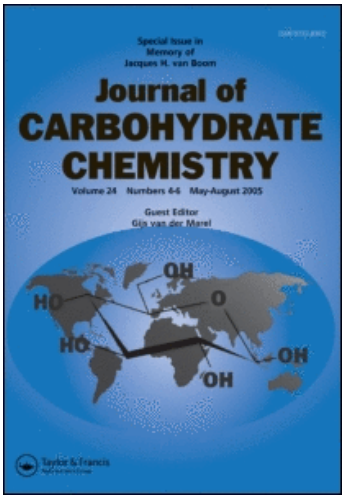

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STEREOSELECTIVE GLYCOSIDIC COUPLING REACTIONS OF FULLY BENZYLATED 1,2-ANHYDRO SUGARS WITH *N*-TOSYL- OR *N*-BENZYLOXYCARBONYL-L-SERINE METHYL ESTER

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ABSTRACT

The glycosidic coupling reaction of 1,2-anhydro-3,4,6-tri-*O*-benzyl-β-D-mannopyranose (**7**), 1,2-anhydro-3,4,6-tri-*O*-benzyl-α-D-galactopyranose (**21**), and 1,2-anhydro-3,4-di-*O*-benzyl-α-D-xylopyranose (**18**) with *N*-tosyl- (**10**) or *N*-benzyloxycarbonyl- (**11**) L-serine methyl ester provides a new stereocontrolled synthesis of 1,2-trans linked glycopeptides. The 1,2-anhydro sugars are shown to react smoothly with **10** or **11** in the presence of Lewis acid ($ZnCl_2$ or AgOTf) as well as powdered 4A molecular sieves in CH_2Cl_2 at room temperature to afford glycosyl serine derivatives with high stereoselectivity and high yield in less than 30 min. An improved method using 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl chloride (**6**) as the key intermediate for ring closure was applied for the synthesis of 1,2-anhydro-3,4,6-tri-*O*-benzyl-β-D-mannopyranose.

