1,3-Dithian-2-ylmethyl Esters as Two-Step Carboxy-Protecting Groups in the Synthesis of N-Glycopeptides[1]

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The synthesis of totally protected *N*-acetylglucosaminylasparagine glycopeptides using the 1,3-dithian-2-ylmethyl (Dim) ester for selective C-terminal deprotection is described. Dim esters of amino acids can be conveniently synthesized by aluminum isopropoxide catalyzed transesterification of amino acid methyl esters with 1,3-dithian-2-ylmethanol or esterification of Boc amino acids with this alcohol followed by selective cleavage of the Boc group under acidic conditions. For the construction of N-glycopeptides Boc-asparatic acid α-Dim ester was synthesized and condensed with 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosylamine. The Dim group was cleaved under very mild conditions (pH 8) after oxidation of the sulfur in the dithiane ring. During this reaction the Boc group, the *O*-acetates, and the glycoside bond remained intact. The selectively deblocked glycosylated asparagine thus obtained was condensed with amino acid Dim esters to yield totally protected glycodipeptides in high yields.

Introduction

Glycopeptides are characteristic partial structures of the glycoproteins that play key roles in recognition on cell membranes, intercellular communication, cell growth, and tumor development.[2] For the chemical synthesis of glycopeptides, numerous functional groups in the carbohydrate parts and in the amino acids have to be protected and deprotected selectively. In general, the glycosidic bonds in these molecules are acid- and, in the case of certain *O*-glycopeptides, also base-labile.[3] Therefore, protecting functions that can be selectively removed under almost neutral conditions are required. Most of the protecting techniques common in peptide synthesis cannot be used to achieve this goal. To meet these high demands, we developed several blocking groups and applied them in glycopeptide synthesis.[4] For instance, the construction of *N*-glycosylasparagine derivatives could be achieved by the noble metal catalyzed cleavage of the allyl esters.[5-7]

Recently we described the use of amino acid 1,3-dithian-2-ylmethyl (Dim) esters **4** in peptide synthesis.[8] They proved to be orthogonally stable to the Z and the Boc groups but could be cleaved in a two-step process at pH 8. Here we report that the Dim esters are also valuable protecting groups for the selective synthesis of N-glycopeptides.

Results and Discussion

Synthesis of Amino Acid Dim Esters. Attempts to build up amino acid Dim esters by azeotropic esterification were unsuccessful. Due to the low stability of 1,3-dithianylmethanol **2**, thionyl chloride also could not be used to activate the carboxy function. However, we found a viable alternative in the transesterification of the easily accessible amino acid methyl esters **1** with **2** in the presence of aluminum isopropoxide[10] (Scheme I). The results of these syntheses and the physical properties of the products are summarized in Table I.

Alternatively, the hydrochlorides **4** may be obtained after esterification of Boc-amino acids and subsequent cleavage of the Boc group with hydrogen chloride in ether. This method was especially advantageous for the construction of serine Dim ester (**7**). The direct esterification of Boc-serine with the alcohol **2** mainly resulted in the formation of the β-lactone and the corresponding α,β-unsaturated amino acid. However, these side reactions were prevented by the use of Boc-serine *O*-*tert*-butyl ether[11] (**5**). The totally protected serine derivative **6** was obtained in acceptable yield. The N-terminal protecting group and the *O*-*tert*-butyl moiety (Scheme II) were then cleaved simultaneously with trifluoroacetic acid.

