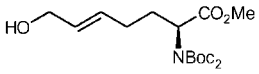
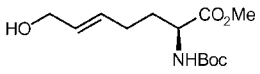
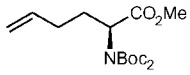
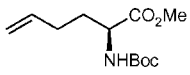
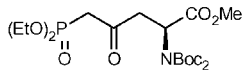
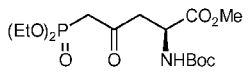
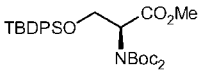
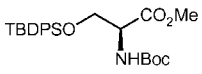
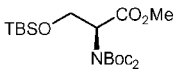
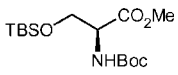
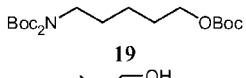
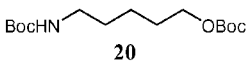
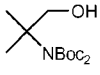
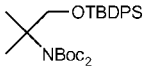
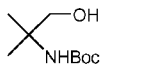
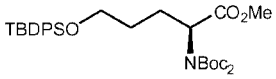
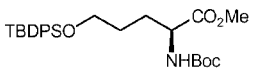
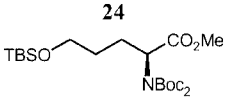
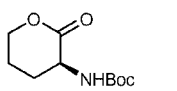
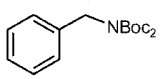
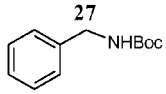
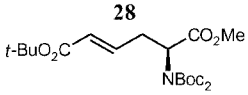
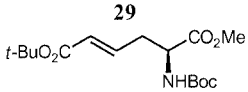
tection of an *N*-Boc group in *N*-Boc-*N*-acyl-protected amines and α-amino acids, in this case taking place without any detectable racemization.[8] The use of Montmorillonite K-10 either in CH_2Cl_2 at room temperature or in toluene

Table 1. Selective cleavage of *N*,*N*-di-Boc-protected amines and α-amino acids using Montmorillonite K-10.

Entry[a]	Substrate	Time / h	Conditions[b]	Product	% Yield
1	 **1**	10	A	 **2**	91
		0.5	B		93
2	 **3**	12	B	 **4**	90
3	 **5**	2	B	 **6**	94
4	 **7**	10	A	 **8**	90
5	 **9**	10	A	 **10**	87
6	 **11**	10	A	 **12**	85
7	 **13**	12	A	 **14**	89
8	 **15**	3	A	 **16**	90
9	 **17**	3	A	 **18**	91
10	 **19**	10	A	 **20**	85
11	 **21**	48	B	–	fully recovered
12	 **22**	12	A	 **23**	65
13	 **24**	3	A	 **25**	94
14	 **26**	80	A	 **27**	55
		80	B		85
15[13]	 **28**	6	A	 **29**	93[14]
16	 **30**	10	A	 **31**	90

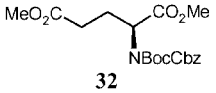
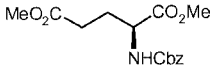
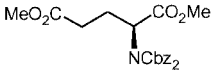
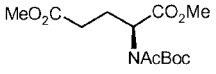
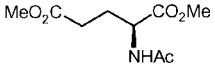
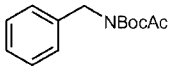
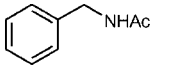
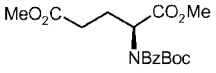
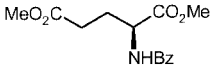
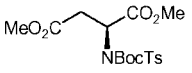
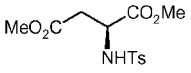
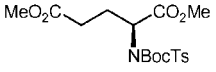
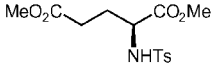
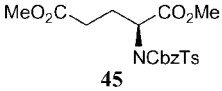
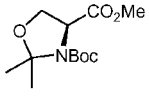
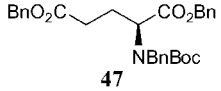
[a] Except in cases indicated, substrates and products are reported in ref.[5f] [b] A: CH_2Cl_2, room temperature; B: toluene, 65 °C.

at 65 °C proved to be an excellent combination with which to achieve selectivity, mildness, and generality in the desired conversion.[9]

Results and Discussion

In order to explore the scope and limitations of our method, we investigated a series of *N*,*N*-di-Boc amino derivatives containing several protecting groups and functionalities (Table 1). We found the procedure to be highly general, affording the corresponding *N*-Boc amino derivatives in excellent yields. The possibility of applying this methodology to an α-amino acid derivative containing an aldehyde function in its structure was of particular interest (Entry 3).[4] When a hydroxy group is present in the substrate, the reaction behavior depends on the position of this group relative to the *N*,*N*-di-Boc amino derivatives; thus, when the hydroxy group was far from the *N*-Boc functions, almost no influence was detected (Entry 5), while when it was close to the protected nitrogen, a negative influence was seen and no reaction occurred (Entry 11). Evidence of possible competition with the reaction sites at the clay in the above case was obtained when the corresponding silyl-protected compound was used: this compound underwent straightforward selective *N*-Boc cleavage (Entry 12).[10] The Montmorillonite K-10 system cleaved silyl ethers (TBS and TBDPS; Entries 12, 14) present in some *N*,*N*-di-Boc-α-amino-protected compounds, but in others the silyl group remained unaffected (Entries 8, 9, 13).[11] The reason for this behavior is not completely clear, but presumably is related to the longer reaction rate relative to the *N*-Boc cleavage in Entries 12 and 14. Interestingly, the cleavage of the *N*-Boc group could be achieved in the presence of *O*-Boc protective groups (Entry 10). In addition, the *tert*-butyl ester function remains unaffected under these conditions (Entry 16). In general, the reaction times were shorter when toluene at 65 °C was used rather than CH_2Cl_2 at room temperature. Additionally, the Montmorillonite K-10 could be recovered by simple filtration from the reaction mixture and was successfully reused four times without losing its activity in the cleavage

Table 2. Selectivity in the cleavage of *N*,*N*-diprotected α-amino acids and amines.

