A Mild Amide to Carbamate Transformation

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The acetamide and benzamide amine protecting groups have long been used in synthesis because they offer the advantage of very good stability to a wide range of conditions.[2] More recently, they have been found to give high selectivities in carbonyl-directed catalysis.[3] We have achieved excellent selectivities in DuPHOS-Rh and BPE-Rh catalyzed asymmetric hydrogenations of various acrylamides.[4] In the hydrogenation of hindered tetra-substituted acrylamides, a very challenging class of substrates, acetamide directing groups were found to be essential for the success of the reaction.[5] The scope of amide-directed catalysis in synthesis and the role of amide-based protecting groups in general would be increased with a more convenient method for the removal of acetamides and benzamides.

In our handling of acetamide and benzamide protected amines, direct cleavage of the amide bonds required harsh conditions such as refluxing in solutions of HCl[6] which was not compatible with sensitive functionality. It has been known for some time that amides can be activated to hydrolysis by prior conversion to the *N*-Boc imide derivatives.[7] Selective hydrolysis of the amide leaves the *N*-*tert*-butoxycarbamate in place. *N*-Boc-protected amino acids can be easily converted to the free amine and are useful in solid phase synthesis.[8] This paper communicates the optimization of a procedure for the conversion of *N*-acetamido and -benzamido amino acids to *N*-(*tert*-butoxycarbonyl)amino acids.

This procedure was optimized in two steps: (1) introduction of the Boc group and (2) cleavage of the acetate (Scheme 1). The two steps were then combined in an efficient standard one-pot procedure. After reviewing current methods we made significant improvements in reaction time and yields and obtained high degrees of chemoselectivity for the one-pot transformation of amides to carbamates.

The initial acylation step with di-*tert*-butyl dicarbonate[9] (Boc_2O) was first examined. *N*-Acetyl-L-valine methyl ester (**1**) was allowed to stir with 2 equiv of Boc_2O and 0.2 equiv of DMAP in solvent for 24 h at rt. The order of reactivity for different solvents was found to be THF > 1-methyl-2-pyrrolidinone (NMP) > $CH_3CN \approx$ pyridine > CH_2Cl_2 > MeOH. The reaction in THF was almost twice as fast as the next best solvent, NMP. NMP was tested due to its combination of strong solvating properties and convenient boiling point (81−82 °C/10 mm). CH_3CN and CH_2Cl_2 were both used in other studies[7] but were unsatisfactory in comparison to THF. The reaction in neat pyridine was also slower. Furthermore, adding 1 and 2 equiv of pyridine to acylations in other solvents slowed the reactions. Methanol simply hydrolyzed the Boc_2O reagent.

Scheme 1

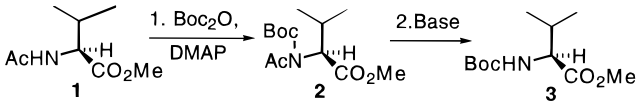
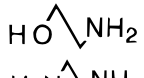
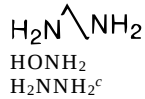


Table 1. Cleavage of Acetamide 2 → 3 in MeOH[a]

entry	base	time (h)	convn (%)[b]	**1** (%)	**3** (%)
1	morpholine	18	7	2	5
2	pyridine	18	3	3	0
3	Et_3N	18	17	2	15
4		4	18	3	15
5		4	45	2	43
6	$HONH_2$	4	32	2	30
7	H_2NNH_2[c]	2	100	0	100
8	$H_2NNH_2 \cdot H_2O$	2	100	0	100
9	NaOH[d]	4	30	2	28
10	LiOH[d]	4	100	0	97

[a] Conditions: 200 mg of **2** was dissolved in 2.9 mL of MeOH, 2 equiv base was added, and the reaction was allowed to stir for the time indicated. An aliquot was removed, diluted with CH_2Cl_2, and washed with 1 N HCl, $CuSO_4$, and $NaHCO_3$, dried over $MgSO_4$, and evaporated. The crude material was dissolved in acetone and assayed by GC. [b] Side products in addition to **1** and **3** were detected in some cases. [c] Identical reactivity was observed in 1:1 THF:MeOH. [d] Reaction products were treated with diazomethane before analysis.