Formation of the N-Glycosidic Bond. To obtain N-glycosidically linked asparagine derivatives, N-protected aspartic acid α-monoesters are required. Their selectively deblocked β-carboxy function can then be condensed with a glycosylamine. As already demonstrated in the synthesis of the analogous allyl esters,[5] we used *N*-(*tert*-butyloxycarbonyl)aspartic acid β-phenacyl ester (**8**) to synthesize the Boc-aspartic acid Dim ester (**10**). The free α-carboxyl group of **8** could be activated as the mixed anhydride with 2,4,6-trichlorobenzoyl chloride[12] and, in the presence of DMAP, gave the desired totally protected aspartic acid derivative **9** in good yield. The application of carbodiimide to effect the esterification did not seem to be the method of choice because it is known that strong racemization occurs if aspartic and glutamic acid derivatives are activated with these reagents.[13] We did not observe any racemization in the reaction described above. After selective removal of the β-phenacyl ester with sodium thiophenolate, the desired α-ester **10** was formed (Scheme III). The β-carboxy group thus liberated was then condensed with the glycosylamine **11**[14] in the presence of ethyl 2-ethoxy-1,2-dihydroquinoline-1-carboxylate (EEDQ)[15] to

(1) Supported by the Fonds der Chemischen Industrie.
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Table I. Amino Acid Dim Ester Hydrochlorides 4 by Transesterification of Amino Acid Methyl Esters Using Aluminum Isopropoxide (3) as Catalyst

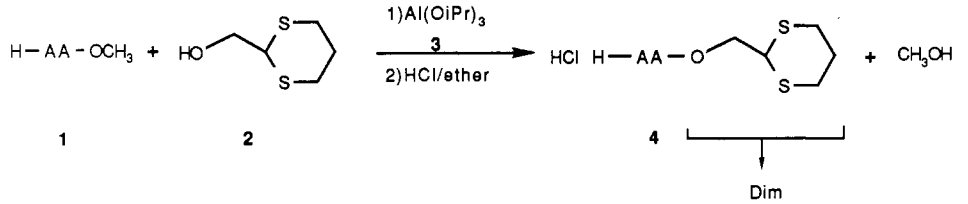
entry	amino acid	yield (%)	mp (°C)	$[\alpha]^{22}_D$ (deg)	elemental anal. mol form.	C	H	N
4a	glycine[a]	18	134–36		$C_7H_{14}NO_2S_2Cl$	calcd 34.40	5.78	5.74
					243.8	found 33.70	5.61	5.80
4b	alanine	30	138–39	−5.1	$C_8H_{16}NO_2S_2Cl$	calcd 37.27	6.26	5.43
				(c 1, CH_3OH)	257.8	found 37.55	6.16	5.56
4c	phenylalanine	55	164–65	6.9	$C_{14}H_{20}NO_2S_2Cl$	calcd 50.36	6.04	4.19
				(c 1, C_2H_5OH)	333.9	found 50.34	6.07	4.58
4d	valine	78	180	3.3	$C_{10}H_{20}NO_2S_2Cl$	calcd 42.02	7.05	4.90
				(c 1, CH_3OH)	285.8	found 41.73	7.24	4.86
4e	leucine	68	176–77	1.1	$C_{11}H_{22}NO_2S_2Cl$	calcd 44.06	7.39	4.67
				(c 1, C_2H_5OH)	295.9	found 44.53	7.29	4.72
4f	isoleucine	75	134–35	7.5	$C_{11}H_{22}NO_2S_2Cl$	calcd 44.06	7.39	4.67
				(c 1, CH_3OH)	295.9	found 43.96	7.68	4.73

[a] Glycine ethyl ester.

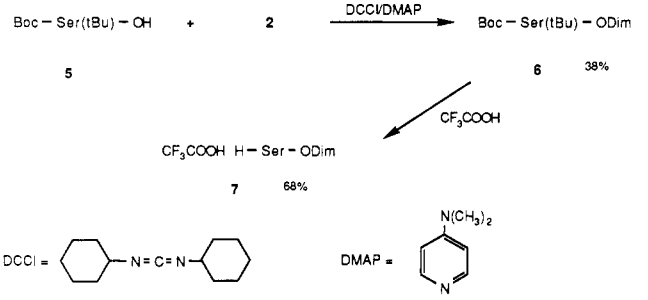
Table II. Synthesis and Properties of Boc-glycodipeptide Dim Esters 15

entry	amino acid	yield (%)	mp (°C)	$[\alpha]^{22}_D$ (deg) (c 1, $CHCl_3$)	elemental anal. mol form.	C	H	N
15a	phenylalanine	86	191–94 dec	2.7	$C_{37}H_{52}N_4O_{14}S_2$	calcd 52.84	6.23	6.66
					840.9	found 53.10	6.02	6.98
15b	isoleucine	94	219–23 dec	−7.1	$C_{34}H_{54}N_4O_{14}S_2$	calcd 50.61	6.74	6.94
					806.9	found 50.37	6.55	7.07
15c	serine	74	194–98 dec	22.8	$C_{31}H_{48}N_4O_{15}S_2$	calcd 47.68	6.20	7.18
					780.8	found 47.33	5.87	7.21