Entry[a]	Substrate	Product	% Yield (conditions,[b] time / h)
1	 **32**	 **33**	90 (A, 10)
2	 **34**	–	fully recovered (A or B, 24)
3	 **35**	 **36**	50 (A, 24) 90 (B, 3)
4	 **37**	 **38**	40 (A, 40)[14] 60 (B, 12)[14]
5	 **39**	 **40**	50 (A, 24)[15] 93 (B, 3)
6	 **41**	 **42**	10 (A, 24) 95 (B, 6)
7	 **43**	 **44**	10 (A, 24) 95 (B, 6)
8	 **45**	–	fully recovered (A or B, 24)
9	 **46**	–	fully recovered (A or B, 24)
10	 **47**	–	fully recovered (A or B, 24)

[a] Except in cases indicated, substrates and products are reported in ref.[5f] [b] A: CH_2Cl_2, room temperature; B: toluene, 65 °C.

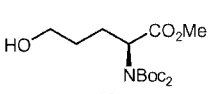
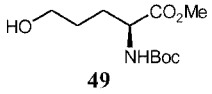
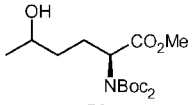
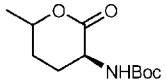
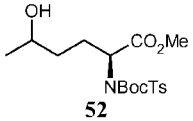
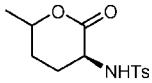
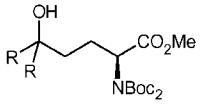
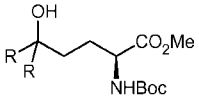
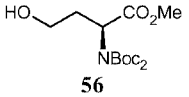
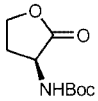
of *N*,*N*-di-Boc-α-amino-protected derivatives.[12] It should be emphasized that in most cases virtually pure samples were obtained after filtration and removal of solvents.

As the method works with the *N*,*N*-di-Boc fragment, we wondered whether the methodology could also be extended to other situations in which the nitrogen is doubly protected with different protecting groups together with the *N*-Boc protection (Table 2). We found that when another carbamoyl-based protecting group, such as Cbz, was used the cleavage of the Boc group was accomplished cleanly and selectively, yielding the corresponding *N*-Cbz amino derivative (Entry 1). However, when the nitrogen was protected as the *N*-Cbz-*N*-acyl derivative the substrate remained unaltered in the presence of Montmorillonite K-10 even after 24 h at 65 °C (Entries 2, 8) demonstrating the high selectivity in favor of *N*-Boc cleavage. When the additional protecting group on the nitrogen atom was an acyl group, cleavage of the *N*-Boc group proceeded in excellent yields with *N*-Boc-*N*-acyl-α-amino acids (Entries 3, 5) but only in moderate yields with the protected *N*-Boc-*N*-acyl-benzylamine (Entry 4). The procedure also worked very well for *N*-Boc-*N*-sulfonyl-α-amino acids, in which case the *N*-carbamoyl cleavage was accomplished in excellent yields (Entries 6, 7).[16] Finally, the procedure leaves *N*-Boc protected secondary amines unaffected (Entries 9, 10).

Taking into account the observation that the use of Montmorillonite K-10 had produced the lactonization of methyl (*S*)-2-(*tert*-butoxycarbonylamino)-5-hydroxypentanoate (Entry 14 in Table 1), through concomitant cleavage of the TBS protecting group and one of the two Boc groups, we pondered the possibility of using Montmorillonite to promote lactonization of δ- and γ-hydroxy-α-amino acids derivatives (Table 3). The process is effective for primary and secondary alcohols since both γ- and δ-lactones were obtained in very good yields. However, when a tertiary alcohol was used the lactone was not obtained (Entry 5). In addition, we found that in acetonitrile as solvent the deprotected δ-hydroxy-α-amino ester was obtained as sole product (Entry 1), but in toluene the reaction afforded the corresponding δ-lactone (Entry 2). In this last case, the originally formed mixture of the hydroxy ester and the δ-lactone, detected after 12 h, evolved to the cyclic product after a longer reaction time (30 h). On the contrary, during the lactonization process to γ-lactones we observed only the cyclic product from the very beginning of the reaction (Entries 6, 7).

In our previous report regarding the use of LiBr as an effective catalysis to cleave one carbamoyl group in *N*,*N*-dicarbamoyl-protected amines,[5f] we provided arguments accounting for the different behavior, regarding selectivity,

Table 3. Lactonization of *N*,*N*-di-Boc-α-amino-δ- and -γ-hydroxy esters using Montmorillonite K-10, at 65 °C.

Entry	Substrate	Time / h	Solvent	Product	% Yield
1	 **48**	12	CH_3CN	 **49**	94[17]
2		30	toluene	**27**	92[17] [a]
3	 **50**	6	toluene	 **51**	89
4	 **52**	44	CH_2Cl_2	 **53**	10[b]
		3	toluene		95
5	 R = TMSC≡C **54**	3	toluene	 R = TMSC≡C **55**	91
6[18]	 **56**	30	toluene	 **57**	88
7	**56**	150	CH_3CN	**57**	80

[a] With a shorter reaction time (12 h), a 94% yield of a mixture (1:1) of mono-deprotected hydroxy-*N*-Boc amino ester (see Entry 1) and lactone was isolated. [b] At 25 °C.

in comparison with the use of $Mg(ClO_4)_2$.[5b] The lithium induces a weak covalent C–O bond (*tert*-butyl oxygen), but this part of the molecule adopts a more ionic character in the case of the magnesium complex. This is coincident with the experimental observations that indicate a greater decarboxylative facility for magnesium-assisted breaking. As the selectivity found with Montmorillonite is roughly similar to that achieved using Mg^{2+} [5f] we propose that interlayer cations (magnesium) may be responsible for the activity, although interstitial water may also exert a general acidic effect.

Conclusions

In conclusion, we have found that clay Montmorillonite K-10 promotes the selective cleavage of a Boc group in *N*-Boc-*N*-acyl-diprotected amines. The methodology is practical, simple to use, easily scalable, and compatible with a wide range of functional groups. Commercially available Montmorillonite K-10 is nontoxic, inexpensive, environmentally friendly, and reusable. In addition, we found that Montmorillonite promotes concomitant Boc cleavage and lactonization when primary or secondary γ- or δ-hydroxy-*N*,*N*-di-Boc-protected α-amino acids are used as substrates.