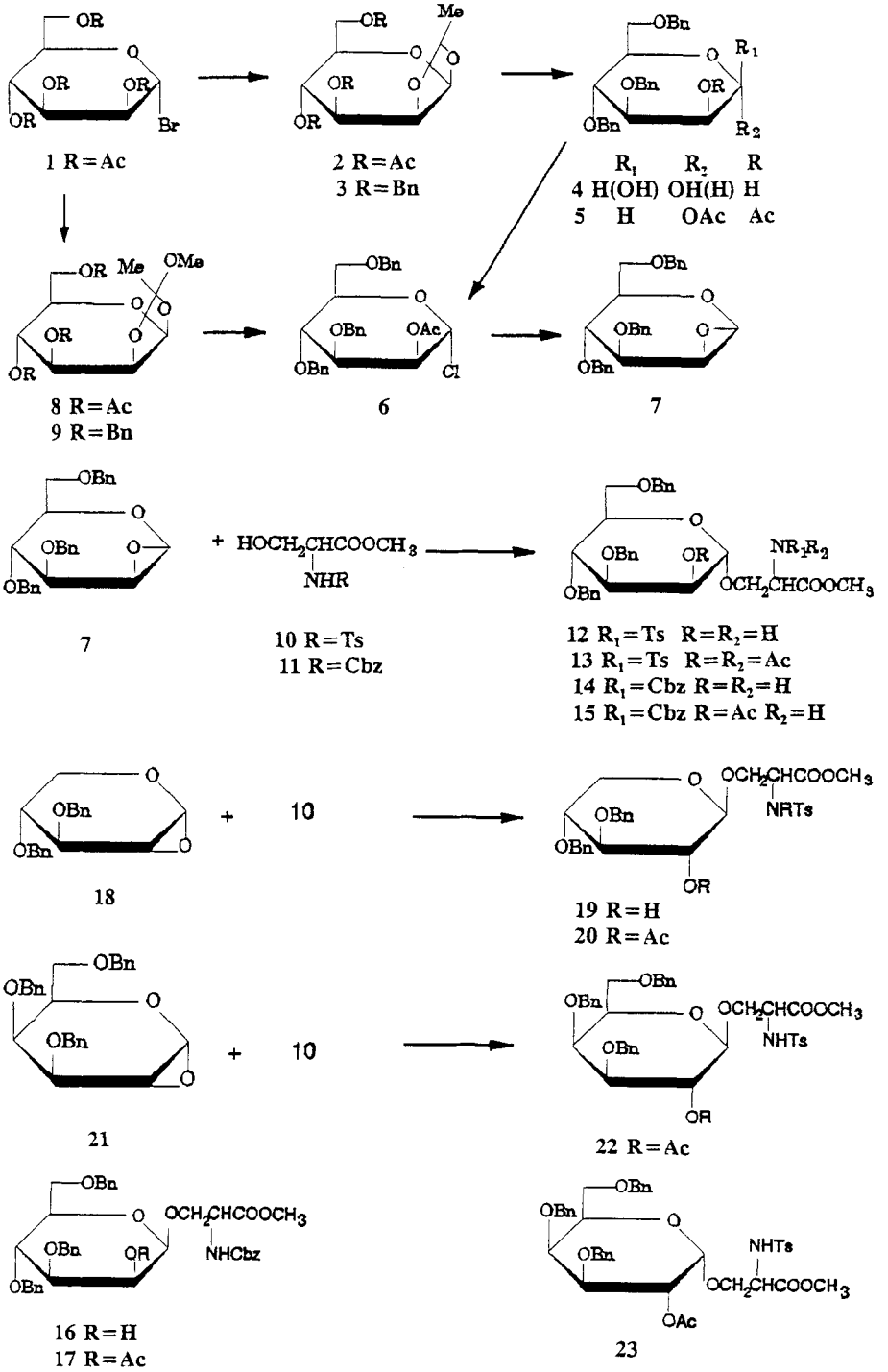
INTRODUCTION

Glycopeptides are fragments of the carbohydrate-protein linkage region in various proteoglycans which serve a variety of functions as antibodies, enzymes, hormones, toxins, and transport proteins. Synthetic glycopeptides may serve as standard compounds in the study of the base-catalyzed β-elimination of carbohydrate residues of the mucin-type glycoproteins and of proteoglycans.[1] A variety of methods are available for

glycosylation of L-serine or L-threonine derivatives[2] such as condensation of the amino acid derivatives with (2,1-d)-oxazolines,[3] with alkyl orthoacetates,[4] with glycosyl halides,[5] and with glycosyl imidate,[6] etc. 1,2-Anhydro sugar derivatives have been proved to be very good glycosyl donors for oligosaccharide and other glycoside syntheses[7-15] giving excellent yield and stereoselectivity. However, to the best of our knowledge, so far there has been no report on the synthesis of a glycopeptide using 1,2-anhydro sugar derivatives as the glycosyl donors. Here we report the synthesis of a series of O-linked L-serine glycopyranoside derivatives from 1,2-anhydromanno-, galacto-, and xylopyranose benzyl ethers.

RESULTS AND DISCUSSION

The fully benzylated 1,2-anhydro-D-xylo- (**18**)[10] and -D-galactopyranose (**21**)[16] were prepared according to the reported methods while 1,2-anhydro-3,4,6-tri-*O*-benzyl-β-D-mannopyranose (**7**) was prepared by improved method. Thus 3,4,6-tri-*O*-acetyl-1,2-*O*-[(*R,S*)-ethylidene]-β-D-mannopyranose (**2**, *S* isomer predominant) was prepared from D-mannose via the intermediate 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl bromide (**1**) by a reported method.[17] Benzylation of **2** with potassium hydroxide and benzyl chloride in boiling toluene yielded 3,4,6-tri-*O*-benzyl-1,2-*O*-[*S*-ethylidene]-β-D-mannopyranose (**3**). Hydrolysis of **3** with sulfuric acid in 1,4-dioxane afforded 3,4,6-tri-*O*-benzyl-D-mannopyranose (**4**) as crystals, and subsequent acetylation of **4** with acetic anhydride in pyridine furnished the diacetate **5**. Chlorination of **5** with hydrogen chloride in diethyl ether gave 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl chloride (**6**) in almost quantitative yield. Compound **6** was quite a stable compound being capable of long term storage in a refrigerator, and it gave physical data the same as those for **6** prepared by chlorinationof3,4,6-tri-*O*-benzyl-1,2-*O*-methoxyethylidene-β-D-mannopyranose(**9**)[18]with chlorotrimethylsilane.[19] Ring closure of **6** with potassium *tert*-butoxide in boiling oxolane almost quantitatively afforded crystalline 1,2-anhydro-3,4,6-tri-*O*-benzyl-β-D-mannopyranose (**7**) in 30 min, which was characterized by ^{1}H NMR spectroscopy. Compared to the previously reported method[20] using unstable 3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl chloride for the preparation of anhydro sugar **7**, the improved method showed some advantages because of the easy preparation, good stability, and high



reactivity of the key intermediate, 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl chloride.