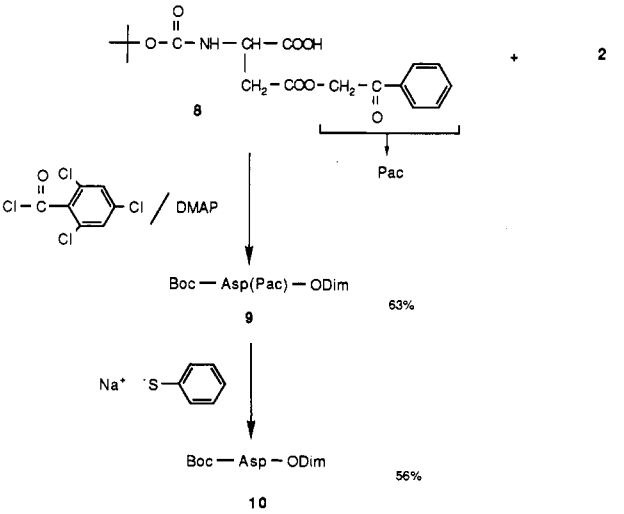
Scheme I. Synthesis of Amino Acid 1,3-Dithian-2-ylmethyl (Dim) Esters 4 by Transesterification



Scheme II. Synthesis of Serine 1,3-Dithianylmethyl Ester (7)



Scheme III. Synthesis of *N*-Boc-aspartic Acid α-Dim Ester (10)



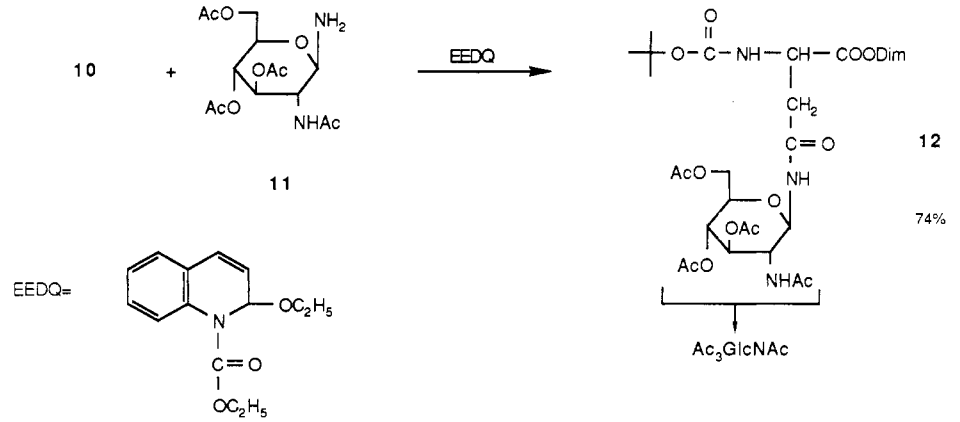
give the asparagine N-glycoside **12** (Scheme IV).