Experimental Section

General Methods: ^1H and ^{13}C NMR spectra were recorded at 25 °C with Bruker Avance 400 and/or 300 spectrometers in $CDCl_3$ as solvent, and chemical shifts are reported relative to Me_4Si. Low- and high-resolution mass spectra were taken with a Micromass Autospec spectrometer. Elemental analyses were performed on a Fisons Instruments EA 1108 CHNS-O. Optical rotations were determined for solutions in chloroform or *n*-hexane with a Perkin–Elmer Model 241 polarimeter. Infrared spectra were recorded on a Bruker IFS 55 spectrophotometer. Column chromatography was performed on Merck silica gel, 60 Å and 0.2–0.5 mm. Visualization of spots was performed with the aid of UV light and/or phosphomolybdic acid in ethanol stain. All solvents were purified by standard techniques.[19] Reactions requiring anhydrous conditions were performed under argon. Anhydrous magnesium sulfate was used for drying solutions.

General Procedure for the Selective Cleavage of One Boc Group in an *N*,*N*-Boc,acyl-diprotected Amine: *N*-Boc-L-aspartic dimethyl ester (**2**). Commercially available Montmorillonite K-10 (9 g) was added to a stirred solution of *N*,*N*-di-Boc-L-aspartic dimethyl ester (**1**,[4a] 2.95 g, 8.2 mmol) in toluene (80 mL). The mixture was stirred at 65 °C for 0.5 h, after which time the reaction was complete. The reaction mixture was filtered, and the solid was washed with ethyl acetate. The solution was concentrated to yield pure *N*-Boc-L-aspartic dimethyl ester (**2**, 2 g, 93% yield) as a white solid with m.p. 66–65 °C. $[a]_{25}^{D}$ = +28.0 (*c* = 5, $CHCl_3$).[5f] ^1H NMR ($CDCl_3$): δ = 1.36 (s, 9 H), 2.77 (dd, *J* = 4.75, 16.9 Hz, 1 H), 2.92 (dd, *J* = 4.1, 17.0 Hz, 1 H), 3.61 (s, 3 H), 3.67 (s, 3 H), 4.48 (br., 1 H), 5.47 (br., 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.2 (q), 36.5 (t), 49.9 (d), 51.8 (q), 52.5 (q), 79.9 (s), 155.3 (s), 171.4 (s), 171.2 (s) ppm. IR ($CHCl_3$): ṽ = 3374, 2979, 1742, 1438, 1166, 1046 cm^{-1}. HRMS: calcd. for $C_{11}H_{19}NO_6$ $[M - 1]^+$: 261.121; found 261.1225. MS: *m*/*z* 284 $[M + Na]^+$, 262 $[M + 1]^+$, 206 $[M - tBu]^+$, 162 $[M - Boc]^+$. $C_{11}H_{19}NO_6$ (261.27): calcd. C 50.57, H 7.33, N 5.36; found C 50.54, H 7.36, N 5.36.

5-[Bis(*tert*-butoxycarbonyl)amino]pentyl *tert*-Butyl Carbonate (19): Et_3N (2.11 mL, 15 mmol) and $(Boc)_2O$ (6.6 g, 30 mmol) were added sequentially to a stirred suspension of commercially available 5-aminopentan-1-ol (1.03 g, 10 mmol) in dry CH_2Cl_2 (100 mL). The reaction mixture was stirred until TLC showed complete protection. The solvent was removed under reduced pressure, and the residue was triturated, washed with Et_2O, and filtered through a pad of Celite. The combined organic layers were concentrated to yield an oily residue. $(Boc)_2O$ (2.5 g, 11 mmol) was added at room temperature to a solution of this compound and DMAP (244 mg, 2 mmol) in dry CH_3CN (15 mL). The reaction mixture became slightly red with gas evolution. The mixture was stirred for 4 h, after which time TLC showed that some starting material still remained. More $(Boc)_2O$ (1.1 g, 5 mmol) was then added, and the mixture was additionally stirred overnight. The solvent was evaporated, and the crude product was purified by silica gel column chromatography to afford **19** (3.6 g, 89% yield) as an oil: ^1H NMR ($CDCl_3$): δ = 1.42 (s, 27 H), 1.49 (m, 6 H), 3.47 (t, *J* = 6.6 Hz, 2 H), 3.96 (t, *J* = 7.4 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.8 (t), 27.5 (q), 27.8 (q), 28.1 (t), 28.4 (t), 45.9 (t), 62.1 (s), 66.6 (t), 81.5 (s), 81.8 (s) 152.4 (s), 153.4 (s) ppm. IR ($CHCl_3$): ṽ = 3690, 2979, 1789, 1709, 1698, 1457, 1368, 1279, 1126, 1037 cm^{-1}. MS: *m*/*z* = 426 $[M + Na]^+$, 404 $[M + 1]^+$, 236 $[M + Na - 2\times Boc]$. HRMS: calcd. for $C_{20}H_{37}NNaO_7$ $[M + Na]^+$: 426.246; found 426.2463. $C_{20}H_{37}NO_7$ (403.51): calcd. C 59.53, H 9.24, N 3.47; found C 59.52, H 9.45, N 3.60.

5-(*tert*-Butoxycarbonylamino)pentyl *tert*-Butyl Carbonate (20): The general procedure described above was applied to **19** on a 5 mmol scale (2 g), yielding **20** (1.29 g, 85% yield) as an oil: ^1H NMR ($CDCl_3$): δ = 1.36 (s, 9 H), 1.39 (m, 4 H), 1.40 (s, 9 H), 1.59 (m, 3 H), 3.04 (br., 2 H), 3.97 (t, *J* = 6.6 Hz, 2 H), 4.5 (br., 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.8 (t), 27.5 (q), 28.2 (q), 29.5 (t), 66.6 (t), 81.6 (s), 153.4 (s) ppm. IR ($CHCl_3$): ṽ = 3691, 2977, 1741, 1519, 1393, 1254, 1169 cm^{-1}. MS: *m*/*z* = 304 $[M + 1]^+$. HRMS: calcd. for $C_{15}H_{30}NO_5$ $[M + 1]^+$: 304.2124; found 304.2111. $C_{15}H_{29}NO_5$ (303.39): calcd. C 59.38, H 9.63, N 4.62; found C 59.39, H 9.76, N 4.49.

