Allyl Esters as Carboxy Protecting Groups in the Synthesis of O-Glycopeptides[1]

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Received April 15, 1988

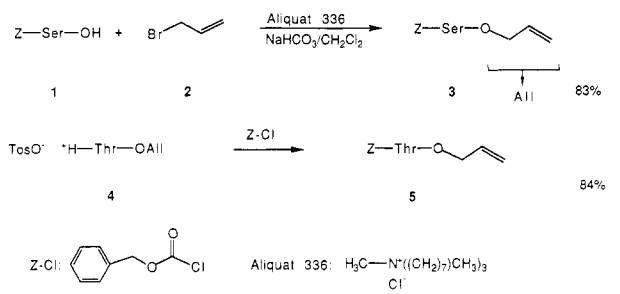
The construction of β-D-xylosyl- and α-D-*N*-acetylgalactosaminylserine and -threonine glycopeptides is carried out by using the allyl ester for selective C-terminal deprotection. The β-glycosidic bond between *N*-(benzyloxycarbonyl)serine allyl ester and 2,3,4-tri-*O*-benzylxylopyranose is formed according to the trichloroacetimidate method. The α-glycosides are built up by glycosylation of N-protected threonine (serine) allyl ester with 2-azido-3,4,6-tri-*O*-acetyl-β-D-glactosyl chloride in the presence of $Ag_2CO_3/AgClO_4$. The azide group is transformed to the *N*-acetyl moiety with phenyldimethylphosphine and acetic acid. From the sensitive glycosides the allyl esters are quantitatively and selectively removed by Pd(0)-catalyzed allyl transfer to morpholine as accepting nucleophile. Elongation of the peptide chain in the C-terminal direction leads to glycodi-, -tri-, and -tetrapeptides, which represent characteristic partial structures of natural glycoproteins (e.g. glycophorin). From the glycosylated oligopeptides, the allyl ester can also be removed quantitatively. The peptide chain of the deprotected xylosyl tripeptide is then further extended to a glycopentapeptide. In all the allyl ester cleavage reactions, the functions in the glycosyl serine (threonine) derivatives that are sensitive to acids, bases, and reduction remain intact.

Introduction

The glycoproteins constitute a class of natural products with most important biological functions. For instance, it has been demonstrated that they are not only responsible for recognition on cell membranes, intercellular communication, and cell growth, but they also may represent tumor-associated antigens.[2] Glycopeptides, the characteristic partial structures of the glycoproteins, are not easily available by gene technological methods. For their chemical synthesis, the glycosidic bonds must be formed stereoselectively, and numerous functional groups have to be protected and deprotected selectively. In the construction of peptides containing an O-glycosidic bond between serine or threonine and the carbohydrate, additional difficulties have to be overcome. Under acidic deprotecting conditions anomerization or even rupture of the glycosidic bond may occur.[3] On the other hand even at pH's lower than 10 the entire carbohydrate part may be lost by a β-elimination reaction.[4] Therefore, the synthesis of these complex, sensitive molecules requires protecting groups that can be selectively removed under almost neutral conditions. Most of the carboxy protecting functions common in peptide synthesis cannot be used to achieve this goal. We have developed several protecting groups in order to solve these problems in the glycopeptide synthesis.[5] For instance, we could selectively deprotect the carboxylic acid in glycosylserine derivatives by reductive elimination of the 2-haloethyl esters with zinc in dimethylformamide.[6] However, under these conditions valuable glycopeptide was adsorbed on the zinc salts and lost.

Recently, we reported that allyl esters can be used in peptide synthesis as carboxy protecting groups.[7] They could be selectively removed in the presence of the benzyloxycarbonyl (Z) and the *tert*-butyloxycarbonyl (Boc) group under mild and neutral conditions by isomerization of the allyl moiety with tris(triphenylphosphine)rhodium(I) chloride[8] at 70 °C. This method was also used for the liberation of the carboxy function in *N*-glycopeptides.[7,9]

Scheme I. Synthesis of Z-Serine 3 and Z-Threonine Allyl Ester 5



In this paper we describe an even milder method for the selective cleavage of amino acid allyl esters, namely the palladium(0)-catalyzed allyl transfer[10] to morpholine as the accepting nucleophile. Prior to our work and unknown to us at the time when we investigated the reaction, the allyl ester was already used as a carboxy protecting group in β-lactam antibiotic synthesis. In these investigations McCombie and co-workers already cleaved this ester group by performing a palladium(0)-catalyzed transesterification.[11]

Results and Discussion

Synthesis of the Serine and Threonine Glycosides. In our investigations we focused on β-D-xylosylserine glycosides, predominating in the proteoglycans,[2] and α-*N*-acetylgalactosaminylserine and -threonine glycosides since they represent the tumor-associated T_N-antigen structure.[2,12]

Z-Serine allyl ester **3** and Z-threonine allyl ester **5** served as acceptors in the glycosylation reactions. The protected

(1) Supported by the Deutsche Forschungsgemeinschaft and by the Fonds der Chemischen Industrie.

(2) For a recent review, see: Montreuil, J. In *Protein Metabolism*; Neuberger, A., van Deenen, L. L., Eds.; Elsevier: Amsterdam, 1984; Vol. 19B/II(1).

(3) Garg, H. G.; Jeanloz, R. W. *Carbohydr. Res.* **1976**, *49*, 482.

(4) (a) Vercellotti, J. R.; Fernandez, R.; Chang, C. J. *Carbohydr. Res.* **1967**, *5*, 97. (b) Wakabayashi, K.; Pigman, W. Ibid. **1974**, *35*, 3.

(5) Kunz, H. *Angew. Chem.* **1987**, *99*, 297; *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 294.

(6) Buchholz, H.; Kunz, H. *Justus Liebigs Ann. Chem.* **1983**, 1561.

(7) Waldmann, H.; Kunz, H. *Justus Liebigs Ann. Chem.* **1983**, 1712.

(8) Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1973**, *38*, 3224.

(9) (a) Kunz, H.; Waldmann, H. *Angew. Chem.* **1985**, *97*, 885; *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 883. (b) Kunz, H.; Waldmann, H. *Helv. Chim. Acta* **1985**, *68*, 618.

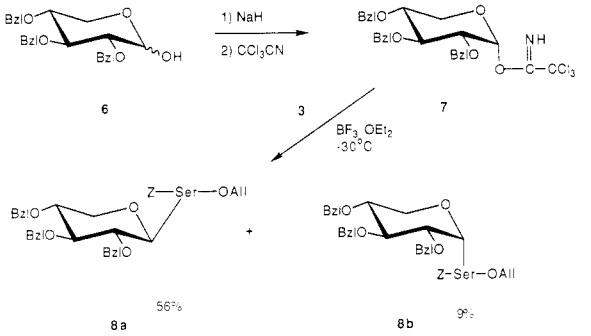
(10) A preliminary report of part of this work has appeared: Kunz, H.; Waldmann, H. *Angew. Chem.* **1984**, *96*, 49; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 71. See also ref 17.

(11) Jeffrey, P. D.; McCombie, S. W. *J. Org. Chem.* **1982**, *47*, 587.

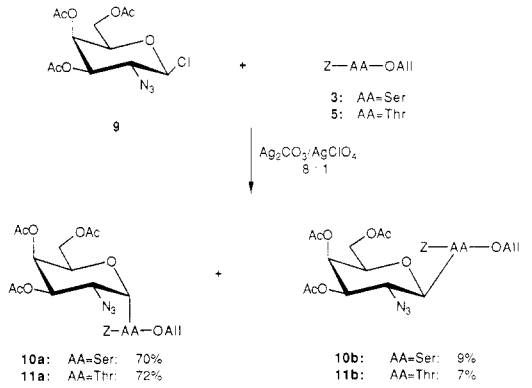
(12) See, e.g.; Springer, G. F.; Desai, P. R.; Murthy, M. S.; Scanlon, E. F. *ACS Symp. Ser.* **1978**, *80*, 311.