Selective Cleavage of the Dim Esters. Synthesis of Glycopeptides. For the liberation of the carboxyl group, the Dim ester **12** was first oxidized to the disulfone **13** by using H_2O_2 and ammonium molybdate. The oxidized glycoside is extremely labile toward bases. Already at pH 8 the C-terminal protecting group was quantitatively removed in a E1cB reaction and the glycosyl amino acid **14** could be isolated in good yield (Scheme V). During this reaction the acetyl groups in the carbohydrate part, the glycosidic linkage, and the Boc group remained unaffected. The carboxy-deblocked product thus obtained allowed for the selective C-terminal elongation of the peptide chain. Amino acid Dim esters **4** were condensed with it to yield the totally protected glycodipeptides **15** in excellent yields (Scheme VI). The results of these syntheses are summarized in Table II. The compounds **15** bear the same combination of protecting groups as are present in **12**. They are therefore suitable for further extensions of the peptide chain. The Dim ester has thus proven to be a very valuable protecting group for the synthesis of N-glycopeptides. It can be removed selectively after oxidation under very mild conditions. Under the mild conditions applied, all the other blocking groups and the glycosidic bond are completely conserved.

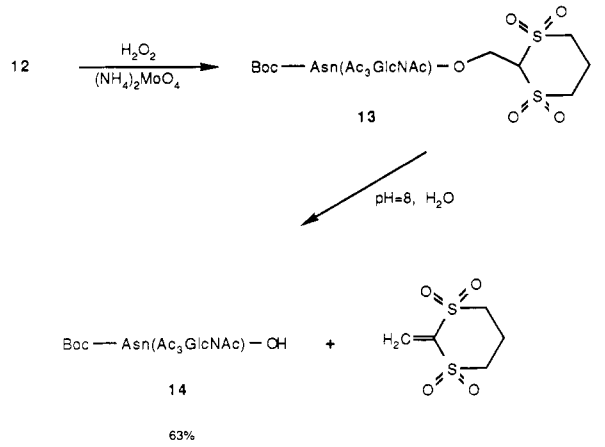
Experimental Section

Materials and Methods. Optical rotations were measured with a Perkin-Elmer 241 polarimeter, IR spectra with a Beckman

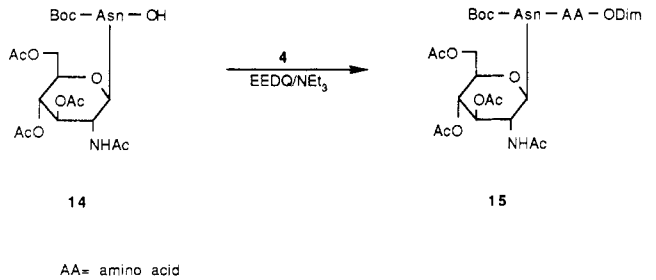
Scheme IV. Formation of the N-Glycosidic Bond



Scheme V. Selective Cleavage of the Dim Ester under Weakly Basic Conditions



Scheme VI. Synthesis of Glycodipeptides by Selective C-Terminal Chain Extension



Acculab-2 spectrometer; 60-MHz ^{1}H NMR spectra were obtained on a JEOL JMN 60-MHz and 90-MHz ^{1}H and 22.63-MHz ^{13}C NMR spectra on a Bruker WH-90 spectrometer. All melting points are uncorrected. Analytical TLC plates (silica gel 60-F_{254}) were purchased from Merck. Visualization was achieved by spraying with a 0.3% solution of ninhydrin in methanol/acetic acid (97:3, v/v) or with a 0.1% solution of 1,3-dihydroxynaphthalene in ethanol/2 *n* H_2SO_4 (1:1, v/v) and heating. Only L-amino acids were used.

Amino Acid 1,3-Dithian-2-ylmethyl Ester Hydrochlorides 4. A mixture of 2-(hydroxymethyl)-1,3-dithiane (**2**) (2.25 g, 15 mmol), aluminum isopropylate (**3**) (60 mg, 0.56 mmol), and 10 mmol of the amino acid methyl ester **1** was placed in a 100-mL flask equipped with a reflux condenser. The head of the condenser was connected to a water aspirator and the reaction mixture was vigorously stirred for 4 h at 70–80 °C under reduced pressure. The volatiles were distilled off with an oil pump. After cooling to room temperature the remaining residue was taken up in ether and after filtration the hydrochlorides were precipitated by the addition of a solution of hydrochloric acid in ether. Recrystallization from methylene chloride/ether or acetone/ether delivered pure products. Yields, physical data, and elemental analyses are given in Table I.