Methyl (*S*)-2-[Bis(*tert*-butoxycarbonyl)amino]-5-(*tert*-butyldiphenylsilyloxy)pentanoate (24): Imidazole (0.62 g, 9 mmol) was added to a stirred solution of methyl (*S*)-2-[bis(*tert*-butoxycarbonyl)amino]-5-hydroxypentanoate[20] (1 g, 3 mmol) in dry CH_2Cl_2 (15 mL). The reaction mixture was cooled to 0 °C, and *tert*-butylchlorodiphenylsilane (0.94 mL, 3.6 mmol) was added. The mixture was stirred for 3 h at the same temperature. After that, the cooling bath was removed, water was added, and the products were extracted with CH_2Cl_2. The organic solution was dried with $MgSO_4$ and filtered through a pad of Celite. The solvent was evaporated, and the crude product was purified by silica gel column chromatography to afford **24** (1.6 g, 91% yield) as an oil; $[a]_{25}^{D}$ = –19.2 (*c* = 3, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 1.02 (s, 9 H), 1.45 (s, 18 H), 1.63 (m, 2 H), 1.99 (m, 1 H), 2.22 (m, 1 H), 3.66 (s, 3 H), 4.84 (m, 1 H), 7.35 (m, 6 H), 7.64 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.0 (s), 26.3 (t), 26.4 (q), 26.7 (q), 29.2 (t), 51.8 (q), 57.8 (d), 63.2 (t), 82.7 (s), 127.4 (d), 129.3 (d), 133.7 (s), 134.6 (s), 135.3 (d), 151.8 (s), 171.0 (s) ppm. IR ($CHCl_3$): ṽ = 3676, 2933, 1757, 1589, 1473, 1367, 1129 cm^{-1}. MS: *m*/*z* = 608 $[M + Na]^+$, 486 $[M - Boc]^+$, 386 $[M - 2\times Boc]^+$, 372 $[M - Boc - 2\times tBu]^+$. HRMS: calcd. for $C_{32}H_{47}NNaO_7Si$ $[M + Na]^+$: 608.3020; found 608.3071. $C_{32}H_{47}NO_7Si$ (585.80): calcd. C 65.61, H 8.09, N 2.39; found C 65.61, H 8.11, N 2.23.

Methyl (*S*)-2-(*tert*-Butoxycarbonylamino)-5-(*tert*-butyldiphenylsilyloxy)pentanoate (25): The general procedure described above was

applied to **24** on a 1.5 mmol scale (0.88 g), yielding **25** (0.685 g, 94% yield) as an oil. $[\alpha]_{25}^{D}$ = +9.0 (*c* = 3, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.02 (s, 9 H), 1.39 (s, 9 H), 1.52 (m, 2 H), 1.72 (m, 1 H), 1.99 (m, 1 H), 3.62 (t, *J* = 6.0 Hz, 2 H), 3.65 (s, 3 H), 4.27 (br., 1 H), 5.08 (br., 1 H), 7.36 (m, 6 H), 7.60 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.0 (s), 26.6 (q), 28.1 (q), 28.9 (t), 51.9 (q), 53.1 (d), 62.8 (t), 79.6 (s), 127.4 (d), 129.4 (d), 133.5 (s), 134.6 (s), 135.3 (d), 155.2 (s), 173.1 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3688, 3071, 2931, 2858, 1717, 1589, 1473, 1391, 1248, 1170, 1008 cm^{-1}. MS: *m*/*z* = 486 [M + 1]$^+$, 386 [M – Boc]$^+$, 372 [M – 2 × *t*Bu]$^+$. HRMS: calcd. for $C_{27}H_{40}NO_5Si$ [M + 1]$^+$: 486.2676; found 486.2722. $C_{27}H_{39}NO_5Si$ (485.69): calcd. C 66.77, H 8.09, N 2.88; found C 67.79, H 7.93, N 2.68.

Methyl (*S*)-2-[Bis(*tert*-butoxycarbonyl)amino]-5-(*tert*-butyldimethylsilyloxy)pentanoate (26): Imidazole (0.47 g, 6.9 mmol) was added to a stirred solution of methyl (*S*)-2-[bis(*tert*-butoxycarbonyl)-amino]-5-hydroxypentanoate[20] (0.8 g, 2.3 mmol) in dry CH_2Cl_2 (23 mL). The reaction mixture was cooled to 0 °C and *tert*-butylchlorodimethylsilane (0.43 g, 2.8 mmol) was added. The mixture was stirred for 3 h at the same temperature. The cooling bath was then removed, water was added, and the products were extracted with CH_2Cl_2.The organic solution was dried with $MgSO_4$ and filtered through a pad of Celite. The solvent was evaporated, and the crude product was purified by silica gel column chromatography to afford **26** (0.95 g, 89% yield) as an oil. $[\alpha]_{25}^{D}$ = –11.9 (*c* = 3, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = –0.05 (s, 6 H), 0.8 (s, 9 H), 1.4 (s, 18 H), 1.52 (m, 2 H), 1.84 (m, 1 H), 2.0 (m, 1 H), 3.54 (t, *J* = 6.3 Hz, 2 H), 3.54 (s, 3 H), 4.79 (dd, *J* = 9.6, 5.2 Hz, 1 H) ppm. ^{13}C NMR (CDC_{13}): δ = –5.6 (q), 18.0 (s), 25.7 (t), 26.2 (q), 27.7 (q), 29.3 (t), 51.8 (q), 57.7 (d), 62.4 (t), 82.7 (s), 151.8 (s), 171.1 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3692, 2954, 1796, 1753, 1460, 1368, 1254, 1124, 1005 cm^{-1}. MS: *m*/*z* = 462 [M + 1]$^+$, 362 [M – Boc]$^+$, 262 [M – 2 × Boc]$^+$. HRMS: calcd. for $C_{22}H_{44}NO_7Si$ [M + 1]$^+$: 462.2887; found 462.2863. $C_{22}H_{43}NO_7Si$ (461.66): calcd. C 57.24, H 9.39, N 3.03; found C 57.25, H 9.54, N 2.98.

***tert*-Butyl [(*S*)-2-Oxotetrahydro-2*H*-pyran-3-yl]carbamate (27):** The general procedure described above was applied to **26** on a 1.37 mmol scale (0.63 g) using toluene at 65 °C instead of CH_2Cl_2 at room temperature, yielding **27** (250 mg, 85% yield) as a white solid with m.p. 110–111 °C. $[\alpha]_{25}^{D}$ = +58 (*c* = 3, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.38 (s, 9 H), 1.55 (m, 1 H), 1.94 (m, 2 H), 2.5 (m, 1 H), 4.27 (t, *J* = 6.0 Hz, 2 H), 4.33 (br., 1 H), 5.32 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.8 (t), 25.4 (t), 28.0 (q), 49.0 (d), 67.1 (t), 79.9 (s), 155.1 (s), 172.4 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3365, 2977, 1741, 1687, 1524, 1464, 1368, 1238, 1154, 1080 cm^{-1}. MS: *m*/*z* = 216 [M + 1]$^+$. HRMS: calcd. for $C_{10}H_{18}NO_4$ [M + 1]$^+$: 216.1236; found 216.1239. $C_{10}H_{17}NO_4$ (215.25): calcd. C 55.80, H 7.96, N 6.51; found C 55.82, H 7.84, N 6.44.