0022-3263/89/1954-0751$01.50/0

Scheme II. Synthesis of *N*-(Benzyloxycarbonyl)-*O*-(2,3,4-tri-*O*-benzyl-β-D-xylopyranosyl)serine Allyl Ester by the Trichloromethylimidate Method



Scheme III. Synthesis of the α-*N*-Acetylgalactosaminyl Glycosides

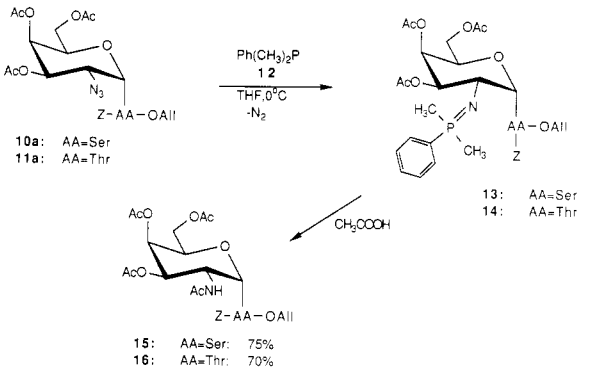


serine derivative **3** was obtained by reacting Z-serine **1** with allyl bromide under phase-transfer conditions (Scheme I). The analogous threonine was formed from threonine allyl ester and Z chloride in excellent yield (Scheme I). The β-glycosidic bond between serine and D-xylose was constructed by applying the trichloromethylimidate method introduced by Schmidt et al.[13] In the presence of sodium hydride 2,3,4-tri-*O*-benzylxylopyranose **6** reacted with trichloroacetonitrile to the α-trichloromethylimidate **7**. Immediately after preparation it was converted to the serine glycosides **8a** and **8b** (Scheme II). Unfortunately the reaction did not proceed with the expected high β-selectivity. Possibly the imidate **7** was not formed exclusively as the α-anomer. Schmidt has recently pointed out that the glycosylimidates equilibrate under basic conditions. In contrast to other pyranoses, in the case of xylose the mixture of anomers at equilibrium was found to be α:β = 4:1.[13] However, the desired glycoside **8a** could be obtained in pure form after chromatographic separation.

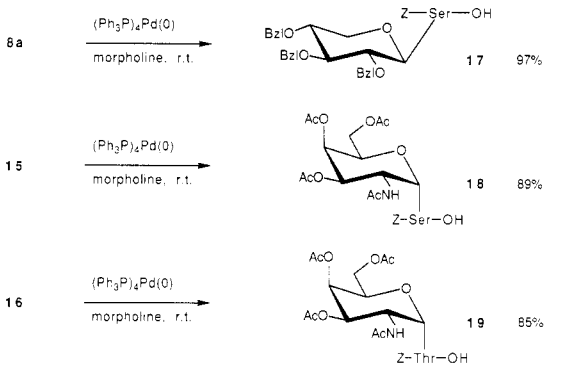
To construct α-*N*-acetylgalactosaminylserine and -threonine glycosides, the 2-azido-β-D-galactosyl chloride[14] **9** was used as the glycosyl donor. Scheme III demonstrates that in the presence of $Ag_2CO_3/AgClO_4$ it predominantly lead to α-configured products. Once more these reactions were not stereospecific, (α:β = 8:1 for serine, α:β = 11:1 for threonine).

However, in both cases the α-anomers could be separated easily by chromatography. For the conversion of the 2-azido to the 2-acetamido function required, the reduction with nickel boride and subsequent acetylation of the amino

Scheme IV. Conversion of the 2-Azido Functions in the Glycosides to the 2-Acetamido Group



Scheme V. Pd(0)-Catalyzed Cleavage of the Allyl Ester of the *O*-Glycosyl Amino Acid Derivatives



group formed has been described.[15] But, under these conditions the allyl ester is also affected. To overcome this difficulty, we adopted the Staudinger reduction of azides with tertiary phosphines.[16] As shown in Scheme IV the 2-azidoglycosides **10a** and **11a** reacted with dimethylphenylphosphine **12** to the phosphinimines **13** and **14**. If these reactions are carried out in dry acetic acid the phosphinimines **13** and **14** are immediately transformed to the desired 2-acetamidogalactosyl derivatives **15** and **16** in good yields.

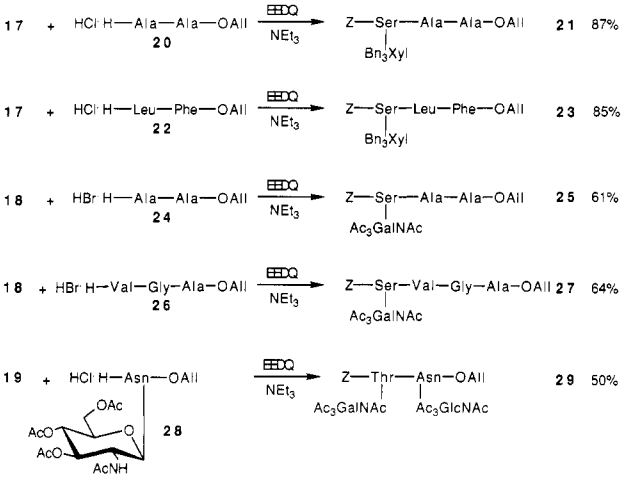
Selective Removal of the Allyl Esters and C-Terminal Extension of the Peptide Chain. For the selective cleavage of the allyl esters in the presence of the very labile O-glycosidic bonds, we found an exceptionally mild method by using the Pd(0)-catalyzed allyl transfer to an accepting nucleophile. This reaction principle has been introduced by Trost et al. and others for the allylation of carbanions.[17] In the presence of 10 mol % of tetrakis(triphenylphosphine)palladium(0) the allyl residues of the esters **8a**, **15**, and **16** were transferred to morpholine at room temperature within 30 min in excellent yields (Scheme V). All the remaining functions of the glycosyl amino acid derivatives that are sensitive to acids, bases, and reduction are completely conserved.

The carboxy-deblocked products could then be condensed with amino acid or oligopeptide allyl esters[7,9,10] in the presence of ethyl 2-ethoxy-1,2-dihydroquinoline-1-carboxylate (EEDQ)[18] (Scheme VI). The glycopeptides are formed in good yields.

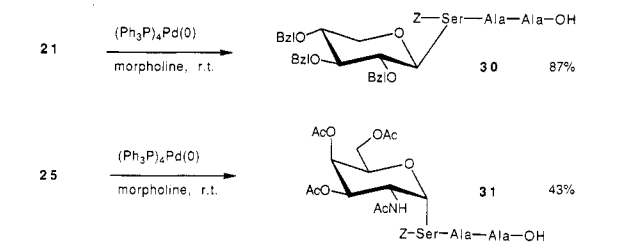
The chain elongation with the N-terminally deblocked asparagine glycoside **28**[9,19] delivered the glycodipeptide **29**.