The IR spectra show characteristic absorption bands at $\bar{\nu}$ 1740–1750 cm^{-1} (C=O, ester) and 900–910 cm^{-1} (dithiane[16]). In the 60-MHz ^{1}H NMR spectra, typical signals for the amino acids are found. In addition the following signals, characteristic for the dithiane,[9] appear: δ 4.6–3.9 (m, 3 H, OCH_2 and CH dithiane), 3.2–2.6 (m, 4 H, SCH_2 dithiane), 2.3–1.8 (m, 2 H, $CH_2CH_2CH_2$ dithiane).

Serine 1,3-Dithian-2-ylmethyl Ester Trifluoroacetate (7). A solution of 1.4 g (5.4 mmol) of Boc-Ser(*t*Bu)-OH **5**, 1.1 g (5.5 mmol) of N,N′-dicyclohexylcarbodiimide, 60 mg (0.5 mmol) of 4-pyrrolidinopyridine, and 0.8 g (9.5 mmol) of 1,3-dithianylmethanol (**2**) in 25 mL of methylene chloride was stirred at ambient temperature for 48 h. After filtration the filtrate was washed three times with 25 mL each of 2 N HCl, 1 N $NaHCO_3$, and water. The organic layer was dried over $MgSO_4$ and concentrated in vacuo and the remaining residue was passed through a layer of silica gel. After elution with ethyl acetate/petroleum ether (1:1, v/v) and evaporation of the solvent the ester **6** (0.8 g, 38%) was identified by its 60-MHz NMR spectrum (^{1}H NMR ($CDCl_3$): δ 5.65 (d, J = 8 Hz, 1 H, NH), 3.0–2.7 (m, 4 H, $CH_2CH_2CH_2$), 2.2–1.9 (m, 2 H, $CH_2CH_2CH_2$), 1.4 (s, 9 H, $(CH_3)_3C$), 1.1 (s, 9 H, $(CH_3)_3C$). It was directly used for the preparation of **7**.

The totally protected serine derivative **6** (0.8 g, 2 mmol) was dissolved in 1.5 g of trifluoroacetic acid and heated to 50–60 °C for 2 h. After evaporation to dryness the residue was dissolved in methylene chloride and reprecipitated with petroleum ether. The supernatant was decanted. From the residue on trituration with ether white crystals were obtained: yield 0.45 g (68%); mp 131–133 °C; $[\alpha]^{22}_D$ −5.1° (*c* 1, CH_2Cl_2); IR (KBr): $\bar{\nu}$ 1740 cm^{-1} (C=O, ester); 60-MHz ^{1}H NMR ($CDCl_3$) δ 4.7–4.4 (d, J = 7 Hz, 2 H, OCH_2), 4.3–3.9 (m, 4 H, OCH_2CH, α-CH and β-CH_2Ser), 3.0–2.6 (m, 4 H, $CH_2CH_2CH_2$), 2.2–1.8 (m, 2 H, $CH_2CH_2CH_2$). Anal. Calcd for $C_{10}H_{16}NO_5S_2F_3$: C, 34.18; H, 4.59; N, 3.99. Found: C, 33.90; H, 4.57; N, 3.92.