By heating the acylation reaction in THF to reflux, only 4 h was required for completion. Decreasing the amount of Boc_2O below 2 equiv gave incomplete reactions.[10] The procedure was repeated for 5 g of **1** to give 6.6 g of *N*-acetyl-*N*-(*tert*-butoxycarbonyl)-L-valine methyl ester (**2**, 85%).

With large amounts of the mixed imide **2** in hand, the subsequent hydrolysis step was optimized for base and solvent, carefully examining the products for any sign of racemization. The results are summarized in Table 1. The mixed imide **2** was treated with 2 equiv of base in MeOH at rt. At the times shown, the products were assayed by GC. The monobasic morpholine, pyridine, and triethylamine gave low conversions and attacked both the carbamate group and the acetamide group to give both the amide starting material **1** as well as the carbamate product **3**.[11] The dibasic ethanolamine and ethylenediamine gave better conversions but also showed

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(2) Green, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991; p 351, 355.

(3) McCulloch, B.; Halpern, J.; Thompson, M. R.; Landis, C. R. *Organometallics* **1990**, *9*, 1392.

(4) (a) Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125. (b) Burk, M. J.; Gross, M. F.; Harper, G. P.; Kalberg, C. S.; Lee, J. R.; Martinez, J. P. *Pure Appl. Chem.* **1996**, *68*, 37.

(5) (a) Burk, M. J.; Gross, M. F.; Martinez, J. P. *J. Am. Chem. Soc.*, **1995**, *117*, 9375. (b) Burk, M. J.; Gross, M. F.; Martinez, J. P.; Straub, J. A. Manuscript in preparation.

(6) Dilbeck, G. A.; Field, L.; Gallo, A. A.; Gargiulo, R. J. *J. Org. Chem.* **1978**, *43*, 4593.

(7) (a) Grehn, L.; Gunnarsson, K.; Ragnarsson, U. *J. Chem. Soc., Chem. Commun.* **1985**, 1317. (b) Grehn, L.; Gunnarsson, K.; Ragnarsson, U. *Acta Chem. Scand.* **1986**, *B40*, 745. (c) Flynn, D. L.; Zelle, R. E.; Greico, P. A. *J. Org. Chem.* **1983**, *48*, 2424.

(8) Green, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991; pp 327−330.

(9) Grehn *et al.* (*J. Chem. Soc., Chem. Commun.* **1985**, 1317) reported that the dicarbonate was required for acylation, rather than the chloroformate or other acylating reagent. This result was confirmed in the current study.

(10) Refluxing for 18 h with 1.2 and 1.5 equiv of Boc_2O gave 80% and 90% completion, respectively.

(11) Free amine formed during the reactions would have been lost during the workup. Its formation however was unlikely due to the stability of amides and carbamates to the reaction conditions.

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some reaction with the carbamate group. Adding 20% DMAP to the ethanolamine and ethylenediamine reactions provided no improvement.[12] Hydroxylamine and hydrazine both have increased nucleophilicity due to the α-effect,[13] and hydrazine gave excellent results after only 2 h. Hydrazine hydrate had identical reactivity to hydrazine. In the effort to develop a one-pot procedure, 1:1 MeOH:THF was substituted for MeOH without losing any reactivity. No racemization was detected with any amine base.[14]

The alkoxide bases NaOH and LiOH were also tested in the amide cleavage reaction. In these trials, **2** was stirred at rt in 1:1 THF:2.0 M base, and the methyl ester was quickly hydrolyzed. The reaction products were extracted into ether and treated with diazomethane before analysis. Interestingly, NaOH and LiOH were found to have very different reactivity. After 4 h with LiOH the acetamide was fully hydrolyzed to give **3** with no loss of the carbamate.[15] With NaOH conversion was incomplete (69.6%) and 2.1% of **1** was formed. It was expected that in the carboxylate formed by ester hydrolysis the α-proton would be less acidic and the amino acid would be protected from racemization. Indeed, even after 22 h <0.6% racemate was formed with either LiOH or NaOH. Although these strongly basic conditions would not be compatible with more sensitive functionality and were not pursued, LiOH hydrolysis was a useful method when the acid was desired.