Synthesis of the methyl ester of *O*-(3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)-*N*-tosyl- (**12**) or -*N*-benzyloxycarbonyl-L-serine (**14**) was best achieved in excellent yield (about 90%) with an α:β ratio of 7:1 by treating the 1,2-anhydro-3,4,6-tri-*O*-benzyl-β-D-mannopyranose (**7**) with *N*-tosyl-L-serine methyl ester (**10**) or *N*-benzyloxycarbonyl-L-serine methyl ester (**11**) in dry CH_2Cl_2 in the presence of freshly fused $ZnCl_2$ and powdered 4A molecular sieves. The use of the nonpolar solvent benzene or much more polar solvent oxolane tended to decrease the yield but also decreased the stereoselectivity. $ZnCl_2$ and AgOTf seemed to be more effective than $BF_3 \cdot Et_2O$ as catalysts for the reaction. The yield and stereoselectivity did not change as the reaction temperature (-10-25 °C) and time (5 min-24 h) were varied over a wide range. Addition of molecular sieves as a moisture scavenger helped to increase overall reaction yield. The order of addition of the reagents was found to influence the results seriously. Addition of the anhydro sugar **7** to a well stirred solution of **10** or **11** containing molecular sieves was appropriate while inverse addition of **10** or **11** to a solution of **7** caused a decrease in yield. The synthesis of the corresponding xylopyranosyl L-serine derivative was even more successful because of the higher reactivity of 1,2-anhydro-3,4-di-*O*-benzyl-α-D-xylopyranose (**18**). Treatment of *N*-tosyl-L-serine methyl ester (**10**) with **18** in the presence of $ZnCl_2$ in dry CH_2Cl_2 under N_2 protection gave *O*-(3,4-di-*O*-benzyl-β-D-xylopyranosyl)-*N*-tosyl-L-serine methyl ester (**19**) in almost quantitative yield. No α isomer was detected by ^1H NMR. TLC showed that the reaction was complete within 5 min. Protection of the reaction system with N_2 is necessary because the 1,2-anhydroxylopyranose benzyl ether is very active in the presence of Lewis acid. It was interesting to note that the coupling reaction of **18** with 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose in dry oxolane proceeded quantitatively in the presence of 4A molecular sieves without any other catalysts,[10] while an attempt under a similar conditions to condense **18** with *N*-tosyl-L-serine methyl ester (**10**) was unsuccessful. It seemed that the free hydroxyl group in 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose was more active than that in *N*-tosyl-L-serine methyl ester. It was also noted that the condensation of **18** with **10** afforded β-glycoside as the sole product while the condensation of **18** with

TABLE. The Influences of Solvent, Catalyst on the Glycosidic Coupling Reaction

compound	solvent	catalyst	time	α:β ratio	yield %[a]
18 + 10	CH_2Cl_2	$ZnCl_2$	5 min	0 : 1	95.9
21 + 10	CH_2Cl_2	AgOTf	20 min	1 : 10	93
7 + 10	CH_2Cl_2	$ZnCl_2$	30 min	7 : 1	92
	CH_2Cl_2	AgOTf	30 min	6.8:1	90
	CH_2Cl_2	$BF_3 \cdot Et_2O$	1 h	3 : 1	75
7 + 10	THF	$ZnCl_2$	45 min	3.5:1[b]	70
	THF	$BF_3 \cdot Et_2O$	3 h[c]	2.5:1[b]	60
7 + 10	Benzene	$ZnCl_2$	8 h	1.5:1[b]	40
	Benzene	$BF_3 \cdot Et_2O$	24 h	1.5:1[b]	45

a. Total isolated yields.
b. Ratios were determined by HPLC.
c. The solvent was polymerized when the reaction time was too long.

1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose gave an α:β mixture (2.7:1).[10] In the synthesis of *O*-(2-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl)-*N*-tosyl-L-serine methyl ester (**22**), AgOTf was chosen as the catalyst, no N_2 protection was needed. Treatment of *N*-tosyl-L-serine methyl ester (**10**) in a dark room with 1,2-anhydro sugar **21**[16] in the presence of AgOTf and molecular sieves in anhydrous CH_2Cl_2 at room temperature, followed by quenching the reaction with Ac_2O afforded the expected target compound **22** in an excellent yield with a β:α ratio of 10:1.

The per-*O*-benzylated 1,2-anhydro-D-xylo- (**18**) and -D-galactopyranose (**21**) gave better yield and stereoselectivity for the coupling reaction with L-serine derivatives than **7**, perhaps because the bulky serine derivatives preferred the less hindered β side. The glycopyranosyl L-serine derivatives **12, 14, 16, 19,** and **22** were identified from ^1H NMR data and they were, except **22**, further characterized by acetylation with acetic anhydride in pyridine. It was found that *N*-tosylated serine glycosides **12** and **19** were acetylated at both the 2-OH and serine N-H, while *N*-benzyloxycarbonylated serine glycosides **14** and **16** were acetylated only at the 2-OH.

The use of 1,2-anhydro sugars as glycosyl donors for glycopeptides synthesis has advantages due to their high reactivity and excellent stereoselectivity, giving products with a free C-2 OH available for further functionalization or glycosylation of the carbohydrate residue.