***N*-(*tert*-Butyloxycarbonyl)aspartic Acid β-Phenacyl α-(1,3-Dithian-2-ylmethyl) Diester (9).** To a solution of 12.1 g (32.8 mmol) of the aspartic acid β-phenacyl ester (**8**) and 3.3 g (32.8 mmol) of triethylamine in 50 mL of methylene chloride at 0 °C was added 8 g (32.8 mmol) of 2,4,6-trichlorobenzoyl chloride slowly. After 2 h a solution of 7.9 g (54.6 mmol) of the alcohol **2** and 8 g (65.6 mmol) of 4-(dimethylamino)pyridine in 20 mL of methylene chloride was added and the reaction mixture was stirred for 24 h at room temperature. It was extracted three times with 50 mL each of 2 N HCl, 1 N $NaHCO_3$, and water, dried over $MgSO_4$, and concentrated in vacuo. The remaining residue was chromatographed (silica gel, petroleum ether/ethyl acetate (3:1, v/v)) to yield an oil (10 g, 63%) which slowly crystallized on standing: mp 58–64 °C; $[\alpha]^{22}_D$ −16.1° (*c* 1, CH_3OH); IR (KBr) $\bar{\nu}$ 1760 and 1750 (C=O, ester), 1710 (urethane); 60-MHz ^{1}H NMR ($CDCl_3$) δ 8.0–7.4 (m, 5 H, phenyl), 5.9 (d, J = 9 Hz, 1 H, NH), 5.4 (s, 2 H, OCH_2CO), 3.3–3.0 (m, 2 H, β-CH_2Asp), 3.0–2.6 (m, 4 H, $CH_2CH_2CH_2$), 2.2–1.8 (m, 2 H, $CH_2CH_2CH_2$), 1.45 (s, 9 H,

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$(CH_3)_3C$). Anal. Calcd for $C_{22}H_{29}NO_7S_2$: C, 54.65; H, 6.04; N, 2.90. Found: C, 54.33; H, 6.23; N, 3.11.

***N*-(*tert*-Butyloxycarbonyl)aspartic Acid α-(1,3-Dithian-2-ylmethyl) Ester (10).** A mixture of the β-phenacyl ester **9** (9 g, 18.6 mmol), sodium thiophenolate (5 g, 37.3 mmol), and 100 mL of dimethylformamide was stirred for 18 h at room temperature. The solvent was removed under reduced pressure, the residue taken up in 150 mL of methylene chloride, and the solution was extracted three times with 50 mL of 2 N $NaHCO_3$ solution. After adjusting the pH of the aqueous layer to 1, it was extracted three times with ether. The combined ethereal solutions were washed five times with brine, dried over $MgSO_4$, and concentrated in vacuo. Recrystallization from methylene chloride/petroleum ether yielded 3.5 g (56%) of α ester **10**: mp 97 °C; $[\alpha]^{22}_D$ 19.9° (*c* 1, cH_3OH); IR (KBr) $\bar{\nu}$ 1750 (C=O, ester), 1700 (COOH); 60-MHz ^1H NMR ($CDCl_3$) δ 10.8 (s, 1 H, NH), 4.7–4.3 (m, 3 H, OCH_2CH), 4.15 (m, 1 H, α-CH), 3.0–2.6 (m, 4 H, $CH_2CH_2CH_2$), 2.2–1.8 (m, 2 H, $CH_2CH_2CH_2$), 1.45 (s, 9 H, $(CH_3)_3C$). Anal. Calcd for $C_{14}H_{23}NO_6S_2$: C, 46.01; H, 6.34; N, 3.83. Found: C, 46.05; H, 6.74; N, 4.08.

***N*⁴-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-*N*²-(*tert*-butyloxycarbonyl)asparagine 1,3-Dithian-2-ylmethyl Ester (12).** Aspartic acid α ester **10** (0.5 g, 1.36 mmol) and 0.56 g (1.6 mmol) of glucosylamine **11** were dissolved in 10 mL of methylene chloride. EEDQ (0.47 g, 1.9 mmol) was added and the mixture was stirred for 18 h at ambient temperature. After diluting with methylene chloride, it was extracted three times with 10 mL of HCl, 10 mL of 1 N $NaHCO_3$, and 10 mL of H_2O, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was recrystallized from methylene chloride/petroleum ether: yield 0.7 g (74%); mp 146–148 °C; $[\alpha]^{22}_D$ + 6.6° (*c* 1, CH_3OH); IR (KBr) $\bar{\nu}$ 1750 (C=O, ester), 1660; 90-MHz ^1H NMR ($CDCl_3$) δ 7.35 (d, *J* = 8.5 Hz, 1 H, NH), 6.6 (d, *J* = 8.8 Hz, 1 H, NH), 5.7 (d, *J* = 8.7 Hz, 1 H, NH, urethane), 3.0–2.7 (m, 6 H, $CH_2CH_2CH_2$ and β-CH_2Asn), 2.09, 2.06 and 2.04 (3 s, 9 H, 3 CH_3COO), 1.98 (s, 3 H, CH_3CONH), 1.43 (s, 9 H, $(CH_3)_3C$); 22.63-MHz ^{13}C NMR (DMSO-d_6) δ 171.3–169.3 (C=O), 155.1 (C=O, urethane), 78.5 ($(CH_3)_3C$), 78.1 (C1); 73.3 (C3), 72.3 (C5), 68.5 (C4), 65.0 (OCH_2CH), 61.8 (C6), 50.0 (α-CHAsn), 41.8 (OCH_2CH), 28.5 ($(CH_3)_3C$), 22.5 (CH_3CONH), 20.4 and 20.3 (CH_3COO). Anal. Calcd for $C_{28}H_{43}N_3O_{13}S_2$: C, 48.47; H, 6.25; N, 6.06. Found: C, 48.58; H, 6.28; N, 6.24.