From these studies we arrived at a set of conditions which were attempted in a one-pot procedure: the acetamide was refluxed with 2 equiv of Boc_2O and 0.2 equiv of DMAP in THF for 4 h. The reaction was cooled, and the volume was doubled with MeOH. Excess hydrazine (4 equiv) was added to both quench unreacted Boc_2O and cleave the acetamide. Results of trials using this method are summarized in Table 2. The Boc-protected amino acids were obtained in high isolated yield without racemization.

Table 2[16] shows a range of protected linear, cyclic, and branched side-chain amino acids obtained commercially or prepared via catalytic asymmetric hydrogenation. Hindered acetamides in entries 1, 4, and 5 were transformed smoothly into the *N*-Boc derivatives. Preservation of the ethyl ester in **8** (entry 6) demonstrated that esters were stable to the conditions of basic methanolysis used in the second step.

We investigated the stability of other functionality and extended the reaction to the cleavage of benzamides (Table 3). In applying these conditions to benzamides, we found that the acylation with Boc_2O proceeded more quickly than with the acetamides and refluxing was not required. Cooling the reaction mixture to 0 °C after adding hydrazine still allowed the amide cleavage to take place, and base-catalyzed hydrolyses were minimized.

Table 2. Substrates Used in *N*-Ac to *N*-BocTransformations

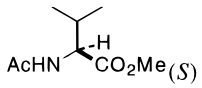
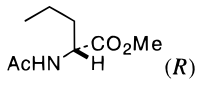
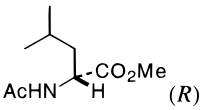
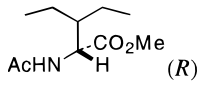
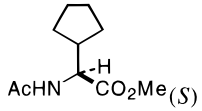
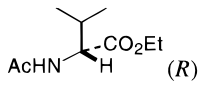
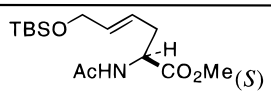
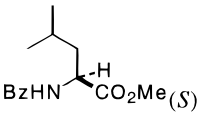
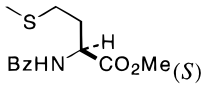
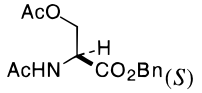
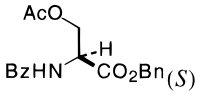
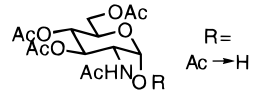
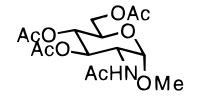
Entry	Substrate	Product no.	Yield (%)
1		**3**	92
2		**4**	80
3		**5**	91
4		**6**	93
5		**7**	93
6		**8**	87

Table 3. Selective Amide to *N*-Boc Transformations

Entry	Substrate	Product no.	Yield (%)
1		**9**[a]	93
2		***ent*-5**[a]	88
3		**10**	94
4		**11**	81
5		**11**	72
6		**12**[b]	80
7		**13**[c]	70

[a] Hydrolysis step performed at rt. [b] Acylation step performed at reflux. [c] Acylation step performed at reflux and with 3 equiv of Boc_2O.

Functionalized acetamides were found to easily survive these conditions as is shown in Table 3.

The allylic silyl ether[17] in entry 1 gave a very good yield of the *N*-Boc derivative **9**. The protected methionine in entry 3 decomposed during acylation at reflux, but a good yield was obtained when the acylation was performed at rt. Entries 4 and 5 demonstrated selectivity for acetamide and benzamide cleavage in the presence of acetate and benzyl esters in slightly diminished yields due to the

(12) After 4 h ethanolamine, 20.3% conversion, 2.0% **1**, 17.6% **3**, ethylenediamine; 43.5% conversion, 2.9% **1**, 42.8% **3**.