(13) (a) Schmidt, R. R.; Michel, J. *Angew. Chem.* **1980**, *92*, 763; *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 731. (b) Schmidt, R. R.; Michel, J.; Roos, M. *Justus Liebigs Ann. Chem.* **1984**, 1343.
(14) Paulsen, H.; Hölck, J. P. *Carbohydr. Res.* **1982**, *109*, 89.
(15) Paulsen, H.; Sinnwell, V. *Chem. Ber.* **1978**, *111*, 879.
(16) Staudinger, H.; Meyer, M. *Helv. Chim. Acta* **1919**, *2*, 635.
(17) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 1.
(18) Belleau, B.; Malek, G. *J. Am. Chem. Soc.* **1968**, *90*, 1651.
(19) Kunz, H.; Waldmann, H., submitted for publication in *Carbohydr. Res.*

Scheme VI. C-Terminal Elongation of the Peptide Chain in the Presence of EEDQ



Scheme VII. Selective Allyl Ester Cleavage from the Glycotripeptides 21 and 25



It represents a very complex partial structure of glycophorin A, the major glycoprotein of human erythrocyte membranes.[20] In addition it is the first example of a synthetic glycopeptide containing a direct connection between an O- and an N-glycosylated amino acid. The amino acid sequence of the glycoside **27** is found as a characteristic partial sequence of human α_2-HS-glycoprotein, a human plasma globuline.[21] The serine derivative **25** is an analogue of the repeating unit of the antifreeze glycoprotein of antartic fish.[22] The xylosylglycoside **21** is derived from a glycoprotein of the plant kingdom (vide infra).

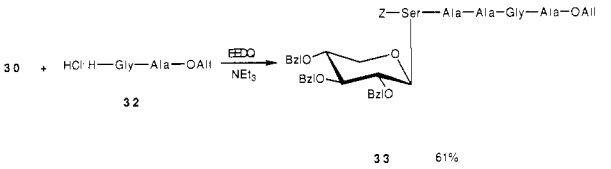
In the chain extension reactions described, additional advantages of the allyl group become evident; its low lipophilicity promotes solubility, its sterically less-demanding size promotes the condensation reactions.

For further elongation of the peptide chains the allyl moiety was again selectively removed from the complex glycotripeptides **21** and **25** (Scheme VII). In both cases the conversion was essentially quantitative; the low yield of **31** was due to loss of material during work up. Once more all the other protecting groups present remained intact, and the sensitive O-glycosidic bonds were not affected.

Finally we have synthesized the glycopentapeptide allyl ester **33** by condensation of the C-terminally deblocked product **30** with the dipeptide unit **32** (Scheme VIII).

The structure of this totally protected peptide is based on data for the linkage region of an extracellular glycoprotein of the alga *Porphyridium crutum*.[23]

Scheme VIII. Synthesis of a Glycopentapeptide by Chain Extension of the C-Terminally Deprotected Glycotripeptide 30



The allyl ester has thus proven to be a valuable carboxy protecting group for glycopeptide synthesis. It is stable to acids and bases but still can be removed selectively and quantitatively under homogeneous and almost neutral conditions. The allyl esters should find extensive applications in peptide and glycopeptide synthesis as well as in other areas where deprotection of the carboxyl group under exceptionally mild conditions is required.

Experimental Section

Material and Methods. Optical rotations were measured with a Perkin-Elmer 241 polarimeter, IR spectra with a Beckmann Acculab-2. 60-MHz ^{1}H NMR spectra were obtained on a JEOL-JMN-60 MHz spectrometer and 90-MHz ^{1}H and 22.63-MHz ^{13}C NMR spectra were obtained on a Bruker WH-90-spectrometer. 80-MHz ^{1}H and 20.15-MHz ^{13}C NMR spectra were recorded on a Bruker WP-80-DS instrument, and 400-MHz ^{1}H and 100.6-MHz ^{13}C NMR spectra were recorded on a Bruker-AM-400 instrument. 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.

***N*-(Benzyloxycarbonyl)serine Allyl Ester (3).** *N*-(Benzyloxycarbonyl)serine (1) (4.8 g, 0.02 mol) and 1.7 g (0.02 mol) of $NaHCO_3$ were dissolved in 30 mL of water, and a solution of 8 g (0.02 mol) of tricaprylmethylammonium chloride (aliquat 336) and 12 g (0.02 mol) of allyl bromide in 30 mL of methylene chloride was added. After being stirred vigorously for 72 h, the reaction mixture was extracted three times with 50 mL of methylene chloride. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The remaining residue was chromatographed (petroleum ether/ethyl acetate, 2:1 (v/v)) to yield 4.63 g (83%) of a colorless oil: $[\alpha]^{22}_D$ 5° (c = 1, $CHCl_3$); IR (neat) ν 1730 (C=O, ester), 1700 (C=O, urethane); 60-MHz ^{1}H NMR ($CDCl_3$) δ 7.4–7.3 (m, 5 H, phenyl), 6.6–6.3 (d, J = 8 Hz, 1 H, NH), 6.2–5.6 (m, 1 H, C*H*=CH_2), 5.45–5.1 (m, 4 H, CH=CH_2 and OCH_2Ph), 4.7–4.3 (d, J = 5 Hz, 2 H, OCH_2CH=CH_2 and m, 1 H, Ser-α-CH), 4.2–3.7 (m, 3 H, CH_2OH). Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.20; H, 6.13; N, 5.02. Found: C, 59.94; H, 6.28; N, 4.94.

***N*-(Benzyloxycarbonyl)threonine Allyl Ester (5).** Threonine allyl ester hydrotosylate[7] (4) (6.6 g, 20 mmol) and 6 g (20 mmol) of potassium hydrogen carbonate were dissolved in 60 mL of water, and a solution of 3.4 g (20 mmol) of chloroformic acid benzyl ester in 60 mL of ethyl acetate was added. After being vigorously stirred for 24 h the organic layer was separated, extracted three times with 40 mL of 2 N $NaHCO_3$ solution and water, dried over $MgSO_4$, and concentrated in vacuo. Chromatography (petroleum ether/ethyl acetate, 2:1 (v/v)) delivered 4.9 g (84%) of **5**. It is identical with the product obtained by esterification of Z-Thr-OH with allyl bromide:[24] 60-MHz ^{1}H NMR ($CDCl_3$) δ 6.87 (m, 5 H, phenyl), 5.83–5.2 (m, 2 H, NH and C*H*=CH_2), 5.17–4.87 (m, 2 H, CH=CH_2), 4.73 (s, 2 H, CH_2Ph), 4.3 (d, 2 H, OCH_2), 4.17–3.72 (m, 2 H, α-CH, Thr and β-CH-Thr), 3.1 (d, 1 H, OH), 1.1 (d, 3 H, CH_3).

***O*-(2,3,4-Tri-*O*-benzyl-α-D-xylopyranosyl)trichloroacetimidate (7).** To a solution of 3.6 g (25 mmol) of trichloro-

(20) Carton, J. P. In *Blood Groups and Other Red Cell Surface Markers in Health and Disease*; Salomon, C., Ed.; Masson: New York, 1982; p 39.
(21) Gejyo, F.; Chang, J. C.; Bürgi, W.; Schmid, W. *J. Biol. Chem.* **1983**, *258*, 4966.
(22) Feeney, R. E.; Yeh, Y. *Adv. Protein Chem.* **1978**, *32*, 191.
(23) Hearney-Kiberas, J.; Rodin, O. L.; Chapman, D. J. *Biochem. J.* **1977**, *165*, 1.
(24) Kunz, H.; Friedrich-Bochnitschek, S., submitted for publication in *Justus Liebigs Ann. Chem.*

acetonitrile and 2.1 g (5 mmol) of 2,3,4-tri-*O*-benzylxylopyranose in 20 mL of methylene chloride was added 0.12 g (5 mmol) of sodium hydride. After being stirred for 30 min at ambient temperature, the solution was filtered and concentrated in vacuo, and the remaining residue was quickly passed through a layer of silica gel with petroleum ether/ethyl acetate, 1:1. After drying over $MgSO_4$ and evaporation of the solvent, 2.7 g (96%) of a yellowish oily residue remained. It was used immediately for glycosylation: IR (neat) ν 1670 (C=NH); 90-MHz ^{1}H NMR ($CDCl_3$) δ 8.6 (s, 1 H, NH), 7.3 (m, 15 H, phenyl), 6.35 (d, J = 3.2 Hz, 1 H, H1), 4.9–4.6 (m, 6 H, 3 CH_2O), 4.0–3.5 (m, 4 H, H2, H3, H5, H5′).

