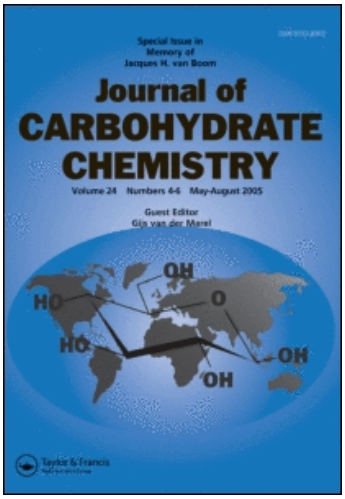

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COMMUNICATION

STUDIES ON GLYCOSIDES XVI. THE USE OF MANNOSYL TRICHLOROACETATE IN THE SYNTHESIS OF α-MANNOSIDES AND RELATED OLIGOSACCHARIDES

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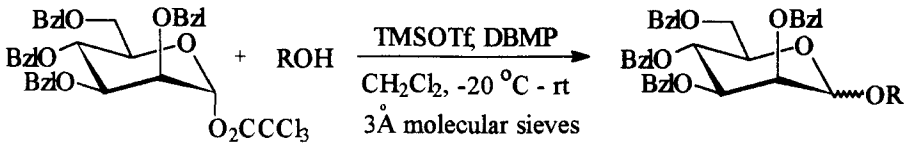
Much attention has been focused on the stereoselective synthesis of glycosides and oligosaccharides, not only for the preparation of natural products,[1] but also for the homologation of sugars to serve as chiral templates for more complex synthetic targets.[2] Most current methods for the preparation of glycosides are based on the activation of a leaving group at the anomeric centre.[3] A wide range of (potential) leaving groups has been proposed. Some of them are stable in the absence of a suitable promoter and function as a temporary protecting group; others are very reactive.[3] The trifluoroacetoxyl group was found to be a good leaving group at the anomeric position and *C*, *O*, *S* and *N*-glycosides,[4] and oligosaccharides [5] were synthesized with high stereoselectivity in our laboratory using derivatives that contain this group. However the glycosyl trifluoroacetates were found to be too reactive, and new glycosyl donors containing the trichloroacetoxy leaving group were studied. We now report a stereoselective and mild method for the synthesis of α-mannosides and related oligosaccharides from benzylated mannopyranosyl trichloroacetate **(1)** .

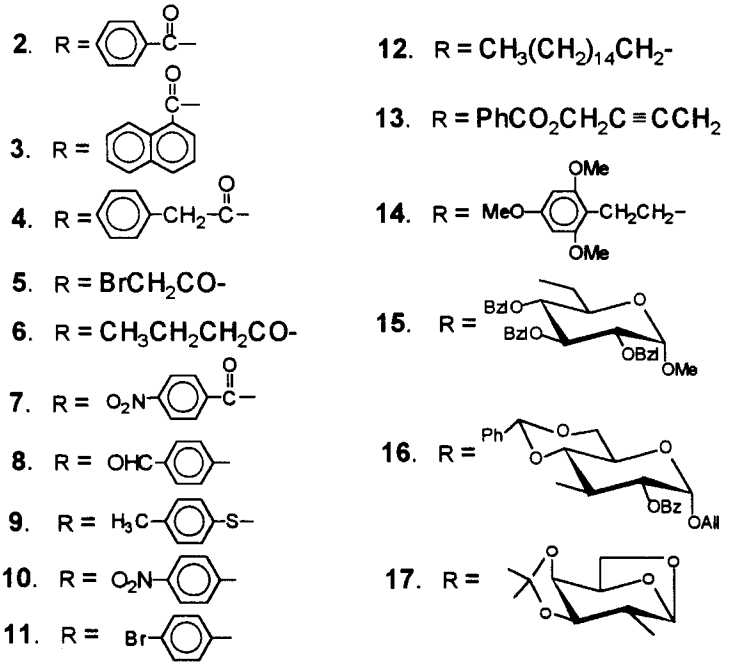


1 **2-17**

Bzl = $PhCH_2$-, TMSOTf = $Me_3SiOSO_2CF_3$

DBMP = 2, 6-Di-*tert*-butyl-4-methylpyridine

Compounds:



A typical procedure was carried out as follows: Compound 1 (140 mg, 0.20 mmol), the mannosyl acceptor (carboxylic acid, phenol, alcohol or saccharide, 0.24 mmol), DBMP (50 mg) and powdered 3Å molecular sieves (100 mg) were added with stirring at -20°C to anhydrous dichloromethane (10 mL). Five drops of a Lewis acid catalyst (TMSOTf or $BF_3{\cdot}OEt_2$) were added, and stirring was continued until 1 was consumed (TLC, eluent, cyclohexane: ethyl acetate = 6:1, 4:1 or benzene: ethyl acetate = 8:1, 12:1). The temperature was increased from -20 °C to rt, the solution was filtered, and the filtrate was concentrated *in vacuo* to a syrup. The product mixture was resolved by preparative TLC to give the pure mannopyranosides or related oligosaccharides (see Table 1).

Table 1. Synthesis of α-D-Mannopyranosides and Related Oligosaccharide by the Trichloroacetate Method

Compd No.	Catalyst	Reaction Time (hr.)	Yield (%)	mp (°C)	Ratio of Anomers (α:β)	$[\alpha]_D^{20}$(CHCl3)
2	TMSOTf	4	85	45-46	1 : 0	44.4° (*c*, 1.58)
3	TMSOTf	4	82	Syrup	1 : 0	35.9° (*c*, 5.47)
4	TMSOTf	8	63	Syrup	1 : 0	13.7° (*c*, 3.06)
5	TMSOTf	4	80	Syrup	1 : 0	19.7° (*c*, 3.36)
6	TMSOTf	3.5	80	Syrup	1 : 0	23.4° (*c*,3.08)
7	TMSOTf	4	73	Syrup	1 : 0	24.7° (*c*, 4.46)
8	BF_3·OEt_2	8	57	Syrup	1 : 0	52.2° (*c*, 3.95)
	TMSOTf	8	71	Syrup	1 : 0	
9	TMSOTf	5	65	Syrup	1 : 0	57.2° (*c*, 2.55)
10	TMSOTf	5	69	Syrup	1 : 0	25.8° (*c*, 1.55)
11	TMSOTf	6	82	Syrup	1 : 0	33.3° (*c*, 7.68)
12	TMSOTf	9	58	Syrup	1 : 0	21.6° (*c*, 3.71)
13	TMSOTf	3.5	83	Syrup	1 : 0	28.1° (*c*, 5.13)
14	TMSOTf	4	72	Syrup	1 : 0	23.7° (*c*, 3.71)
15	TMSOTf	4.5	81	Syrup	1 : 0	40.5° (*c*, 2.97)
16	TMSOTf	10	85	Syrup	1 : 0	49.1° (*c*, 3.83)
17	TMSOTf	8	83	Syrup	1 : 0	18.1° (*c*, 2.33)

Compound **1** reacted with the mannosyl acceptors to afford only α-anomers. The rate of reaction and yields depend upon the reactivity of the mannosyl acceptor and the Lewis acid. In the synthesis of **8**, the yield using TMSOTf as a promoter was higher (71%) than that obtained using BF_3·OEt_2 (57%), showing that the use of a stronger Lewis acid catalyst was favorable. When the D-mannopyranosyl trichloroacetate (**1**) was treated with alcohols of a large molecular weight, the 1-*O*-alkyl-D-mannopyranosides were obtained in good yields (see compounds **12, 13, 14**); but when **1** was treated with alcohols of small molecular weight (e.g. isopropyl alcohol) under the same conditions (-20 °C→rt), no product was detected. When the reaction temperature was raised to 40 °C for 3 h, an α, β mixture was obtained in 77% yield (α:β = 1.2:1).[6] Three disaccharides (compounds **15, 16, 17**) were obtained stereoselectively in yields above 80% by reactions of **1** with 6-, 3-,