EXPERIMENTAL

General Methods. Melting points were determined with a "Mel-Temp" apparatus and are uncorrected. Optical rotations were determined at 20 °C with a Perkin-Elmer model 241-MC automatic polarimeter for solutions in a 1-dm, jacketed cell. ^{1}H NMR spectra were recorded with Varian XL-400 and Varian XL-200 spectrometers, for solutions in $CDCl_3$, with tetramethylsilane (Me_4Si) as internal standard. Chemical shifts were expressed in ppm down field from the Me_4Si absorption. Analytical LC was performed by use of a pump (model YSB-2, made in China), stainless-steel columns packed with silica gel (10 x 150 mm, or 4.6 x 250 mm), a differential refractometer (Perkin-Elmer LC-25 RI Detector), and EtOAc-petroleum ether (bp 60-90 °C) as the eluent at a flow rate of 2-4 mL/min. Thin-layer chromatography (TLC) was performed on silica gel HF, detection being affected by charring with 30% (V/V) sulfuric acid in methanol or sometimes by a UV detector. Column chromatography was conducted by elution of column (10 x 200 mm, 16 x 240 mm, 18 x 300 mm, 35 x 400 mm) of silica gel (100-200 mesh).

3,4,6-Tri-*O*-benzyl-1,2-*O*-[*S*-ethylidene]-β-D-mannopyranose (3). To a solution of 3,4,6-tri-*O*-acetyl-1,2-*O*-[*S*-ethylidene]-β-D-mannopyranose[17] (3.8 g, 11.4 mmol) in toluene (25 mL) was added with vigorous agitation finely powdered potassium hydroxide (10 g, 178 mmol). The mixture was boiled under reflux, and benzyl chloride (11.8 mL, 102.6 mmol) was added dropwise within 10 min. The reaction was carried out under reflux and vigorous stirring for 3.5 h, at the end of which time TLC (1:3 EtOAc-petroleum ether) indicated that the reaction was complete. The mixture was diluted with toluene (10 mL), then subjected to steam distillation to remove excess benzyl chloride and the by-product dibenzyl ether. The mixture was extracted with CH_2Cl_2 and the organic layer was concentrated. Purification of the product was effected by column

chromatography with 1:4 EtOAc-petroleum ether as the eluent to give crystalline **3**: mp 69-71 °C; $[\alpha]_D$ +25.6° (*c* 0.6, $CHCl_3$); ^1H NMR δ 7.40-7.22 (m, 15H, Ph), 5.35 (q, 1H, J = 5.0 Hz, CH_3CH), 5.25 (d, 1H, $J_{1,2}$ = 2.5 Hz, H-1), 4.90, 4.61 (2d, 2H, J = 10.7 Hz, CH_2Ph), 4.82, 4.77 (2d, 2H, J = 11.3 Hz, CH_2Ph), 4.63, 4.57 (2d, 2H, J = 11.3 Hz, CH_2Ph), 4.20 (dd, 1H, $J_{1,2}$ = 2.5 Hz, $J_{2,3}$ = 3.1 Hz, H-2), 4.00 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 10.1 Hz, H-4), 3.83 (dd, 1H, $J_{2,3}$ = 3.1 Hz, $J_{3,4}$ = 10.1 Hz, H-3), 3.80 (dd, 1H, $J_{5,6}$ = 5.7 Hz, $J_{6,6'}$ = 11.0 Hz, H-6), 3.70 (dd, 1H, $J_{5,6'}$ = 1.9 Hz, $J_{6,6'}$ = 11.0 Hz, H-6'), 3.48 (m, 1H, $J_{4,5}$ = 10.1 Hz, $J_{5,6}$ = 5.7 Hz, $J_{5,6'}$ 1.9 Hz, H-5), 1.55 (d, 3H, J = 5.0 Hz, CH_3CH).

Anal. Calcd for $C_{29}H_{32}O_6$: C, 73.10; H, 6.72. Found: C, 73.28; H, 6.68.

2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl chloride (6). To a solution of **3** (10 g, 22.2 mmol) in 1,4-dioxane (80 mL) was added 1 M H_2SO_4 (15 mL), and the mixture was boiled under reflux for 5 h. The mixture was cooled, made neutral with solid sodium hydrogencarbonate, and concentrated to dryness. The residue was partitioned between water and CH_2Cl_2, and the organic layer dried over Na_2SO_4 and concentrated to a syrup. Pure **4** (7.68 g, 82%) was obtained as crystals after column chromatographic separation with 1:2 EtOAc-petroleum ether as the eluent: mp 97-98 °C; $[\alpha]_D$ +25° (*c* 2.2, $CHCl_3$); Lit.[21] mp 98-99 °C, $[\alpha]_D$ +22.7° (*c* 1.9, $CHCl_3$).