***N*-(Benzyloxycarbonyl)-*O*-(2,3,4-tri-*O*-benzyl-β- and -α-D-xylopyranosyl)serine Allyl Esters 8a and 8b.** The imidate **7** (2.6 g, 4.6 mmol) and 1.28 g of the serine derivative **3** were dissolved in 20 mL of methylene chloride. The mixture was cooled to −30 °C, and a solution of 13 g (0.92 mmol) of BF_3·OEt_2 in 5 mL of methylene chloride was added during 30 min. After an additional hour, 1 g of solid $NaHCO_3$ and 20 mL of saturated $NaHCO_3$ solution were added subsequently. The organic layer was extracted three times with cold $NaHCO_3$ solution, dried over $MgSO_4$, and evaporated to dryness. From the remaining residue the anomers **8a** and **8b** were isolated as a mixture by chromatography with petroleum ether/ethyl acetate, 4:1 (v/v); **8a** and **8b** were separated by column chromatography or preparative HPLC (waters Prep 500) with chloroform/ether, 95:5 (v/v) as the eluent, yield 1.75 g (56%) of β-anomer **8a** and 0.3 g (9%) of α-anomer **8b** (β:α = 6:1). **β-Anomer 8a**: mp 68–69 °C; $[\alpha]^{22}_D$ 12.4° (c = 1, $CHCl_3$); IR (KBr) ν 1750 (C=O, ester), 1690 (C=O, urethane); 270-MHz ^{1}H NMR ($CDCl_3$) δ 7.38–7.2 (m, 20 H, phenyl), 5.95–5.8 (m, 1 H, C*H*=CH_2), 5.64 (d, J = 8 Hz, 1 H, NH), 5.31 (dd, J_{trans} = 17.2 Hz, J_{gem} = 1.1 Hz, 1 H, CH=C*H*$_2$ (trans)), 5.21 (dd, J_{cis} = 10.9 Hz, J_{gem} = 1.1 Hz, 1 H, CH=C*H*$_2$ (cis)), 5.1 (s, 2 H, CH_2OC), 4.86–4.39 (m, 9 H, 4 CH_2 and Ser-α-CH), 4.34–4.28 (dd, 1 H, Ser-β-CH_2, and d, J = 7.6 Hz, 1 H, H1), 3.9–3.81 (m, 2 H, Ser-β-CH_b and H3), 3.62–3.51 (m, 2 H, H2 and H4), 3.33–3.27 (dd, 1 H, H5), 3.18–3.1 (dd, 1 H, H5′); 20.16-MHz ^{13}C NMR (acetone-d_6) δ 170.3 (C=O, ester), 156.7 (C=O, urethane), 133 (*C*H=CH_2), 129.1–128 (phenyl), 118.1 (CH=*C*H$_2$), 104.75 (C1), 55.4 (α-C-Ser); GATED-decoupled 20.16-MHz ^{13}C NMR (acetone-d_6) $J_{C1/H1}$ = 166.2 Hz. Anal. Calcd for $C_{40}H_{43}NO_9$: C, 70.47; H, 6.36; N, 2.05. Found: C, 70.14; H, 6.22; N, 2.33. **α-Anomer 8b**: mp 70–71 °C; $[\alpha]^{22}_D$ 44.8° (c = 1, $CHCl_3$); IR (neat) ν 1735 (C=O, ester); 270-MHz ^{1}H NMR ($CDCl_3$) δ 7.38–7.28 (m, 20 H, phenyl), 5.90–5.78 (m, NH and C*H*=CH_2), 5.26 (dd, J_{trans} = 17.2 Hz, J_{gem} = 1 H, CH=C*H*$_2$ (trans)), 5.17 (dd, J_{cis} = 10.6 Hz, J_{gem} = 1 Hz, 1 H, CH=CH_2 (cis)), 5.13 (s, 2 H, $PhCH_2OCO$), 4.84–4.53 (m, 10 H, 3 OCH_2Ph, α-CH-Ser and H1), 4.02 (dd, J_1 = 3.1 Hz, J_2 = 8.3 Hz, 1 H, β-CH_a-Ser), 3.87 (dd, β-CH_b-Ser), 3.81 (dd, J_1 = 8.1 Hz, J_2 = 8.3 Hz, 1 H, H3), 3.62–3.38 (m, 4 H, H2, H4, H5, H5′); 22.63-MHz ^{13}C NMR (CD_3OD) δ 171.4 (C=O, ester), 158.6 (C=O, urethane), 133.1 (CH=CH_2), 129.3–128.5 (phenyl), 118.8 (CH=CH_2), 56.4 (α-C-Ser). Anal. Calcd for $C_{40}H_{43}NO_9$: C, 70.47; H, 6.36; N, 2.05. Found: C, 70.56; H, 6.4; N, 2.2.

***N*-(Benzyloxycarbonyl)-*O*-(3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α-D-galactopyranosyl)serine Allyl Ester (10a).** A mixture of 2.85 g (10.2 mmol) of serine allyl ester (**3**), 60 mL of toluene, 6.5 g (23.5 mmol) of silver carbonate, 6.5 g of molecular sieves, 4 Å, and 6.5 g of Drierite was stirred at −30 °C for 30 min; 0.65 g of silver perchlorate was added, and after an additional 20 min a solution of 4.3 g (9.72 mmol) of the β-chloride **9** in 100 mL of toluene/methylene chloride, 1:1 (v/v), was slowly added. After the reaction was complete (TLC toluene/acetone, 7:2), the reaction mixture was diluted with methylene chloride and filtered through Celite. It was washed three times with 50 mL of 2 N sodium hydrogen carbonate solution and water, dried over $MgSO_4$, and evaporated to dryness. Two successive separations by flash chromatography (toluene/acetone, 9:1, and ethyl acetate/petroleum ether, 1:3 (v/v)) delivered 3.9 g (70%) of **10a** and 0.5 g (9%) of **10b** as amorphous solids. α-Glycoside **10a**: $[\alpha]^{22}_D$ 108.7° (c = 1.2, $CHCl_3$); IR (neat) 2120 (N_3), 1760–1720 (C=O, ester), 1520–1490 (amide); 90-MHz ^{1}H NMR ($CDCl_3$) ν 7.35 (m, 5 H, phenyl), 6.1–5.7 (m, 2 H, NH and C*H*=CH_2), 5.45–5.22 (m, 4 H, CH=C*H*$_2$, H3, H4), 5.14 (s, 2 H, CH_2Ph), 4.96 (d, $J_{1/2}$ = 3.5 Hz, 1 H, H1), 4.7–4.5 (m, 3 H, α-CH-Ser, CH_2CH=CH_2), 4.2–4.0 (m, 5 H, β-CH_2-Ser, H5, $H6_{a,b}$), 3.6 (dd, $J_{2,3}$ = 10.9 Hz, 1 H, H2), 2.12, 2.04, 2.01 (3 s, 9 H, CH_3CO); 22.63-MHz ^{13}C NMR ($CDCl_3$) δ 170.4–169.1 (C=O), 155.7 (C=O, urethane), 136.2 (ipso-C), 131.3 (*C*H=CH_2), 99.2 (Cl) 61.6 (C6), 57.3 (C2), 54.5 (α-CH-Ser), 20.5 (CH_3CO). Anal. Calcd for $C_{26}H_{32}N_4O_{12}$: C, 52.70; H, 5.44; N, 9.45. Found: C, 52.81; H, 5.45; N, 9.32.