(13) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry Part A: Structure and Mechanisms*, 2nd ed.; Plenum: New York, 1991; p 228.

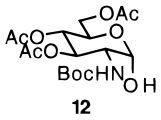
(14) NaOMe was used (18 h, rt, MeOH) to intentionally racemize the amino acid in the reaction **2** to **3** for comparison to the chiral products. In these reactions, racemization was faster than acetamide cleavage. Cleavage of the carbamate was also detected. Racemic DL-valine was also purchased and derivatized for comparison.

(15) 0.3% of the enantiomer was detected.

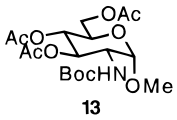
(16) Substrates for compounds **4** and **5** were obtained in >99% ee and 98.9% ee, respectively, using (*R*,*R*)-PrDuPHOS-Rh and (*R*,*R*)-EtDuPHOS-Rh (see ref 4a). Substrates for compounds **6**, **7**, and **8** were obtained in 96.9% ee and 95.9% ee and 97.4% ee, respectively, using (*R*,*R*)-MeBPE-Rh, (*S*,*S*)-MeBPE-Rh, (*R*,*R*)-MeBPE-Rh (see ref 5a).

(17) Substrate for compound **9** obtained in 96.6% ee by the use of (*S*,*S*)-MeDuPHOS-Rh. See: Burk, M. J.; Allen, J. A.; Kiesman, W. F. Manuscript in preparation.

formation of small amounts of hydrolysis products. The lower yield for entry 5 reflects the greater stability of the benzamide. The peracetylated GlcNAc in entry 6 was converted into the Boc derivative **12** in good yield with loss only of the highly labile anomeric acetate group. Lowering the temperature to −20 °C did not allow the anomeric acetate to survive: the acetamide and anomeric acetate were cleaved at the same rate. The corresponding methyl glycoside required forcing conditions to achieve acylation, and some decomposition occurred. The hydrolysis step went smoothly, however, and a good yield of methyl 3,4,6-tri-*O*-acetyl-2-(*N*-(*tert*-butoxycarbonyl)amino)-2-deoxy-α-D-glucopyranoside (**13**) resulted.



12



13

The convenient conversion of amides into useful *N*-Boc derivatives under mild conditions has been demonstrated and will facilitate the synthesis of amines and amino acids. Amide-forming preparations such as the Beckmann rearrangement,[18] the Ritter reaction,[19] and others may become more useful entries into syntheses. Their mild cleavage should allow amides themselves more use as versatile protecting groups. Work is currently underway to extend these methods to the preparation of benzylcarbamates from amides.[20]

Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra were recorded on a General Electric QE-300 spectrometer at 300.15 and 75.48 MHz, respectively, in $CDCl_3$, and the shifts are reported in ppm downfield from TMS. High-resolution mass spectra were obtained using a JEOL JMS-SX102A spectrometer. Chiral capillary GC was performed on a Chrompack Chirasil-L-Val column (25 m). For TLC, system A was (petroleum ether:ethyl acetate), system B was ($CHCl_3$:acetone). DMAP was crystallized from toluene and THF was distilled from sodium/benzophenone before use. Other unspecified reagents were from commercial sources and used as obtained.