Compound **4** was acetylated with acetic anhydride in pyridine by the standard method to give **5** in a quantitative yield as a syrup: $[\alpha]_D$ +34.2° (*c* 4.8, $CHCl_3$); ^1H NMR δ 7.38-7.15 (m, 15H, 3Ph), 6.12 (d, 1H, $J_{1,2}$ = 1.8 Hz, H-1), 5.37 (dd, 1H, $J_{1,2}$ = 1.8 Hz, $J_{2,3}$ = 2.2 Hz, H-2), 4.85, 4.49 (2d, 2H, J = 10.8 Hz, CH_2Ph), 4.73, 4.53 (2d, 2H, J = 11.2 Hz, CH_2Ph), 4.68, 4.55 (2d, 2H, J = 12.1 Hz, CH_2Ph), 4.13-3.96 (m, 2H, H-4,5), 3.83-3.79 (m, 2H, $J_{5,6}$ 3.9 Hz, $J_{5,6'}$ = 7.8 Hz, H-6,6'), 3.70 (dd, 1H, $J_{2,3}$ = 2.2 Hz, $J_{3,4}$ = 9.4 Hz, H-3).

Compound **5** (3 g, 5.62 mmol) was dissolved in anhydrous diethyl ether (50 mL), and dry HCl gas was bubbled in under N_2 at 0 °C, to saturation. The solution was kept at room temperature in a sealed bottle for 3 h, and TLC (1:3 EtOAc-petroleum ether) then indicated that the reaction was complete. The solution was concentrated under diminished pressure to a syrup which was dissolved in dry CH_2Cl_2 (10 mL) again.

Powdered 4A molecular sieves was added and the mixture was stirred for 0.5 h at room temperature, then filtered, and concentrated. The syrup was then purified by chromatography on a very short column of silica gel with 1:3 EtOAc-petroleum ether to give pure **6** as a syrup (2.64 g, 91.7%): $[\alpha]_D$ +56° (*c* 5.0, $CHCl_3$); ^1H NMR δ 7.33-7.14 (m, 15H, Ph), 6.06 (d, 1H, $J_{1,2}$ = 2.1 Hz, H-1), 5.45 (dd, $J_{1,2}$ = 2.1 Hz, $J_{2,3}$ = 3.8 Hz, H-2), 4.85, 4.50 (2d, 2H, J = 10.4 Hz, CH_2Ph), 4.70, 4.58 (2d, 2H, J = 11.7 Hz, CH_2Ph), 4.65, 4.48 (2d, 2H, J = 13.0 Hz, CH_2Ph), 4.25 (dd, 1H, $J_{2,3}$ = 3.8, $J_{3,4}$ = 9.8 Hz, H-3), 4.05 (m, 1H, H-5), 3.95 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.8 Hz, H-4), 3.83 (dd, 1H, $J_{5,6}$ = 5.2 Hz, $J_{6,6'}$ = 11.7 Hz, H-6), 3.69 (dd, 1H, $J_{5,6'}$ = 2.5 Hz, $J_{6,6'}$ = 11.7 Hz, H-6'), 2.16 (s, 3H, CH_3CO).

Anal. Calcd for $C_{29}H_{31}ClO_6$: C, 68.17; H, 6.07. Found: C, 67.90; H, 6.15.

Chlorination of **9** with chlorotrimethylsilane[19] also gave **6** in high yield.

1,2-Anhydro-3,4,6-tri-*O*-benzyl-β-D-mannopyranose (7). To a solution of **6** (500 mg, 0.98 mmol) in dry oxolane (12 mL) was added potassium *tert*-butoxide (270 mg, 2.44 mmol) and the mixture was stirred under reflux for 30 min, then cooled and concentrated to dryness under vacuum. The residue was repeatedly extracted with 1:2 EtOAc-petroleum ether, and the completely colourless extracts were combined and concentrated to yield **7** as white crystals (390 mg, 92.3%): mp 88-89 °C; $[\alpha]_D$ +5.7° (*c* 1.1, $CHCl_3$); Lit.[20] mp 89.5-90 °C, $[\alpha]_D$ +4.5° (*c* 1, $CHCl_3$).

***O*-(3,4,6-Tri-*O*-benzyl-α-D-mannopyranosyl)-*N*-benzyloxycarbonyl-L-serine methyl ester (14) and *O*-(3,4,6-Tri-*O*-benzyl-β-D-mannopyranosyl)-*N*-benzyloxycarbonyl-L-serine methyl ester (16).** To a solution of *N*-benzyloxycarbonyl-L-serine methyl ester[22,23] **11** (116 mg, 0.46 mmol) in dry CH_2Cl_2 (12 mL) was added powdered 4A molecular sieves, The mixture was stirred for 5-10 min, freshly fused $ZnCl_2$ (60 mg, 0.6 mmol) was added, the mixture was stirred for another 5-10 min, and then **7** (100 mg, 0.23 mmol) was added. The mixture was kept at room temperature for about 30 min under vigorous stirring. TLC (1:2 EtOAc-petroleum ether) showed that the starting material had completely disappeared. After filtering, the filtrate was washed with water (3 x 25 mL), dried with Na_2SO_4, and then concentrated to a syrup. Purification and separation by analytical LC on silica gel with 1:2 EtOAc-petroleum ether as the eluent furnished pure **14** and **16** as colourless syrups in a ratio of 5:1 with a total yield of 86%: For **14**, $[\alpha]_D$