***N*-(Benzyloxycarbonyl)-*O*-(3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α-D-galactopyranosyl)threonine Allyl Ester (11a).** As described for the serine analogue, 1.22 g (4.16 mmol) of the threonine ester **5** and 1.2 g (3.43 mmol) of β-chloride **9** at 5 °C yielded 1.43 g (72%) of α-glycoside **11a** and 0.13 g (7%) of β-glycoside **11b**. The anomers were separated by two flash chromatographies [(1) toluene/ethyl acetate, 6:1, (2) petroleum ether/ethyl acetate, 3:1]. α-Glycoside **11a** $[\alpha]^{22}_D$ 87.3 (c = 1, $CHCl_3$); ^{1}H NMR δ 7.35 (m, 5 H, phenyl), 6.1–5.44 (m, 2 H, NH and C*H*=CH_2), 5.4–5.18 (m, 4 H, CH=C*H*$_2$, H3 and H4), 5.15 (s, 2 H, CH_2Ph), 5.02 (d, $J_{1/2}$ = 3.8 Hz, 1 H, H1), 4.7–3.9 (m, 8 H, OCH_2CHCH_2, α-CH-Ser, β-CH_2Ser, H5, $H6_{a,b}$), 3.66 (dd, $J_{2,3}$ = 10.9 Hz, H2), 2.12, 2.03, 2.01 (3 s, 9 H, CH_3CO), 1.34 (d, J = 6.4 Hz, 3 H, CH_3-Thr); 22.63-MHz ^{13}C NMR ($CDCl_3$) δ 170.2 (C=O), 156.7 (C=O, urethane), 136.1 (ipso-C), 131.3 (*C*H=CH_2), 128.4–127.9 (phenyl), 119.1 (CH=*C*H$_2$), 99.3 (C1), 61.7 (C6), 58.7 (C2), 57.7 (α-CH-Thr), 20.4 (CH_3CO), 18.3 (CH_3-Thr). Anal. Calcd for $C_{27}H_{34}N_4O_{12}$: C, 53.46; H, 5.65; N, 9.24. Found: C, 53.28; H, 5.81; N, 9.24.

***N*-(Benzyloxycarbonyl)-*O*-(3,4,6-tri-*O*-acetyl-2-acetamido-2-deoxy-α-D-galactopyranosyl)serine Allyl Ester (15) and -threonine Allyl Ester (16). General Procedure.** Azido compound **10a** or **11a** (3.37 mmol) was dissolved in 10 mL of tetrahydrofuran at 0 °C under argon. A solution of 0.48 mL of dimethylphenylphosphine and 0.3 mL (4.4 mmol) of glacial acetic acid in 2 mL of THF was added. After the vigorous N_2 evolution had ceased, the reaction mixture was stirred for additional 2 h at ambient temperature and then treated overnight with acetic anhydride/pyridine at 0 °C. The solvents were evaporated, and the residue was taken up in methylene chloride and extracted three times with water. After being dried over $MgSO_4$, the solvent was evaporated, and the remaining residue was codistilled with toluene. Chromatography with petroleum ether/ethyl acetate, 1:1 (v/v), delivered **15** and **16** as amorphous solids; **16** was recrystallized from methylene chloride/ether.

Serine glycoside 15: yield 75%; IR (neat) ν 1750–1720 (C=O, ester), 1660 (C=O, ester), 1660 (C=O, amide); 80-MHz ^{1}H NMR ($CDCl_3$) δ 7.34 (m, 5 H, phenyl), 5.82–5.7 (m, 3 H, 2 NH, C*H*=CH_2), 5.41–5.17 (m, 3 H, CH=C*H*$_2$, H4), 5.12 (s, 2 H, CH_2Ph), 5.02 (m, 1 H, H3), 4.84 (d, $J_{1/2}$ = 3.8 Hz, 1 H, H1), 4.73–4.38 (m, 4 H, CH-Ser, H2, CH_2CH=CH_2), 4.19–3.85 (m, 5 H, $H6_{a,b}$, H5, β-CH_2-Ser), 2.13, 2.0, 1.96, 1.93 (4 s, 12 H, CH_3CO); 22.63-MHz ^{13}C NMR ($CDCl_3$) δ 170.8–169.7 (4 s, C=O), 155.7 (C=O, urethane), 135.8 (ipso-C), 130.9 (*C*H=CH_2), 128.4–128.0 (phenyl), 119.3 (CH=C*H*$_2$), 98.6 (C1), 61.8 (C6), 54.3 (α-CH-Ser), 47.4 (C2), 22.9 (CH_3CONH), 20.45 (CH_3COO). Anal. Calcd for $C_{28}H_{36}N_2O_{13}$·$0.5H_2O$: C, 54.48; H, 6.04; N, 4.54. Found: C, 54.60; H, 6.02; N, 4.56.

Threonine glycoside 16: yield 70%; mp 122–124; IR (neat) ν 1750–1710 (C=O, ester), 1660 (amide); 80-MHz ^{1}H NMR ($CDCl_3$) δ 7.3 (m, 5 H, phenyl), 6.08–5.68 (m, 3 H, 2 NH, C*H*=CH_2), 5.4–5.25 (m, 2 H, CH=C*H*$_2$), 5.2–5.1 (m, 1 H, H4), 5.08 (s, 2 H, CH_2Ph), 4.97 (d, $J_{3/4}$ = 3.2 Hz, 1 H, H3), 4.84 (d, $J_{1/2}$ = 3.5 Hz, 1 H, H1), 4.65–4.24 (m, 4 H, α-CH-Thr, CH_2CH=CH_2, H2), 4.29–3.93 (m, 4 H, H5, $H6_{a,b}$, β-CH-Thr), 2.08, 1.97, 1.92, 1.90 (4 s, 12 H, CH_3CO), 1.29 (d, J = 6.1 Hz, CH_3-Thr). Anal. Calcd for $C_{29}H_{38}N_2O_{13}$·H_2O: C, 54.37; H, 6.29; N, 4.37. Found: C, 54.21; H, 5.99; N, 4.26.

Selective Removal of the Allyl Ester from the Glycosides 8a, 15, and 16. General Procedure. A solution of 1.32 mmol of the allyl esters **8a**, **15**, or **16** in 10 mL of tetrahydrofuran was stirred in an argon atmosphere at ambient temperature, and 0.15 g (0.132 mmol; 10 mol %) of tetrakis(triphenylphosphine)palladium(0) and 1.15 mL (13.2 mmol) of morpholine were added subsequently. After 30 min the solvent was evaporated, and the residue was taken up in 50 mL of methylene chloride. The resulting solution was extracted three times with 30 mL of 2 N HCl, dried over $MgSO_4$, and concentrated in vacuo. In the case of **8a** the residue was taken up in 20 mL of ether, filtered, dried over $MgSO_4$, and evaporated to dryness. The desired acid was obtained as a colorless amorphous solid; **15** was obtained as amorphous solid after chromatography (ethyl acetate). Crude

19 was used directly for the subsequent transformations.