***N*-(*tert*-Butoxycarbonyl)-L-valine Methyl Ester (3). General Procedure.** *N*-Acetyl-L-valine methyl ester (0.2 g, 1.15 mmol) and *N*,*N*-dimethyl-4-aminopyridine (28 mg, 0.23 mmol) was dissolved in THF (4 mL). Di-*tert*-butyl dicarbonate (0.53 mL, 2.30 mmol) was added, and the mixture was heated to reflux for 4 h. After the solution was cooled to room temperature, MeOH (4 mL) and hydrazine (0.14 mL, 4.6 mmol) were added and the mixture was stirred at rt for 4 h. The reaction mixture was poured into CH_2Cl_2, washed with 1 N HCl, $CuSO_4$, and $NaHCO_3$, dried ($MgSO_4$), and evaporated. Chromatography on silica gave 0.24 g of pure **3** (92%): R_f, 0.33 (9:1 system A); t_R 2.89 min (120 °C, 20 psi, *N*-Ac >99% ee, *N*-Boc >99% ee)[21]; $[\alpha]^{22}_D = +12.9°$ ($_c$ = 2.43, $CHCl_3$) ^{1}H NMR δ 0.79 (d, 3H, J = 6.9Hz), 0.85 (d, 3H, J = 6.8Hz), 1.34 (s, 9H), 2.00−2.10 (m, 1H), 4.12 (s, 3H), 4.10−4.20 (m, 3H), 5.02 (br d, 1H, J = 8.5Hz); ^{13}C NMR δ 17.4, 18.8, 28.1, 31.1, 51.8, 58.3, 79.5, 155.5, 172.7; HRMS calcd for $C_{11}H_{22}NO_4$ (M + H^+) 232.1549, found 232.1543.

(*R*)-Methyl 2-((*tert*-butoxycarbonyl)amino)pentanoate (4). The general procedure gave 0.22 g (80%): R_f, 0.30 (9:1 system A); t_R 3.70 min (120 °C, 20 psi, *N*-Ac >99% ee, *N*-Boc >99% ee); $[\alpha]^{22}_D = -5.72°$ (c = 2.08, $CHCl_3$); ^{1}H NMR δ 0.87 (t, 3H, J = 7.3 Hz), 1.30−1.80 (m, 4H), 1.38 (s, 9H), 3.68 (s, 3H), 4.20−4.30 (m, 1H), 4.98 (br d, 1H, J = 8.3Hz); ^{13}C NMR δ 13.6, 18.6, 28.2, 34.8, 52.1, 53.2, 79.7, 155.3, 173.5; HRMS calcd for $C_{11}H_{22}NO_4$ (M + H^+) 232.1549, found 232.1546.

***N*-(*tert*-Butoxycarbonyl)-D-leucine Methyl Ester (5).** The general procedure gave 0.24 g (91%): R_f 0.39 (9:1 system A); t_R 4.58 min (120 °C, 20 psi, *N*-Ac 98.9% ee, *N*-Boc 99.0% ee); $[\alpha]^{22}_D = +4.21°$ (c = 2.40, $CHCl_3$); ^{1}H NMR δ 1.80−1.90 (m, 6H), 1.30−1.80 (m, 3H), 1.36 (s, 9H), 3.65 (s, 3H), 4.15−4.30 (m, 1H), 4.93 (br d, 1H, J = 8.6Hz); ^{13}C NMR δ 21.7, 22.7, 24.6, 28.2, 41.6, 51.8, 52.0, 79.6, 155.3, 173.9; HRMS calcd for $C_{12}H_{23}NO_4$ (M + H^+) 246.1705, found 246.1703.

(*R*)-Methyl 2-((*tert*-butoxycarbonyl)amino)-3-ethylpentanoate (6). The general procedure gave 54 mg (93%): R_f 0.33 (9:1 system A); t_R 2.41 min (145 °C, 20 psi, *N*-Ac 96.9% ee, *N*-Boc 96.9% ee); $[\alpha]^{22}_D$=-14.1° (c = 1.08, $CHCl_3$); ^{1}H NMR δ 0.60−1.00 (m, 6H), 1.20−1.70 (m, 5H), 1.40 (s, 9H), 3.68 (s, 3H), 4.30−4.40 (m, 1H), 4.91 (br d, 1H, J = 8.3Hz); ^{13}C NMR δ 21.7, 22.7, 24.6, 28.2, 41.6, 51.8, 52.0, 79.6, 155.3, 173.9; HRMS calcd for $C_{13}H_{26}NO_4$ (M + H^+): 260.1862, found 260.1855.