***tert*-Butyl Acetyl(benzyl)carbamate (37):** A solution of benzylamine (1 g, 9.3 mmol) in CH_2Cl_2 (50 mL) was treated with Et_3N (1.7 mL, 12 mmol) and AcCl (0.8 mL, 11 mmol). The mixture was stirred at room temperature for 12 h. The reaction mixture was then diluted with EtOAc, treated with HCl (5%), washed with brine, dried, and concentrated to yield the corresponding *N*-Ac amino ester, which was used without purification. $(Boc)_2O$ (2.5 g, 11 mmol) was added at room temperature to a stirred solution of the crude *N*-benzylacetamide and DMAP (244 mg, 2 mmol) in dry CH_3CN (15 mL). The reaction became slightly red with gas evolution. The mixture was stirred for 4 h, after which time TLC showed that some starting material still remained. More $(Boc)_2O$ (1.1 g, 5 mmol) was then added, and the mixture was additionally stirred overnight. The solvent was evaporated, and the crude product was purified by silica gel column chromatography, to afford **37** (1.8 g, 72% yield) as an oil. ^{1}H NMR ($CDCl_3$): δ = 1.38 (s, 9 H), 2.51 (s, 3 H), 4.87 (s, 2 H), 7.2 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 26.6 (q), 27.8 (q), 47.0 (t), 83.1 (s), 127.0 (d), 127.5 (d), 128.2 (d), 138.3 (s), 153.1 (s), 172.9 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2980, 1737, 1698, 1369, 1281, 1040. MS: *m*/*z* = 250 [M + 1]$^+$, 194 [M – *t*Bu]$^+$. HRMS: calcd for $C_{14}H_{20}NO_3$ [M + 1]$^+$: 250.1443; found 250.1414. $C_{14}H_{19}NO_3$ (249.31): calcd. C 67.45, H 7.68, N 5.82; found C 67.43, H 7.77, N 5.62.

Dimethyl (*S*)-2-[*N*-(*tert*-Butoxycarbonyl)benzamido]pentanedioate (39): Na_2CO_3 (2.4 g, 22.5 mmol) and benzoyl chloride (1.29 mL, 11 mmol) were added at room temperature to a stirred suspension of commercially available (*S*)-glutamic acid (1.47 g, 10 mmol) in water (100 mL). The reaction mixture was heated at reflux overnight. The reaction mixture was then diluted with EtOAc, treated twice with HCl, washed with brine, dried, and concentrated, yielding an oily residue. A solution of this compound in dry MeOH (33 mL) was added slowly to Me_3SiCl (5.6 mL, 44 mmol) in an ice-cold bath. After the addition was complete, the ice-cold bath was removed and the reaction mixture was stirred overnight until TLC showed complete conversion. The mixture was then concentrated to yield the corresponding *N*-Bz-amino ester, which was used without purification. $(Boc)_2O$ (2.5 g, 11 mmol) was added at room temperature to a stirred solution of this crude product and DMAP (244 mg, 2 mmol) in dry CH_3CN (15 mL). The reaction became slightly red with gas evolution. The mixture was stirred for 4 h, after which time TLC showed that some starting material still remained. More $(Boc)_2O$ (1.1 g, 5 mmol) was then added, and the mixture was additionally stirred overnight. The solvent was evaporated, and the crude product was purified by silica gel column chromatography, to afford **39** (3 g, 80% yield) as an oil. $[\alpha]_{25}^{D}$ = –37.3 (*c* = 3, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.07 (s, 9 H), 2.37 (m, 1 H), 2.41 (m, 2 H), 2.42 (m, 1 H), 3.59 (s, 3 H), 3.68 (s, 3 H), 5.01 (m, 1 H), 7.39 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 24.4 (t), 27.0 (q), 30.5 (t), 51.4 (q), 52.2 (q), 56.7 (d), 83.5 (s), 127.4 (d), 127.9 (d), 131.1 (d), 136.9 (s), 152.4 (s), 170.3 (s), 172.6 (s), 172.7 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2980, 2360, 1748, 1449, 1369, 1235, 1149, 1016. MS: *m*/*z* = 380 [M + 1]$^+$, 280 [M – Boc]$^+$. HRMS: calcd. for $C_{19}H_{26}NO_7$ [M + 1]$^+$, 380.170; found 380.1729. $C_{19}H_{25}NO_7$ (379.40): calcd. C 60.15, H 6.64, N 3.69; found C 60.16, H 6.64, N 3.48.

Dimethyl (*S*)-2-Benzamidopentanedioate (40): The general procedure described above was applied to **39** on a 2 mmol scale (0.76 g) using toluene at 65 °C instead of CH_2Cl_2 at room temperature, yielding **40** (519 mg, 93% yield) as a white solid with m.p. 69–70 °C. $[\alpha]_{25}^{D}$ = +5.4 (*c* = 3, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 2.01 (m, 1 H), 2.26 (m, 1 H), 2.44 (m, 2 H), 3.60 (s, 3 H), 3.73 (s, 3 H), 4.77 (m, 1 H), 6.99 (br., 1 H), 7.42 (m, 3 H), 7.76 (d, *J* = 8.1 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 27.0 (t), 30.0 (t), 51.7 (q), 52.0 (t), 52.4 (q), 126.9 (d), 128.4 (d), 131.6 (d), 133.3 (s), 172.2 (s), 173.4 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3335, 2954, 1739, 1579, 1438, 1213, 1103, 1027 cm^{-1}. HRMS: calcd. for $C_{14}H_{18}NO_5$ [M + 1]$^+$: 280.1185; found 280.1184. MS: *m*/*z* 280 [M + 1]$^+$. $C_{14}H_{17}NO_5$ (279.29): calcd. C 60.21, H 6.14, N 5.02; found C 60.21, H 6.21, N 4.72.