By this procedure the following compounds were obtained.

N-(Benzyloxycarbonyl)-O-(2,3,4-tri-O-benzyl-β-D-xylopyranosyl)serine (17): yield 97%; $[\alpha]^{22}_D$ 18.3° (c = 1, $CHCl_3$); IR (neat) ν 1720 (COOH), 1700 (urethane); 20.16-MHz ^{13}C NMR ($CDCl_3$) δ 173 (COOH), 158 (C=O, urethane), 129.3–128.6 (phenyl), 104.9 (C1), 55.6 (α-CH-Ser); GATED-decoupled 20.16-MHz ^{13}C NMR ($CDCl_3$) $J_{C1/H1}$ = 164 Hz. Anal. Calcd for $C_{37}H_{39}NO_9 \cdot 0.5H_2O$: C, 68.29; H, 6.19; N, 2.15. Found: C, 68.27; H, 6.19; N, 2.09.

N-(Benzyloxycarbonyl)-O-(3,4,6-tri-O-acetyl-2-acetamido-2-deoxy-α-D-galactopyranosyl)serine (18): yield 89%; $[\alpha]^{22}_D$ 117 °C (c = 0.82, $CHCl_3$); 90-MHz ^1H NMR ($CDCl_3$) δ 7.32 (m, 5 H, phenyl), 6.5–6.0 (m, 2 H, 2 NH), 5.45–5.22 (m, 2 H, H3 and H4), 5.11 (s, 2 H, CH_2Ph), 4.95 (d, 1 H, $J_{1/2}$ = 3.5 Hz, 1 H, H1), 4.8–4.3 (m, 2 H, α-CH-Ser and H2), 4.25–3.85 (m, 5 H, β-CH_2-Ser, H5 and $H6_{a,b}$), 2.14 (s, 3 H, CH_3CONH), 2.01–1.94 (9 H, CH_3COO); 22.63-MHz ^{13}C NMR ($CDCl_3$) δ 2.9–170.2 (C=O), 155.9 (C=O, urethane), 135.9 (ipso-C), 128.7–128.6 (phenyl), 98.3 (C1), 61.9 (C6), 54.4 (α-CH-Ser), 48.1 (C2), 22.6 (CH_3CONH), 20.65 (CH_3CO). Anal. Calcd for $C_{25}H_{32}N_2O_{13} \cdot H_2O$: C, 51.19; H, 5.84; N, 4.78. Found: C, 50.75; H, 5.68; N, 4.70.

N-(Benzyloxycarbonyl)-O-(3,4,6-tri-O-acetyl-2-acetamido-2-deoxy-α-D-galactopyranosyl)threonine (19): yield 85%. The crude product was used directly for the elongation of the peptide chain.

Elongation of the Peptide Chain with EEDQ. General Procedure. Synthesis of Glycotri- (21, 23, 25), -di- (29), and -tetrapeptide (27). The carboxy-deblocked serine or threonine derivatives **17**, **18**, or **19** (1.4 mmol), 1.4 mmol of the N-terminally deblocked compounds **20**, **22**, **24**, **26**, or **28**, and 0.14 g (1.4 mmol) of triethylamine were dissolved in 20 mL of methylene chloride; 0.52 g (2.1 mmol) of EEDQ dissolved in chloroform was added; and the reaction mixture was stirred for 48 h at ambient temperature. The solution then was extracted three times with 10 mL of 2 N HCl, 2 N $NaHCO_3$ solution, and water, dried over $MgSO_4$, and evaporated to dryness. The products were obtained in pure form by recrystallization from ether/petroleum ether (**21**), crystallization from methylene chloride/petroleum ether (**23**), and chromatography using petroleum ether/acetone, 1:1 (v/v), as the eluent (**25**, **27**). For the isolation of **29** the reaction mixture was evaporated to dryness, and the remaining residue was chromatographed directly (methylene chloride/acetone, 1.5:1 (v/v)).

By this procedure the following compounds were obtained.

N-(Benzyloxycarbonyl)-O-(2,3,4-tri-O-benzyl-β-D-xylopyranosyl)serylalanylalanine Allyl Ester (21): yield 87%; mp 154 °C; $[\alpha]^{22}_D$ 9.1 (c = 1, $CHCl_3$); IR (KBr) ν 1745 (C=O, ester), 695 (C=O, urethane), 1645 (C=O, amide); 22.63-MHz ^{13}C NMR δ 172–168.7 (C=O), 155.9 (C=O, urethane), 132.3 (CH=CH_2), 128.2–127.2 (phenyl), 117.5 (CH=CH_2), 103 (C1), 54.9 (α-CH-Ser), 47.7 and 47.6 (2 CH-Ala), 18.4 and 16.7 (2-β-CH_3Ala). Anal. Calcd for $C_{46}H_{53}N_3O_{11}$: C, 67.06; H, 6.48; N, 5.10. Found: C, 67.43; H, 6.59; N, 5.22.

N-(Benzyloxycarbonyl)-O-(2,3,4-tri-O-benzyl-β-D-xylopyranosyl)serylleucylphenylalanine Allyl Ester (23): yield 85%; mp 112–113 °C; $[\alpha]^{22}_D$ 22.2° (c = 0.6, $CHCl_3$); IR (KBr) ν 1750 (C=O, ester) 1710 (C=O, urethane), 1650 (amide); 22.63-MHz ^{13}C NMR (DMSO-d_6) δ 171.8–168.7 (C=O), 155.8 (C=O, urethane), 132.4 (CH=CH_2), 129.8–125.8 (phenyl), 118.3 (CH=CH_2), 103.1 (C1), 23.9 ($CH(CH_3)_2$), 22.8 and 21.7 ($CH(CH_3)_2$). Anal. Calcd for $C_{55}H_{63}N_3O_{11}$: C, 70.12; H, 6.74; N, 4.46. Found: C, 70.30; H, 6.93; N, 4.78.

N-(Benzyloxycarbonyl)-O-(3,4,6-tri-O-acetyl-2-acetamido-2-deoxy-α-D-galactopyranosyl)serylalanylalanine Allyl Ester (25): Yield 61%; $[\alpha]^{22}_D$ 66.3 ° (c = 0.82, $CHCl_3$); 400-MHz ^1H NMR ($CDCl_3$) δ 7.26 (m, 6 H, phenyl and NH), 7.21 (d, J = 7.4 Hz, 1 H, NH), 7.09 (d, $J_{NH/H2}$ = 9 Hz, 1 H, NHAc), 6.21 (d, J = 7.4 Hz, 1 H, NH), 5.86–5.76 (m, 1 H, CH=CH_2), 5.31 (d, $J_{3/4}$ = 3.3 Hz, H1, H4), 5.24 (dd, 1 H, J_{trans} = 17.2 Hz, J_{gem} = 1.3 Hz, 1 H, CH=CH_2 (trans)), 5.18 (dd, J_{cis} = 10 Hz, J_{gem} = 1.3 Hz, 1 H, CH=CH_2 (cis)), 5.06–5.0 (m, 3 H, CH_2Ph and H3), 4.92 (d, $J_{1,2}$ = 3.8 Hz, 1 H, H1), 4.58–4.39 (m, 6 H, OCH_2CH=CH_2, α-CH-Ser, H2 and 2 α-CH-Ala), 4.12–3.94 (m, 3 H, $H6_a$, $H6_b$ and β-CH_a-Ser), 3.81 (dd, $J_{\beta\text{-}CH_b/\beta\text{-}CH_a}$ = 10 Hz, β-CH_b-Ser), 3.66 (dd, 1 H, H5), 2.08 (s, 3 H, CH_3CONH), 1.95, 1.93, 1.92 (3 s, 9 H, CH_3CO), 1.4–1.3 (m, 6 H, 2 CH_3-Ala). Anal. Calcd for $C_{34}H_{46}N_4O_{15}$: C, 54.39; H, 6.18; N, 7.46. Found: C, 54.30; H, 6.23; N, 7.45.