+19.1° (*c* 1.9, $CHCl_3$); ^1H NMR δ 7.45-7.10 (m, 20H, 4Ph), 5.76 (d, 1H, J = 7.8 Hz, N-*H*), 5.13 (s, 2H, PhCH_2OCO), 4.84 (d, 1H, $J_{1,2}$ = 1.2 Hz, H-1), 4.80-4.40 (m, 6H, 3CH_2Ph), 3.78 (s, 3H, OCH_3), 2.20 (bs, 1H, O*H*).

Compound **14** was acetylated with acetic anhydride in pyridine by the standard method and pure **15** was obtained after working up the reaction mixture: $[\alpha]_D$ +32.4° (*c* 0.9, $CHCl_3$); ^1H NMR δ 7.34-7.13 (m, 20H, 4Ph), 5.75 (d, 1H, J = 8.9 Hz, N-*H*), 5.26 (bs, 1H, H-2), 5.12, 5.09 (2d, J = 10.5 Hz, PhCH_2OCO), 4.82, 4.55 (2d, 2H, J = 12.2 Hz, CH_2Ph), 4.80 (s, 1H, H-1), 4.70-4.40 (m, 5H, $CHCH_2$ and 2CH_2Ph), 3.98-3.95 (2dd, ^2J = 11.1 Hz, $J_{CH,CH}$ = 2.5, 5.7 Hz, $CHCH_2$), 3.88-3.87 (m, 2H, H-3,5), 3.78 (s, 3H, OCH_3), 3.74-3.60 (m, 3H, H-4,6,6'), 2.15 (s, 3H, CH_3CO).

Anal. Calcd for $C_{41}H_{45}NO_{11}\cdot H_2O$: C, 66.04, H, 6.31; Found: C, 66.15, H, 6.28.

Acetylation of **16** gave **17** as a syrup: ^1H NMR δ 7.40-7.10 (m, 20H, 4Ph), 5.70 (d, 1H, J = 8.3 Hz, N-*H*), 5.56 (d, 1H, $J_{2,3}$ = 2.4 Hz, H-2), 5.14, 5.11 (2d, J = 11.8 Hz, PhCH_2OCO), 4.90-4.40 (m, 8H, J = 11.7, 11.2, 10.5 Hz, 3CH_2PH; H-1, $J_{NH,CH}$ = 8.3 Hz, $CHCH_2$), 4.25, 3.85 (2dd, 2H, ^2J = 10 Hz, $J_{CH,CH}$ = 3.1, 4.8 Hz, CH_2CH), 3.78-3.40 (m, 5H, H-3,4,5,6,6'), 3.70 (s, 3H, OCH_3), 2.15 (s, 3H, CH_3CO).

***O*-(3,4,6-Tri-*O*-benzyl-α-D-mannopyranosyl)-*N*-tosyl-L-serine methyl ester (12).** A solution of *N*-tosyl-L-serine methyl ester[24,25] **10** (60 mg , 0.26 mmol) in dry CH_2Cl_2 (12 mL) was stirred together with powdered 4A molecular sieves for 5-10 min, then freshly fused $ZnCl_2$ (25 mg, 0.25 mmol) and **7** (100 mg, 0.23 mmol) were added. The mixture was kept at room temperature for about 30 min under vigorous stirring. TLC (1:2 EtOAc-petroleum ether) showed that the starting material had completely disappeared. After filtering, the filtrate was washed with water (3 x 25 mL), dried with Na_2SO_4, and then concentrated to a syrup. The syrup was purified by analytical LC on silica gel with 1:2 EtOAc-petroleum ether as the eluent and pure **12** was obtained as a colourless syrup (132 mg, 81%) together with a syrupy β isomer as the minor product (17.9 mg, 11%): For **12**, ^1H NMR δ 7.70 (d, 2H, TsPh), 7.40-7.10 (m, 17H, 3Ph, TsPh), 5.75 (d, 1H, $J_{NH,CH}$ = 9.0 Hz, N-*H*), 4.80-4.40 (m, 8H, 3CH_2Ph; $J_{1,2}$ = 1.7 Hz, H-1; $J_{NH,CH}$ = 9.0 Hz, $CHCH_2$), 3.55 (s, 3H, OCH_3), 2.37 (s, 3H, CH_3 of Ts), 2.30 (bs, 1H, O*H*). For β isomer, ^1H NMR δ 7.78 (d, 2H, TsPh), 7.40-7.10 (m, 17H, 3Ph, TsPh), 5.85 (d, 1H, $J_{NH,CH}$ = 7.6 Hz, N-*H*), 4.90-4.46 (m, 7H, 3CH_2Ph, $CHCH_2$), 4.35 (s, 1H, H-1), 3.58 (s, 3H, OCH_3), 2.39 (s, 3H, CH_3 of Ts).