(*S*)-Methyl 2-((*tert*-Butoxycarbonyl)amino)-2-cyclopentylethanoate ethanoate (7). The general procedure gave 68 mg (93%): R_f 0.43 (9:1 system A); t_R 4.12 min (120 °C, 20 psi, *N*-Ac 95.9% ee, *N*-Boc 95.9% ee); $[\alpha]^{22}_D = +7.0°$ (c = 1.36, $CHCl_3$); ^{1}H NMR δ 1.20−1.70 (m, 8H), 1.39 (s, 9H), 2.10−2.20 (m, 1H), 3.68 (s, 3H), 4.20−4.30 (m, 1H), 4.90−5.00 (br, 1H); ^{13}C NMR δ 24.1, 25.2, 28.2, 28.8, 42.6, 52.0, 56.4, 79.7, 155.5, 173.3; HRMS calcd for $C_{13}H_{24}NO_4$ (M + H^+) 258.1705, found 258.1703.

***N*-(*tert*-Butoxycarbonyl)-D-leucine Ethyl Ester (8).** The general procedure gave 0.24 g (86%): R_f 0.55 (9:1 system A); t_R 3.52 min (120 °C, 20 psi, *N*-Ac 97.4% ee, *N*-Boc 97.8% ee); $[\alpha]^{22}_D = -11.6°$ (c = 2.43, $CHCl_3$); ^{1}H NMR δ 0.79 (d, 3H, J = 6.9Hz), 0.86 (d, 3H, J = 6.9Hz), 1.84 (t, 3H, J = 7.1Hz), 1.35 (s, 9H), 2.00−2.10 (m, 1H), 4.10−4.20 (m, 3H), 5.01 (br d, 1H, J = 8.0 Hz); ^{13}C NMR δ 14.1, 17.4, 18.8, 28.1, 31.2, 58.3, 60.9, 79.4, 155.5, 172.2; HRMS calcd for $C_{12}H_{24}NO_4$ (M + H^+): 246.1705, found 246.1712.

(2*S*,4*E*)-Methyl 2-((*tert*-Butoxycarbonyl)amino)-6-*O*-(*tert*-butyldimethylsilyl)hex-4-eneoate (9). (*S*)-Methyl 2-acetamido-6-*O*-(*tert*-butyldimethylsilyl)hex-4-eneoate (0.20 g, 0.63 mmol) and *N*,*N*-dimethyl-4-aminopyridine (14 mg, 0.13 mmol) were dissolved in THF (1.6 mL). Di-*tert*-butyl dicarbonate (0.29 mL, 1.30 mmol) was added, and the mixture was stirred at rt for 8 h. MeOH (4 mL) was added, and the mixture was treated with hydrazine (79 μL, 2.5 mmol) for 8 h. The reaction mixture was poured into CH_2Cl_2, washed with 1 N HCl, $CuSO_4$, and $NaHCO_3$, dried ($MgSO_4$), and evaporated. Chromatography on silica gave 0.22g of pure **9** (93%): R_f 0.31 (9:1 system A); t_R 3.61 min (180 °C, 30 psi, *N*-Ac 98.8% ee, *N*-Boc 99.4% ee); $[\alpha]^{22}_D = +17.4°$ (c = 2.21, $CHCl_3$); ^{1}H NMR δ −0.02 (s, 6H), 0.82 (s, 9H), 1.35 (s, 9H), 2.30−2.50 (m, 2H), 3.64 (s, 3H), 4.04 (d, 2H, J = 4.4Hz), 4.20−4.30 (m, 1H), 5.00 (br d, 1H, J = 8.0Hz), 5.40−5.60 (m, 2H); ^{13}C NMR δ 18.2, 25.8, 28.2, 32.1, 32.3, 35.0, 52.0, 52.9, 63.2, 79.6, 123.9, 133.8, 155.0, 172.4; HRMS calcd for $C_{18}H_{36}NO_5$ (M + H^+): 374.2363, found 374.2355.