N-(Benzyloxycarbonyl)-O-(3,4,6-tri-O-acetyl-2-acetamido-2-deoxy-α-D-galactopyranosyl)serylvalylglycylalanine Allyl Ester (27): yield 64%; $[\alpha]^{22}_D$ 60.3° (c = 1, $CHCl_3$); IR (neat) ν 1750–1730 (C=O, ester); 22.63-MHz ^{13}C NMR ($CDCl_3$) δ 172.2–168.3 (C=O), 155.8 (C=O, urethane), 136.2 (ipso-C), 131.4 (CH=CH_2), 128.4–128 (phenyl), 118.6 (CH=CH_2), 98.5 (C1), 62 (C6), 53.8 (α-CH-Ser), 47.3 (C2), 42.7 (CH_2Gly), 31.8 (β-CH Val), 22.8 (CH_3CONH), 20.8–20.5 (CH_3COO), 19.0 (CH_3-Ala), 18.2 and 18.0 ($CH(CH_3)_2$). Anal. Calcd for $C_{38}H_{53}N_5O_{16} \cdot 1.5H_2O$: C, 52.89; H, 6.54; N, 8.10. Found: C, 52.82; H, 6.40; N, 8.07.

N-(Benzyloxycarbonyl)-O-(3,4,6-tri-O-acetyl-2-acetamido-2-deoxy-α-D-galactopyranosyl)threonyl-N⁴-(3,4,6-tri-O-acetyl-2-acetamido-2-deoxy-β-D-glucopyranosyl)asparagine Allyl Ester (29): yield 50%; $[\alpha]^{22}_D$ 63° (c = 0.9, $CHCl_3$); 400-MHz ^1H NMR ($CDCl_3$) δ 7.76 (d, J = 8.7 Hz, 1 H, NH), 7.53 (d, J = 9 Hz, 1 H, NH), 7.34 (m, 5 H, phenyl), 6.93 (d, J = 10 Hz, 1 H, NH), 6.49 (d, J = 8.7 Hz, 1 H, NH), 5.9–5.76 (m, 2 H, NH, CH=CH_2), 5.32 (d, 1 H, H4′) 5.28 dd, 1 H, CH=CH_2 (trans)), 5.22 (dd, 1 H, CH=CH_2 (cis)), 5.15–4.98 (m, 6 H, H1, H1′, H3, H3′, CH_2Ph), 4.88–4.82 (m, 1 H, H4) 4.68–4.5 (m, 3 H, OCH_2CH=CH_2, CH-Thr), 4.4 (dd, 1 H, H2′), 4.3–3.98 (m, 8 H, H5′, $H6'_{a,b}$, β-CH-Thr, H2, $H6_{a,b}$, CH-Asn), 3.62 (m, 1 H, H5) 2.85 (dd, 1 H, β-CH_aCOO), 1.93, 1.88 (2 s, 6 H, 2 CH_3CONH) 1.24 (d, J = 6.4 Hz, 3 H, CH_3-Thr); 100.6-MHz ^{13}C NMR (CD_3OD) δ 173.7–171.2 (C=O), 158.8 (C=O, urethane), 138 (ipso-C), 133.2 (CH=CH_2), 129.5–129 (phenyl), 119.1 (CH=CH_2), 100.8 (C1′), 79.6 (C1), 67.9, 67.3 (C6 and CH_2Ph), 63.4, 6.3 (C6′ and CH_2CH=CH_2), 60 (α-CH-Thr), 54 (C4), 50.3 (α-CH-Asn), 48.8 (C2′), 38 (β-CH-Asn), 23, 22.9 (2 CH_3CONH), 20.7–20.5 (CH_3COO), 18.9 (CH_3Thr); FAB-mass spectrum, m/e_{calcd} 1066, m/e_{found} 1067 (M + H). Anal. Calcd for $C_{47}H_{63}N_5O_{23} \cdot 2H_2O$: C, 51.22; H, 6.13; N, 6.35. Found: C, 51.13; H, 6.10; N, 6.40.

Carboxy-Deblocked Glycotripeptides 30 and 31. As described for the glycosides **8a**, **15**, and **16**, the following selectivity deprotected glycopeptides were obtained.

N-(Benzyloxycarbonyl)-O-(2,3,4-tri-O-benzyl-β-D-xylopyranosyl)serylalanylalanine (30): obtained in pure form by recrystallization from methylene chloride/ether/petroleum ether: yield 97%; mp 196–198 °C; $[\alpha]^{22}_D$ −7.3 °C (c = 0.2, dimethylformamide); IR (KBr) ν 1720 (COOH), 1680 (urethane), 1650 (amide); 90-MHz ^1H NMR (DMSO-d_6) δ 7.65 (d, J = 6.2 Hz, 1 H, NH)), 7.42 (d, J = 7.1 Hz, 1 H, NH), 7.3–7.2 (m, 20 H, phenyl), 6.33 (d, J = 7 Hz, 1 H, NH urethane), 5.1 (s, 2 H, $PhCH_2OCO$), 1.38 (d, J = 2.4 Hz, 3 H, CH_3), 1.30 (d, J = 2.4 Hz, 3 H, CH_3); field-desorption mass spectrum, m/e_{calcd} 783, m/e_{found} 783 (M^+). Anal. Calcd for $C_{43}H_{49}N_3O_{11} \cdot 0.5H_2O$: C, 65.14; H, 6.35; N, 5.30. Found: C, 64.93; H, 6.00; N, 5.59.

N-(Benzyloxycarbonyl)-O-(3,4,6-tri-O-acetyl-2-deoxy-2-acetamido-α-D-galactopyranosyl)serylalanylalanine (31): yield 43%; $[\alpha]^{22}_D$ 88.7° (c = 1, $CHCl_3$); 400-MHz ^1H NMR ($CDCl_3$) δ 7.78 (broad, 1 H, NH), 7.47 (broad, 1 H, NH), 7.32 (m, 5 H, phenyl), 6.13 (broad, 1 H, NH), 5.3 (d, 1 H, H4), 5.12–5.05 (m, 3 H, H3 and CH_2-phenyl), 4.92 (d, $J_{1/2}$ = 3 Hz, 1 H, H1), 4.58–4.4 (m, 4 H, α-CH-Ser, H2, CH-Ala), 4.15–3.95 (m, 5 H, β-CH_2-Ser, $H6_{a,b}$, H5), 2.11–1.93 (12 H, CH_3CO), 1.37–1.26 (m, 6 H, CH_3-Ala).