Dimethyl (*S*)-2-[*N*-(*tert*-Butoxycarbonyl)-4-methylphenylsulfonamido]succinate (41): Na_2CO_3 (2.4 g, 22.5 mmol) and *p*-toluenesulfonyl chloride (2.1 g, 11 mmol) were added at room temperature to a stirred suspension of commercially available (*S*)-aspartic acid (1.33 g, 10 mmol) in water (100 mL). The reaction mixture was heated at reflux overnight. The reaction mixture was then diluted with EtOAc, treated twice with HCl, washed with brine, dried, and concentrated to yield an oily residue. To a solution of this com-

pound in dry MeOH (33 mL) was added slowly Me_3SiCl (5.6 mL, 44 mmol) in an ice-cold bath. After the addition was complete, the ice-cold bath was removed and the reaction mixture was stirred overnight until TLC showed complete conversion. The mixture was then concentrated to yield the corresponding *N*-Ts-amino ester, which was used without purification. $(Boc)_2O$ (2.5 g, 11 mmol) was added at room temperature to a stirred solution of the crude *N*-Ts-amino ester and DMAP (244 mg, 2 mmol) in dry CH_3CN (15 mL). The reaction mixture became slightly red with gas evolution. The mixture was stirred for 4 h, after which time TLC showed that some starting material still remained. More $(Boc)_2O$ (1.1 g, 5 mmol) was then added and the mixture was additionally stirred overnight. The solvent was evaporated, and the crude product was purified by silica gel column chromatography, to afford **41** (3.4 g, 82% yield) as a white solid with m.p. 91–92 °C. $[\alpha]_{25}^{D} = -56.1$ (c = 3, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 1.23 (s, 9 H), 2.36 (s, 3 H), 2.75 (m, 1 H), 3.29 (m, 1 H), 3.62 (s, 3 H), 3.63 (s, 3 H), 5.57 (m, 1 H), 7.23 (d, J = 8.3 Hz, 2 H), 7.81 (d, J = 8.2 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.4 (q), 27.3 (t), 27.5 (q), 36.2 (t), 51.8 (q), 52.5 (q), 55.2 (d), 85.2 (s), 128.4 (d), 128.8 (d), 136.2 (s), 144.3 (s), 149.7 (s), 169.3 (s), 170.3 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3667, 2955, 1743, 1438, 1355, 1255, 1147, 1088 cm^{-1}. MS: m/z = 416 $[M + 1]^+$, 360 $[M - t\text{Bu}]^+$, 316 $[M - \text{Boc}]^+$. HRMS: calcd. for $C_{18}H_{26}NO_8S$ $[M + 1]^+$: 416.1379; found 430.1519. $C_{18}H_{25}NO_8S$ (415.46): calcd. C 52.04, H 6.07, N 3.37, S 7.72; found C 52.08, H 5.95, N 3.29, S 7.62.

Dibenzyl (*S*)-2-(*tert*-Butoxycarbonyl)pentanedioate (47): CAN (2.1 equiv.) was added portionwise at room temperature to a stirred solution of dibenzyl (*S*)-2-(dibenzylamino)pentanedioate[4a] (5.07 g, 10 mmol) in $MeCN/H_2O$ (5:1). The reaction was quenched by the addition of saturated aqueous sodium hydrogen carbonate solution and the mixture was stirred vigorously for 10 min before extraction with Et_2O. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated to yield an oily residue. To a solution of this compound and DMAP (244 mg, 2 mmol) in dry CH_3CN (15 mL, 0.68 M) was added $(Boc)_2O$ (2.5 g, 11 mmol) at room temperature. The reaction mixture became slightly red with gas evolution. The mixture was stirred for 4 h, after which time TLC showed that some starting material still remained. More $(Boc)_2O$ (1.1 g, 5 mmol, 0.5 equiv.) was then added and the mixture was additionally stirred overnight. The solvent was evaporated, and the crude product was purified by silica gel column chromatography, to afford **47** (4.2 g, 81% yield) as an oil: $[\alpha]_{25}^{D} = -40.7$ (c = 3, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 1.36 (s, 9 H), 2.07 (m, 1 H), 2.30 (m, 3 H), 4.25 (m, 1 H), 4.65 (br., 1 H), 5.01 (m, 4 H), 7.29 (m, 15 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.0 (q), 30.4 (t), 58.5 (d), 66.1 (t), 66.6 (t), 128.0 (d), 128.0 (d), 128.1 (d), 128.3 (d), 128.3 (d), 135.6 (s), 155.2 (s) 170.7 (s), 172.4 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3542, 2976, 1731, 1695, 1454, 1366, 1029 cm^{-1}. MS: m/z = 518 [M + 1], 418 [M – Boc]. HRMS: calcd for $C_{31}H_{36}NO_6$ $[M + 1]^+$: 518.2543; found 518.2529. $C_{31}H_{35}NO_6$ (517.61): calcd. C 71.93, H 6.82, N 2.71; found C 71.92, H 6.71, N 2.88.

Methyl (*S*)-2-[Bis(*tert*-butoxycarbonyl)amino]-5-hydroxypentanoate (48): DIBAL (12 mL, 1.0 M in hexane, 12 mmol) was added dropwise at –78 °C to a stirred solution of **3**[4a] (3.45 g, 10 mmol) in dry Et_2O (27 mL). The reaction mixture was stirred for 5 min and then quenched with H_2O. The mixture was stirred for 30 min, dried with $MgSO_4$, and filtered through a pad of Celite. The solvent was evaporated, and the crude aldehyde was used in the next step without purification. The procedure used to obtain the aldehyde was again applied to provide the corresponding alcohol, which was purified by silica gel column chromatography to afford **48** (3 g, 86% overall yield) as an oil. $[\alpha]_{25}^{D} = -34$ (c = 3, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 1.42 (s, 18 H), 1.58 (m, 2 H), 1.84 (m, 1 H), 2.16 (m, 1 H), 3.59 (t, J = 6.4 Hz, 2 H), 3.64 (s, 3 H), 4.81 (dd, J = 9.1, 5.4 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 26.2 (t), 27.7 (q), 29.1 (t), 51.9 (q), 57.6 (d), 62.0 (t), 82.9 (s), 151.9 (s), 171.1 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3691, 2980, 1748, 1368, 1252, 1144 cm^{-1}. MS: m/z = 360 $[M + Na]^+$, 248 $[M - Boc]^+$, 148 $[M - 2 \times Boc]^+$. HRMS: calcd. for $C_{16}H_{29}NNaO_7$ $[M + Na]^+$ 360.1842; found 360.1859. $C_{16}H_{29}NO_7$ (347,40): calcd. C 55.32, H 8.41, N 4.03; found C 55.33, H 8.41, N 3.94.