***N*-(*tert*-Butoxycarbonyl)-L-leucine Methyl Ester (*ent*-5).** *N*-Acetamido-L-valine benzyl ester (0.20 g, 0.8 mmol) and *N*,*N*-dimethyl-4-aminopyridine (18 mg, 0.16 mmol) was dissolved in THF (2 mL). Di-*tert*-butyl dicarbonate (0.37 mL, 1.60 mmol) was added, and the mixture was heated at reflux for 6 h. The mixture was cooled to rt, MeOH (2 mL) and hydrazine (0.1 mL, 3.2 mmol) were added, and the mixture was stirred for 3 h. The reaction mixture was poured into CH_2Cl_2, washed with 1 N HCl, $CuSO_4$, and $NaHCO_3$, dried ($MgSO_4$), and evaporated. Chromatography on silica gave 0.17 g of pure ***ent*-5** (88%): t_R 2.53 min (140 °C, 20 psi, *N*-Ac >99% ee, *N*-Boc 99.3% ee); $[\alpha]^{22}_D = -4.21°$ (c = 1.56, $CHCl_3$). Other characterization data were identical to those of **5**.

***N*-(*tert*-Butoxycarbonyl)-L-methionine Methyl Ester (10).** *N*-Benzamido-L-methionine methyl ester (0.31 g, 1.15 mmol) and *N*,*N*-dimethyl-4-aminopyridine (28 mg, 0.23 mmol) was dissolved in THF (3 mL). Di-*tert*-butyl dicarbonate (0.53 mL, 2.30 mmol) was added, and the mixture was stirred at rt for 7 h. MeOH (3 mL) was added, and the mixture was cooled to 0 °C and treated

(18) For a review, see: Gawley, R. E. *Org. React.* **1988**, *35*, 1.

(19) For a review, see: Krimen, L. I.; Cota, D. J. *Org. React.* **1969**, *17*, 213.

(20) In several trials, the commercially available dibenzyl dicarbonate (Cbz_2O) gave only dibenzyl carbonate, the product of catalytic decomposition of the reagent by benzyl oxide released by the first acylation event. Trapping agents did not improve the reaction. In an effort to use a bulkier leaving group, the mixed dicarbonate benzyl *tert*-butyl dicarbonate (**14**) was prepared from sodium *tert*-butoxide, carbon dioxide, and benzyl chloroformate. Acylation of *O*-acetyl-*N*-benzoyl-L-serine benzyl ester gave a 4:1 mixture of the Cbz imide to the Boc imide. Please see Supporting Information.

(21) All GC samples were of crude material before purification by column chromatography.

with hydrazine (0.15 mL, 4.6 mmol) for 2 h. The reaction mixture was poured into CH_2Cl_2, washed with 1 N HCl, $CuSO_4$, and $NaHCO_3$, dried ($MgSO_4$), and evaporated. Chromatography on silica gave 0.28 g of pure **10** (94%): R_f 0.52 (4:1 system A); t_R 6.59 min (145 °C, 20 psi, *N*-Bz >99% ee, *N*-Boc 98.7% ee); $[\alpha]^{22}_D = +24.6°$ ($c = 2.84$, $CHCl_3$); ^{1}H NMR δ 1.31 (s, 9H), 1.80−1.90 (m, 2H), 1.96 (s, 3H), 2.41 (t, 2H, $J = 7.5$Hz), 3.62 (s, 3H), 4.30−4.40 (m, 1H), 5.25 (br d, 1H, $J = 8.1$Hz); ^{13}C NMR δ 15.1, 28.0, 29.7, 31.7, 52.1, 52.4, 79.6, 155.1, 172.6; HRMS calcd for $C_{11}H_{23}NO_4S$ ($M + H^+$) 264.1272, found 264.1273.