Acetylation of **12** afforded **13** as a syrup: $[\alpha]_D$ -1.9° (*c* 1.4, $CHCl_3$); ^1H NMR δ 7.96 (d, 2H, TsPh), 7.45-7.10 (m, 17H, 3Ph, TsPh), 5.48 (dd, 1H, $J_{1,2}$ = 2.0 Hz, $J_{2,3}$ = 3.2 Hz, H-2), 5.28 (dd, 1H, $J_{CH,CH}$ = 5.1, 8.9 Hz, C*H*CH_2), 4.82 (d, 1H, $J_{1,2}$ = 2.0 Hz, H-1), 4.84, 4.46 (2d, 2H, J = 10.7 Hz, C*H*$_2$Ph), 4.72, 4.54 (2d, 2H, J = 11.2 Hz, C*H*$_2$Ph), 4.70, 4.52 (2d, 2H, J = 12.0 Hz, C*H*$_2$Ph), 4.40 (m, 2H, J = 4.90, 10.0 Hz, CHC*H*$_2$), 4.18-4.08 (m, 1H, $J_{2,3}$ = 3.2 Hz, $J_{3,4}$ = 8.5 Hz, H-3), 3.96-3.76 (m, 4H, H-4,5,6,6'), 3.72 (s, 3H, OC*H*$_3$), 2.45 (s, 3H, C*H*$_3$ of Ts), 2.12 (s, 3H, N-C*H*$_3$CO), 2.08 (s, 3H, C*H*$_3$CO).

Anal. Calcd for $C_{42}H_{47}NO_{12}S$: C, 63.88, H, 5.96; Found: C, 64.03; H, 6.09.

***O*-(3,4-Di-*O*-benzyl-β-D-xylopyranosyl)-*N*-tosyl-L-serine methyl ester (19).** *N*-tosyl-L-serine methyl ester **10** (90 mg, 0.4 mmol) was dissolved in dry CH_2Cl_2 (20 mL) in the presence of powdered 4A molecular sieves and the mixture was stirred for 10 min. Freshly fused $ZnCl_2$ (30 mg, 0.3 mmol) and 1,2-anhydro-3,4-di-*O*-benzyl-α-D-xylopyranose **9** (100 mg, 0.32 mmol) were then consecutively added with vigorous stirring under N_2. Ten minutes later the reaction mixture was filtered and the filtrate was washed with water (3 x 25 mL), dried with Na_2SO_4, then concentrated to dryness. The crude product was purified by analytical LC on silica gel with 1:2 EtOAc-petroleum ether as the eluent. Pure **19** was obtained almost quantitatively as a colourless syrup (165 mg, 95.9%): ^1H NMR δ 7.75 (d, 2H, J = 8.5 Hz, TsPh), 7.50-7.10 (m, 12H, 2Ph, TsPh), 5.95 (d, 1H, J = 8.4 Hz, N*H*), 4.90, 4.69 (2d, 2H, J = 11.3 Hz, C*H*$_2$Ph), 4.71, 4.68 (2d, 2H, J = 11.7 Hz, C*H*$_2$Ph), 4.30 (d, 1H, $J_{1,2}$ = 6.6 Hz, H-1), 4.15 (m, 1H, $J_{CH,CH}$ = 3.6, 2.9 Hz, C*H*CH_2), 3.90, 3.70 (2dd, 2H, $J_{CH,CH}$ = 3.6, 2.9 Hz, ^2J = 10.7 Hz, CHC*H*$_2$), 3.60-3.50 (m, 2H, H-2,4), 3.53 (s, 3H, OC*H*$_3$), 3.50-3.40 (m, 2H, H-5,5'), 3.25 (dd, $J_{2,3}$ = 8.0 Hz, $J_{3,4}$ = 10.3 Hz, H-3), 2.45 (s, 3H, C*H*$_3$ of Ts), 2.40 (bs, 1H, O*H*).