Methyl (*S*)-2-[Bis(*tert*-butoxycarbonyl)amino]-5-hydroxyhexanoate (50): Trimethylaluminium (2.0 M in toluene, 1.8 mL, 3.6 mmol) was added by syringe pump at –78 °C over 40 min to a solution of methyl (2*S*)-2-{(*tert*-butoxy)-*N*-[(*tert*-butyl)oxycarbonyl]carbonyl-amino}-5-oxopentanoate[4a] (1 g, 3 mmol) in toluene (60 mL, 0.05 M). After the mixture had been stirred for 15 min at the same temperature, $BF_3{\cdot}OEt_2$ (0.46 mL, 3.6 mmol) in Et_2O (6 mL) was added slowly along the walls of the flask over 15 min. The contents were stirred at –78 °C for 1 h. The reaction mixture was warmed to –50 °C over 25 min before saturated aqueous NH_4Cl was added. After stirring at room temperature for additional 30 min, the contents were diluted with water, extracted with diethyl ether, dried with $MgSO_4$, filtered, and concentrated. The solvent was evaporated, and the crude product was purified by silica gel column chromatography to afford **50** (0.95 g, 88% yield) as an oil: ^1H NMR ($CDCl_3$): δ = 1.02 (d, J = 6.1 Hz, 3 H), 1.32 (m, 2 H), 1.33 (s, 18 H), 1.54 (m, 1 H), 2.05 (m, 1 H), 2.22 (br., 1 H), 3.54 (s, 3 H), 3.64 (m, 1 H), 4.69 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 23.1 (q), 25.8 (t), 26.0 (t), 27.6 (q), 35.3 (t), 51.7 (t), 57.5 (d), 57.8 (d), 66.6 (d), 67.1 (d), 151.8 (s), 151.8 (s), 170.9 (s), 171.1 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3529, 2978, 2860, 1749, 1458, 1368, 1257, 1128 cm^{-1}. MS: m/z = 391 $[M + K]^+$, 362 $[M + 1]^+$. HRMS: calcd. for $C_{17}H_{32}NO_7$ $[M + 1]^+$ 362.2179; found 362.2209. $C_{17}H_{31}NO_7$ (361.43): calcd. C 56.49, H 8.65, N 3.88; found C 56.47, H 8.75, N 3.91.

***tert*-Butyl [(3*S*)-6-Methyl-2-oxotetrahydro-2*H*-pyran-3-yl]carbamate (51):** The general procedure described above was applied to **50** on a 0.67 mmol scale (0.242 g) using toluene at 65 °C instead of CH_2Cl_2 at room temperature, yielding **51** (0.137 g, 89% yield) as a white solid with m.p. 104–105 °C. ^1H NMR ($CDCl_3$): δ = 1.32 (m, 3 H), 1.39 (s, 9 H), 1.64 (m, 2 H), 1.95 (m, 1 H), 2.52 (m, 1 H), 4.00 (br., 0.5 H), 4.48 (m, 1.5 H), 5.24 (br., 0.5), 5.33 (br., 0.5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 23.1 (q), 25.8 (t), 26.0 (t), 27.6 (q), 35.3 (t), 51.7 (t), 57.5 (d), 57.8 (d), 66.6 (d), 67.1 (d), 151.8 (s), 151.8 (s), 170.9 (s), 171.1 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2930, 1702, 1647, 1530, 1367, 1167 cm^{-1}. MS: m/z = 230 $[M + 1]^+$. HRMS: calcd. for $C_{11}H_{20}NO_4$ $[M + 1]^+$: 230.1392; found 230.1404. $C_{11}H_{19}NO_4$ (229.27): calcd. C 57.62, H 8.35, N 6.11; found C 57.66, H 8.17, N 5.95.

Methyl (2*S*)-2-[*N*-(*tert*-Butoxycarbonyl)-4-methylphenylsulfonamido]-5-hydroxyhexanoate (52): The procedure described to obtain **50** was applied to **43** on a 3.3 mmol scale (1.32 g), yielding **52** (1.2 g, 88% yield) as an oil: ^1H NMR ($CDCl_3$): δ = 1.16 (m, 3 H), 1.24 (s, 9 H), 1.58 (m, 2 H), 2.06 (m, 1 H), 2.29 (m, 1 H), 2.38 (s, 3 H), 3.64 (s, 3 H), 3.82 (m, 1 H), 5.03 (m, 1 H), 5.24 (m, 1 H), 7.24 (m, 2 H), 7.88 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.4 (q), 23.2 (q), 23.4 (q), 26.0 (t), 26.4 (t), 27.5 (q), 35.5 (t), 35.6 (t), 52.2 (q), 58.9 (s), 59.2 (s), 67.0 (s), 67.5 (s), 84.7 (s), 128.4 (d), 128.8 (d), 136.3 (s), 144.1 (s), 149.7 (s), 170.3 (s), 170.4 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3676, 2976, 2360, 1736, 1351, 1254, 1148, 1047 cm^{-1}. MS: m/z = 454 $[M + K]^+$, 316 $[M - \text{Boc}]^+$, 416 $[M + 1]^+$. HRMS: calcd. for $C_{19}H_{30}NO_7S$ $[M + 1]^+$, 416.1743; found 416.1728. $C_{19}H_{29}NO_7S$ (415.50): calcd. C 54.92, H 7.03, N 3.37, S 7.72; found C 54.92, H 7.21, N 3.54, S 7.58.