***N*⁴-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-*N*²-(*tert*-butyloxycarbonyl)asparagine (14).** To a mixture of 1 g (1.44 mmol) of Dim ester **12** were added 15 mL of acetone and 3 mL of a 0.05 M solution of ammonium molybdate, and 5.8 mL of a 33% aqueous H_2O_2 solution at 0 °C. After stirring to room temperature for 4 h the acetone was distilled off under reduced pressure (caution: the heating bath temperature should not exceed 20 °C). The pH was adjusted to 1 and the aqueous solution was extracted three times with 20 mL of methylene chloride. The combined organic layers were washed twice with brine and once with water, dried over $MgSO_4$, and concentrated in vacuo: yield 0.5 g (63%); mp 194 °C (lit.[5] mp 194–195 °C); $[\alpha]^{22}_D$ +11.5° (*c* 1, CH_3OH) (lit.[5] 11.7° (*c* 1, CH_3OH).

N-Glycodipeptide 1,3-Dithian-2-ylmethyl Esters 15. General Procedure. The acid **14** (0.6 g (1 mmol)), 0.1 g (1 mmol) of triethylamine, and 1 mmol of dithianyl ester **4** or **7** were dissolved in 10 mL of methylene chloride and 0.4 g (1.6 mmol) of EEDQ was added. After being stirred for 72 h the solution was extracted three times with 10 mL each of 2 N HCl, 1 N $NaHCO_3$, and water, dried over $MgSO_4$, and evaporated to dryness (if the product crystallizes from the reaction mixture it is isolated by filtration and washed with methylene chloride and the filtrates are treated as described above). The remaining residue is recrystallized from methylene chloride/petroleum ether. Yields, physical data, and elemental analyses are given in Table II. By this procedure the following glycopeptides were obtained.

***N*⁴-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-*N*²-(*tert*-butyloxycarbonyl)asparaginylphenylalanine 1,3-dithian-2-ylmethyl ester (15a)**: IR (KBr) $\bar{\nu}$ 1750 (C=O, ester), 1660 (amide I); 90-MHz ^1H NMR ($CDCl_3$) δ 7.3 (m, 6 H, NH and phenyl), 6.0 (d, *J* = 8.5 Hz, 1 H, NH), 3.1 (dd, 2 H, β-CH_2Asn), 2.9–2.6 (m, 4 H, $CH_2CH_2CH_2$), 2.08, 2.06, and 2.04 (3 s, 9 H, 3 CH_3COO), 1.98 (s, 3 H, CH_3CONH), 1.4 (s, 9 H, $(CH_3)_3C$); 22.63-MHz ^{13}C NMR (DMSO-d_6/CD_3OD 1:1) δ 172–170.3 (C=O), 155.9 (C=O, urethane), 137.5 (ipso C), 80.2 ($(CH_3)_3C$), 74.1 (C3), 73.6 (C5), 28.4 ($(CH_3)_3C$), 27.4 ($CH_2CH_2CH_2$), 26.0 ($CH_2CH_2CH_2$), 22.7 (CH_3CONH), 20.5 and 20.3 (CH_3COO).