Acetylation of **19** gave **20** as a syrup: $[\alpha]_D$ -35.4° (*c* 2.5, $CHCl_3$); ^1H NMR δ 7.95 (d, J = 9.4 Hz, TsPh), 7.45-7.25 (m, 12H, 2Ph, TsPh), 5.28 (dd, $J_{CH,CH}$ = 4.7, 7.6 Hz, C*H*CH_2), 4.91 (t, 1H, $J_{1,2}$ = $J_{2,3}$ = 7.5 Hz, H-2), 4.84, 4.61 (2d, 2H, J = 11.3 Hz, C*H*$_2$Ph), 4.72, 4.68 (2d, 2H, J = 11.7 Hz, C*H*$_2$Ph), 4.44 (d, 1H, $J_{1,2}$ = 7.5 Hz, H-1), 4.32, 4.28 (2dd, 2H, $J_{CH,CH}$ = 4.7, 7.6 Hz, ^2J = 11.3 Hz, CHC*H*$_2$), 3.92 (dd, 1H, $J_{3,4}$ = 11.7 Hz, $J_{4,5}$ = 4.5 Hz, H-4), 3.75 (s, 3H, OC*H*$_3$), 3.62 (m, 2H, $J_{4,5}$ = 4.5 Hz, $J_{5,5'}$

= 8.0 Hz, H-5, H-5'), 3.25 (m, 1H, $J_{2,3}$ = 7.5 Hz, $J_{3,4}$ = 11.7 Hz, H-3), 2.46 (s, 3H, CH_3 of Ts), 2.23 (s, 3H, N-CH_3CO), 1.99 (s, 3H, CH_3CO).

Anal. Calcd for $C_{34}H_{39}NO_{11}S$: C, 60.99, H, 5.83; Found: C, 61.25, H, 5.70.

***O*-(2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl)-*N*-tosyl-L-serine methyl ester (22).** A mixture of *N*-tosyl-L-serine methyl ester **10** (100 mg, 0.44 mmol) and powdered 4A molecular sieves in dry CH_2Cl_2 was stirred vigorously for 10 min, then 1,2-anhydro-3,4,6-tri-*O*-benzyl-α-D-galactopyranose[16] (150 mg, 0.35 mmol) and AgOTf (90 mg, 0.35 mmol) were added simultaneously. The mixture was kept in a dark room with agitation for 20 min at room temperature, then Ac_2O (1.0 mL) was added. The mixture was allowed to stand at room temperature overnight, then filtered to remove the solid material, and the filtrate was washed with water (3 x 30 mL), dried with Na_2SO_4, then concentrated to a syrup. Purification by analytical LC (1:2 EtOAc-petroleum ether) yielded syrupy **22** (219 mg, 84.5%) and **23** (21.9 mg, 8.5%): For **22**, $[\alpha]_D$ +4.3° (*c* 2.4, $CHCl_3$); ^{1}H NMR δ 7.68, 7.20 (2d, 4H, J = 8.1 Hz, TsPh), 7.37-7.26 (m, 15H, 3Ph), 5.56 (d, 1H, J = 7.5 Hz, N*H*), 5.24 (dd, 1H, $J_{1,2}$ = 7.9 Hz, $J_{2,3}$ = 10.0 Hz, H-2), 4.90, 4.57 (2d, 2H, J = 11.4 Hz, CH_2Ph), 4.66, 4.52 (2d, 2H, J = 12.4 Hz, CH_2Ph), 4.48, 4.42 (2d, 2H, J = 11.7 Hz, CH_2Ph), 4.34 (d, 1H, $J_{1,2}$ = 7.9 Hz, H-1), 4.06 (dd, 1H, $J_{2,3}$ = 10.0 Hz, $J_{3,4}$ = 3.8 Hz, H-3), 3.95-3.85 (m, 2H, $J_{NH,CH}$ = 7.5 Hz, $CHCH_2$; $J_{4,5}$ = 3.8 Hz, H-4), 3.77, 3.47 (2dd, 2H, $J_{CH,CH}$ = 3.2, 2.9 Hz, ^2J = 10.5 Hz, $CHCH_2$), 3.61 (m, 2H, $J_{5,6}$ = 7.6 Hz, $J_{5,6'}$ = 1.6 Hz, H-6, H-6'), 3.56 (m, 1H, H-5), 3.54 (s, 1H, OCH_3), 2.58 (s, 3H, CH_3 of Ts), 2.07 (s, 3H, CH_3CO).

Anal. Calcd for $C_{40}H_{45}NO_{11}S$: C, 64.26, H, 6.02; Found: C, 63.96, H, 6.04.

For **23**, $[\alpha]_D$ +46.1° (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 7.75 (2 d, 2 H, TsPh), 7.48-7.20 (m, 17H, 3CH_2Ph, TsPh), 5.80 (d, 1H, J = 9.2 Hz, N*H*), 5.20 (dd, 1H, $J_{1,2}$ = 3.6 Hz, $J_{2,3}$ = 9.8 Hz, H-2), 4.95 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 3.52 (s, 3H, OCH_3), 2.41 (s, 3H, CH_3 of Ts), 2.02 (s, 3H, CH_3CO).

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