***O*-Acetyl-*N*-(*tert*-butoxycarbonyl)-L-Serine Benzyl Ester (11). From the Corresponding Acetamide.** The procedure for **10** was followed except the acylation reaction mixture was refluxed for 3 h, and the hydrolysis step required 3 h to give 0.31 g of **11** (81%): t_R 6.73 min (180 °C, 30 psi, *N*-Ac 98.4% ee, *N*-Boc >99% ee). **From the Corresponding Benzamide.** The procedure for **10** was followed except the acylation reaction required 2 h, and the hydrolysis step required 2 h to give 0.15 g of **11** (72%): R_f 0.46 (4:1 system A); t_R 6.71 min (180 °C, 30 psi, *N*-Bz >99% ee, *N*-Boc >99% ee); $[\alpha]^{22}_D = +1.56°$ ($c = 2.11$, $CHCl_3$); ^{1}H NMR δ 1.41 (s, 9H), 1.91 (s, 3H), 4.20−4.30 (m, 1H), 4.30−4.50 (m, 1H), 4.50−4.60 (m, 1H), 5.09 (d, 1H, $J = 12.2$Hz), 5.19 (d, 1H, $J = 12.2$Hz), 5.33 (br d, 1H, $J = 8.2$Hz); ^{13}C NMR δ 20.4, 28.2, 52.8, 64.3, 67.4, 80.2, 128.3, 128.4, 128.5, 135.0, 155.0, 169.6, 170.3; HRMS calcd for $C_{17}H_{24}NO_6$ ($M + H^+$): 338.1603, found 338.1593.

3,4,6-Tri-*O*-acetyl-2-(*tert*-butoxycarbamido)-2-deoxy-D-glucopyranose (12). The procedure for **10** was followed except the acylation reaction was refluxed for 2.5 h, and the hydrolysis step required 2 h to give 0.20 g of **12** (80%): R_f 0.43 (4:1 system B); $[\alpha]^{22}_D = +56.1°$ ($c = 1.29$, $CHCl_3$); ^{1}H NMR δ 1.34 (s, 9H), 1.96, 1.97, 2.02 (3s, 9H), 3.88 (dd, 1H, $J = 10.3$Hz), 4.00−4.30 (m, 3H), 4.62 (d, 1H, $J = 3.5$Hz), 4.93 (d, 1H, $J = 10.0$Hz), 5.03 (dd, 1H, $J = 9.5$Hz), 5.10−5.30 (m, 2H); ^{13}C NMR δ 20.6, 28.1, 53.2, 62.0, 67.2, 68.3, 71.4, 79.9, 91.8, 155.2, 169.4, 170.9; HRMS calcd for $C_{17}H_{28}NO_{10}$ ($M + H^+$): 406.1713, found 406.1717.

Methyl 3,4,6-Tri-*O*-acetyl-2-((*tert*-butoxycarbonyl)amino)-2-deoxy-α-D-glucopyranoside (13). The procedure for **10** was followed except the acylation reaction required 6 h reflux followed by stirring 14 h with an additional equivalent Boc_2O, and the hydrolysis step required 2 h to give 0.20 g of **13** (70%): R_f 0.77 (4:1 system B); $[\alpha]^{22}_D = +83.0°$ ($c = 1.05$, $CHCl_3$); ^{1}H NMR δ 1.35 (s, 9H), 1.95, 1.96, 2.03 (3s, 9H), 3.32 (s, 3H), 3.80−4.30 (m, 4H), 4.67 (d, 1H, $J = 3.6$Hz), 4.71 (d, 1H, $J = 10.2$Hz), 5.01 (dd, 1H, $J = 9.8$Hz), 5.12 (dd, 1H, $J = 10.2$Hz); ^{13}C NMR δ 20.6, 28.1, 52.9, 55.3, 62.0, 67.5, 68.2, 71.6, 79.8, 98.6, 155.0, 169.3, 170.6, 170.8; HRMS calcd for $C_{18}H_{30}NO_{10}$ ($M + H^+$): 420.1870, found 420.1854.

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Supporting Information Available: NMR spectra for compounds **3**, **4**, **7**, **8**, **9**, and **11** and experimental details for the preparation of benzyl *tert*-butyl dicarbonate (**14**) (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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