(3S)-4-Methyl-*N*-(6-methyl-2-oxotetrahydro-2*H*-pyran-3-yl)benzenesulfonamide (53): The general procedure described above was applied to **52** on a 0.8 mmol scale (0.33 g) using toluene at 65 °C instead of CH_2Cl_2 at room temperature, yielding **53** (0.214 g, 95% yield) as a white solid with m.p. 112–114 °C. ^{1}H NMR ($CDCl_3$): δ = 1.25 (d, J = 6.0 Hz, 3 H), 1.6 (m, 2 H), 1.97 (m, 2 H), 2.34 (s, 3 H), 3.5 (m, 0.5 H), 3.91 (m, 0.5 H), 4.39 (br., 1 H), 5.65 (br., 1 H), 7.23 (m, 2 H), 7.70 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.5 (q), 21.3 (q), 21.5 (q), 25.7 (t), 27.6 (t), 28.3 (t), 29.9 (t), 50.0 (d), 52.9 (d), 74.1 (d), 79.6 (d), 126.8 (d), 127.0 (d), 129.4 (s), 129.6 (d), 143.7 (s), 169.7 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3279, 2978, 1739, 1598, 1449, 1332, 1162, 1091 cm^{-1}. MS: m/z = 284 [M + 1]$^+$. HRMS: calcd. for $C_{13}H_{18}NO_4S$ [M + 1]$^+$, 284.0957; found 284.0964. $C_{13}H_{17}NO_4S$ (283.34): calcd. C 55.11, H 6.05, N 4.94, S 11.32; found C 55.11, H 6.22, N 4.97, S 11.43.

Methyl (*S*)-2-{(*tert*-Butoxy)-*N*-[(*tert*-butyl)oxycarbonyl]carbonylamino}-5-hydroxy-7-(trimethylsilyl)-5-[2-(trimethylsilyl)ethynyl]hept-6-ynoate (54): *n*BuLi (1.5 M in hexane, 5.28 mL, 8.0 mmol) was added at –78 °C over 20 min to a solution of trimethylsilylacetylene (1.24 mL, 8.6 mmol) in THF (9 mL). After the mixture had been stirred at –78 °C for an additional 20 min, trimethylaluminium (2.0 M in toluene, 4.0 mL, 8.0 mmol) was added by syringe pump over 40 min. The reaction mixture was stirred at –78 °C for 30 min, –45 °C for 30 min, and then cooled to –78 °C, whereupon **3** (1.24 g, 3.31 mmol) in toluene (23 mL) was added over 15 min. The content was stirred at –78 °C for 1 h, whereupon methanol was added along the walls of the flask. The reaction was warmed to –50 °C over 25 min, after which saturated aqueous NH_4Cl (20 mL) was added. After stirring at room temperature for additional 30 min, the contents were diluted with water, extracted with diethyl ether, dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel, yielding **54** (1.5 g, 84% yield) as an oil; $[\alpha]_{25}^{D}$ = +22.4 (c = 3, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 0.12 (s, 18 H), 1.45 (s, 18 H), 1.90 (m, 2 H), 2.11 (m, 1 H), 2.37 (m, 1 H), 3.67 (s, 3 H), 4.88 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = –0.5 (q), 24.9 (t), 27.7 (q), 40.2 (t), 51.9 (q), 57.7 (d), 82.9 (s), 88.1 (s), 88.2 (s), 104.4 (s), 104.6 (s), 151.6 (s), 170.7 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3691, 2961, 1749, 1457, 1368, 1251, 1128, 846 cm^{-1}. MS: m/z = 578 [M + K]$^+$, 438 [M – Boc]$^+$, 322 [M – 2 × TMS – Boc – *t*Bu]$^+$. HRMS: calcd. for $C_{26}H_{45}KNO_7Si_2$ [M + K]$^+$: 578.2372; found 578.2333. $C_{26}H_{45}NO_7Si_2$ (539.81): calcd. C 57.85, H 8.40, N 2.59; found C 57.86, H 8.27, N 2.52.

Methyl (*S*)-2-(*tert*-Butoxycarbonyaminol)-5-hydroxy-7-(trimethylsilyl)-5-[2-(trimethylsilyl)ethynyl]hept-6-ynoate (55): The general procedure described above was applied to **54** on a 1.4 mmol scale (0.78 g) using toluene at 65 °C instead of CH_2Cl_2 at room temperature, yielding **55** (0.51 g, 91% yield) as a white solid with m.p. 109–110 °C. $[\alpha]_{25}^{D}$ = –12.8 (c = 3, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 0.07 (s, 18 H), 1.34 (s, 9 H), 1.82 (m, 3 H), 2.06 (m, 1 H), 3.55 (s, 3 H), 4.26 (br., 1 H), 5.04 (br., 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 27.5 (t), 39.2 (t), 52.0 (q), 52.8 (d), 65.1 (s), 88.0 (s), 88.1 (s), 155.2 (s), 172.8 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2957, 2857, 1745, 1498, 1343, 1216, 1079 cm^{-1}. MS: m/z = 422 [M – OH]$^+$, 322 [M – OH – Boc]$^+$. HRMS: calcd. for $C_{21}H_{36}NO_4Si_2$ [M – OH]$^+$: 422.2183; found 422.2172. $C_{21}H_{37}NO_5Si_2$ (439.69): calcd. C 57.36, H 8.48, N 3.19; found C 57.35, H 8.57, N 3.36.

(*S*)-*tert*-Butyl (2-Oxotetrahydrofuran-3-yl)carbamate (57): The general procedure described above was applied to **56**[18] on a 1.4 mmol scale (0.467 g) using toluene at 65 °C instead of CH_2Cl_2 at room temperature, yielding (*S*)-*tert*-butyl (2-oxotetrahydrofuran-3-yl)carbamate (0.25 g, 88% yield) as a white solid with m.p. 120–122 °C. $[\alpha]_{25}^{D}$ = +8.6 (c = 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.39 (s, 9 H), 2.14 (m, 1 H), 2.69 (br., 1 H), 4.22 (m, 3 H), 5.07 (br., 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.0 (q), 30.3 (t), 50.0 (d), 65.5 (t), 80.4 (s), 155.2 (s), 175.1 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3367, 2933, 1777, 1685, 1529, 1364, 1254, 1164 cm^{-1}. MS: m/z = 202 [M + 1]$^+$. HRMS: calcd. for $C_9H_{16}NO_4$ [M + 1]$^+$, 202.1079; found 202.1077. $C_9H_{15}NO_4$ (201.22): calcd. C 53.72, H 7.51, N 6.96; found C 53.71, H 7.57, N 6.85.

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[9] Montmorillonite, molecular formula $(Na,Ca)(Al,Mg)_6(Si_4O_{10})_3(OH)_6$-$n\,H_2O$, is made up of one octahedral aluminate layer sandwiched between two octahedral silicate layers. This clay is nontoxic, noncorrosive, economical, and recyclable.

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