N-(Benzyloxycarbonyl)-O-(2,3,4-tri-O-benzyl-β-D-xylopyranosyl)serylalanylalanylglycylalanine Allyl Ester (33): 0.35 g (0.44 mmol) of acid **30**, 0.12 g (0.44 mmol) of glycylalanine allyl ester hydrobromide **32** and 0.06 mL of triethylamine were dissolved in 10 mL of dimethylformamide; 0.22 g (0.9 mmol) of EEDQ were added, and the mixture was stirred for 5 days at ambient temperature. Water (5 mL) was added, and after 1 h the solvent was removed under reduced pressure. The remaining residue was taken up in 20 mL of chloroform and extracted three times with 10 mL of 2 N HCl, 2 N $NaHCO_3$ solution, and water. The organic layer was dried over $MgSO_4$ and evaporated to dryness. Recrystallization from acetone/petroleum ether yielded 0.26 g (61%) of the product: mp 163–164 °C; $[\alpha]^{22}_D$ −24.2° (c = 0.5, $CHCl_3$); IR (KBr) ν 1740 (C=O, ester), 1700 (C=O, urethane), 1640 (amide); 20.16-MHz ^{13}C NMR (DMSO-d_6) δ 172.3–168.5 (C=O), 155.9 (C=O, urethane), 132.2 (CH=CH_2), 128.2–127.2 (phenyl), 117.6 (CH=CH_2), 102.9 (C1), 54.9 (α-CH-Ser), 48.1, 47.8, and 47.6 (3 α-CH-Ala), 41.6 (α-CH_2-Gly), 18.0, 17.7, and 16.9 (3 β-CH_3-Ala); GATED-decoupled 20.16-MHz ^{13}C NMR (DMSO-d_6)

$J_{C1/H1}$ = 163 Hz; field desorption mass spectrum, m/e_{calcd} 952, m/e_{found} 952 (M^+). Anal. Calcd for $C_{51}H_{61}N_5O_{13}\cdot 0.5H_2O$: C, 63.14; H, 6.54; N, 7.22. Found: C, 63.21; H, 6.34; N, 7.26.

Registry No. **1**, 1145-80-8; **2**, 106-95-6; **3**, 88295-41-4; **4**, 88224-11-7; **5**, 117710-12-0; α-**6**, 20787-16-0; β-**6**, 77943-32-9; **7**, 83441-63-8; **8a**, 88287-93-8; **8b**, 88287-92-7; **9**, 67817-37-2; **10a**, 118417-95-1; **10b**, 118417-98-4; **11a**, 118417-76-8; **11b**, 118490-32-7; **12**, 672-66-2; **13**, 118398-50-8; **14**, 118417-77-9; **15**, 118417-96-2; **16**, 118417-78-0; **17**, 88287-94-9; **18**, 118398-51-9; **19**, 118417-79-1; **20**, 88287-95-0; **21**, 88287-96-1; **22**, 88224-21-9; **23**, 118398-52-0; **24**, 118398-53-1; **25**, 118398-54-2; **26**, 118398-55-3; **27**, 118417-97-3; **28**, 118398-56-4; **29**, 118398-57-5; **30**, 88287-97-2; **31**, 118398-58-6; **32**, 88287-99-4; **33**, 118398-59-7.

S_NAr, S_N2, and Aromatic Addition Processes in the Reactions of Picryl Ethers with Nitrogen and Carbon Bases

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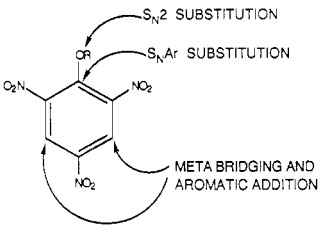
Received June 20, 1988

The reactions of methyl, cyclohexyl, and phenyl picryl ethers with diethyl- and triethylamine in chloroform, acetone, and 1,3-dicarbomethoxyacetone have been studied. A number of different processes were observed, depending on substrate structure. Both amine nitrogen and enolate carbon act as nucleophiles in these reactions. With unhindered picryl ethers like 2,4,6-trinitroanisole, dealkylation often occurs via S_N2 attack on the methyl group. With more hindered picryl ethers, addition to the ring is more common, resulting in covalent σ complexes, substituted picramides, or bicyclo [3.3.1] nitropropenenitronates. In this paper, structural features that influence reaction path are discussed.

Introduction

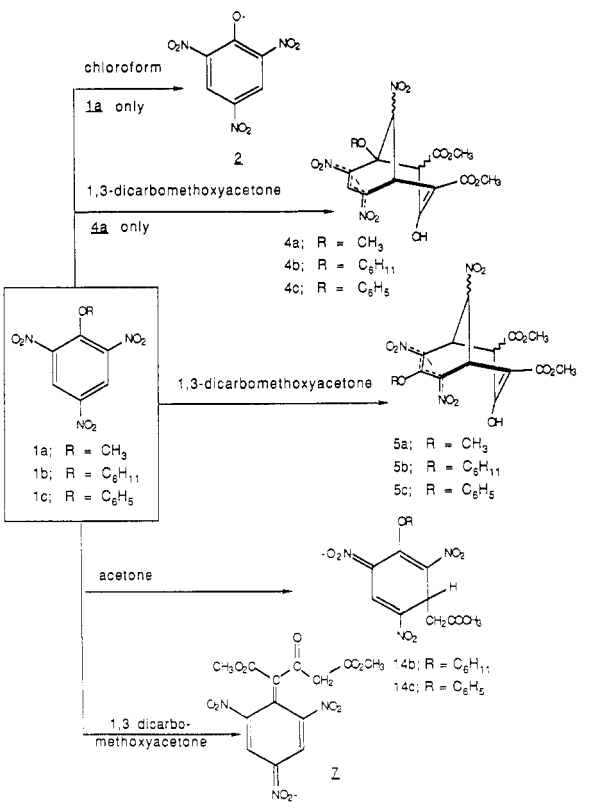
While there has been much interest in the reactions of picryl ethers and related compounds with oxygen nucleophiles,[1-4] the behavior of these aromatics with carbon and nitrogen nucleophiles has been less well studied. Because of the multiplicity of reaction sites in compounds like 2,4,6-trinitroanisole (TNA), **1a**, we were prompted to more fully characterize the alternative substitution and addition processes that this compound and similar picryl ethers can undergo.



Different substitution and addition reactions occur with different aromatic substrates $(O_2N)_3C_6H_2OR$ (R = CH_3, C_6H_{11}, C_6H_5) and nucleophiles (enolate or amine). Analysis of the results provides a clearer picture of the processes that occur with this interesting type of electron-deficient aromatic. A summary of possible products is shown in Schemes I and II. These are formed from secondary and tertiary amines in ketonic and nonketonic solvents. With tertiary amines dealkylation often occurs in nonacidic solvents, whereas in acidic solvents proton abstraction is sometimes followed by lyate attack on the aromatic substrate.

The reactions of picryl ethers in solution of amines and carbon acids are complex.[4-6] It is therefore important to understand the behavior of these aromatic substrates with amines in nonketonic solvents. Early work by Servis[5] and Clapp[6] on the reactions of TNA and other more hindered picryl ethers with primary amines is particularly important in this regard. With 2,4,6-trimethylphenyl picryl ether

Scheme I. Reactions of Picryl Ethers with NEt_3



(1) Strauss, M. J. *Chem. Rev.* **1970**, *70*, 667.
(2) Bernasconi, C. F. *J. Am. Chem. Soc.* **1971**, *93*, 6975.
(3) Crampton, M. R. *Adv. Phys. Org. Chem.* **1969**, *7*, 211.
(4) Fendler, J. H.; Fendler, E. J.; Griffen, C. E. *J. Org. Chem.* **1969**, *34*, 689.
(5) Servis, K. L. *J. Am. Chem. Soc.* **1967**, *89*, 1508.
(6) Clapp, L. B.; Lacey, H.; Beckwith, G. G.; Srivastava, R. M.; Muhammed, N. *J. Org. Chem.* **1968**, *33*, 4262.

0022-3263/89/1954-0756$01.50/0