***N*⁴-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-*N*²-(*tert*-butyloxycarbonyl)asparaginylisoleucine 1,3-dithian-2-ylmethyl ester (15b)**: IR (KBr) $\bar{\nu}$ 1755 (C=O, ester), 1665 (amide I); 90-MHz ^1H NMR (DMSO-d_6) δ 7.4 (d, *J* = 7.6 Hz, 1 H, NH), 6.3 (d, *J* = 7.9 Hz, 1 H, NH), 6.1 (d, *J* = 7.9 Hz, 1 H, NH), 2.8–2.6 (m, 6 H, β-CH_2Asn and $CH_2CH_2CH_2$), 2.08, 2.07, 2.04, and 2.01 (4 s, 12 H, 4 CH_3CO), 1.44 (s, 9 H, $(CH_3)_3C$), 0.97–0.82 (m, 6 H, 2 CH_3Ile); 22.63-MHz ^{13}C NMR (DMSO-d_6) δ 171.6–169.2 (C=O), 155.2 (C=O, urethane), 78.3 ($(CH_3)_3C$), 78.0 (C1), 73.2 (C3), 72.2 (C5), 68.4 (C4), 64.8 (OCH_2CH), 61.8 (C6), 56.1 (α-CHIle), 52.1 (C2), 50.6 (α-CHAsn), 28.0 ($(CH_3)_3C$), 26.4 ($CH_2CH_2CH_2$), 25.1 ($CH_2CH_2CH_2$), 24.3 (γ-CH_2Ile), 22.7 (CH_3CONH), 20.5 and 20.3 (CH_3COO), 15.3 (γ-CH_2Ile), 11.1 (δ-CH_3Ile).

***N*⁴-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-*N*²-(*tert*-butyloxycarbonyl)asparaginylserine 1,3-dithian-2-ylmethyl ester (15c)**: IR (KBr) $\bar{\nu}$ 1750 (C=O, ester), 1660 (amide I); 90-MHz ^1H NMR (DMSO-d_6) δ 8.5 (d, *J* = 8.9 Hz, 1 H, NH), 8.0–7.8 (m, 2 H, 2 NH), 6.8 (d, *J* = 7.8 Hz, 1 H, NH), 3.0–2.8 (m, 4 H, $CH_2CH_2CH_2$), 2.0, 1.96, 1.92, and 1.78 (4 s, 12 H, 4 CH_3CO), 1.38 (s, 9 H, $(CH_3)_3C$); 22.63-MHz ^{13}C NMR (DMSO-d_6) δ 172.2–169.8 (C=O), 155.8 (C=O, urethane), 79.4 ($(CH_3)_3C$), 78.3 (C1), 73.6 (C3), 72.7 (C5), 68.3 (C4), 65.6 (OCH_2CH), 28.5 ($(CH_3)_3C$), 27.0 ($CH_2CH_2CH_2$), 25.5 ($CH_2CH_2CH_2$), 22.9 (CH_3CONH), 20.7 (CH_3COO).

Fructose 1,6-Diphosphate Aldolase Catalyzed Stereoselective Synthesis of *C*-Alkyl and N-Containing Sugars: Thermodynamically Controlled C–C Bond Formations[1]

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Fructose 1,6-diphosphate aldolase catalyzed aldol condensations have been used in syntheses of several new N-containing and *C*-alkyl sugars on 4–20-mmol scales. The enzyme is highly specific for dihydroxyacetone phosphate as donor but accepts a number of achiral and chiral aldehydes (both D and L isomers) as acceptors. Due to the reversible nature of the aldol reaction, a thermodynamically controlled approach was employed for the syntheses in which racemic aldehydes were used as substrates and thermodynamically more stable products were preferentially produced.

Enzymatic transformations have been increasingly used as alternative methods in enantioselective synthesis.[2] Many useful reactions, particularly those based on the use of hydrolases and oxidoreductases have been demon-

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