Table 2. Proposed ^1H , ^{13}C NMR Chemical Shifts of Mannopyranosyl Sugar Ring

Compd.	^1H NMR		^{13}C NMR (ppm)					
No.	δ_{H1} (ppm)	$^3J_{H1,2}$(Hz)	C-1	C-2	C-3	C-4	C-5	C-6
1	6.36	2.20	96.9	73.4	75.4	73.9	78.4	68.4
2	6.49	1.98	92.4	73.7	74.9	74.3	79.2	68.9
3	6.59	2.10	92.3	73.5	74.9	74.3	79.1	68.9
4	6.22	1.97	96.0	73.9	75.0	74.4	79.0	68.9
5	6.30	2.33	93.7	72.2	75.1	74.1	78.4	68.8
6	6.30	2.51	96.5	73.3	75.1	74.3	78.9	68.8
7	6.25	2.15	91.9	72.1	75.7	74.1	78.0	67.7
8	5.70	2.20	96.2	74.4	79.6	74.9	72.4	68.7
9	5.58	1.97	96.6	73.2	79.9	74.7	72.5	69.0
10	5.02	2.22	97.2	75.1	80.3	75.5	72.2	69.4
11	5.62	2.20	96.3	74.4	79.6	74.9	72.7	68.7
12	4.98	2.00	97.8	73.3	80.4	75.1	71.8	69.4
13	5.14	1.79	96.4	74.4	79.9	74.9	72.2	69.1
14	5.02	1.98	97.3	73.2	80.4	74.9	71.6	69.3
15	4.84	1.60	97.7	74.7	79.8	75.6	72.2	69.6
16	4.70	1.95	98.1	73.3	79.5	74.8	71.7	68.7
17	4.82	2.33	98.0	73.2	79.7	74.7	72.0	69.0

and 2-OH unprotected monosaccharides, respectively. This was the first example of the synthesis of oligosaccharides using the trichloroacetate method.

Compound **1** was prepared easily by the treatment of 2,3,4,6-tetra-*O*-benzyl-D-mannopyranose with trichloroacetic anhydride in the presence of sodium trichloroacetate.[7] The product was isolated by column chromatography and it could be stored for periods of 3~5 months in a refrigerator.

The anomeric configurations of the benzylated D-mannopyosides and related oligosaccharides were assigned as α using the values of δ_{H1} and $^3J_{H1,2}$.[8,9] This result was supported by the values of $^2J_{C1\text{-}H1}$.[10] The products were confirmed by spectral data and on the basis of analytical data.[11,12] ^1H and ^{13}C NMR data of compounds **1~17** are listed in Table 2.

ACKNOWLEDGMENT

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6. Treatment of compound 1 with isopropyl alcohol at 40 °C for 3h gave an α,β mixture (Yield 77%, α : β 1.2:1).

   α-anomer: white solid, 59-60 °C, $[\alpha]_D$ 31.85° (*c* 1.51, $CHCl_3$), δ_{H1} = 5.00 ppm (J=1.97 Hz), δ_{C1} = 95.8 ppm. Anal. Calcd for $C_{37}H_{42}O_6$: C, 76.26; H, 7.26. Found: C, 76.24; H, 7.31.

   β-anomer: white needles, 45-46.5 °C, $[\alpha]_D$ -52.27° (*c* 1.70, $CHCl_3$), δ_{H1} = 4.86 ppm (J=1.08 Hz), δ_{C1} = 95.9 ppm. Anal. Calcd for $C_{37}H_{42}O_6$: C, 76.26; H, 7.26. Found: C, 76.29; H, 7.35.
7. Compound 1 was prepared as follows: To a solution of 2,3,4,6-tetra-*O*-benzyl-D-mannopyranose (1.08 g) in anhydrous dichloromethane (10 mL) were added trichloroacetyl anhydride (1.5 mL) and anhydrous sodium trichloroacetate (200 mg). The solution was boiled under reflux for 30 min. After cooling to rt, the sodium trichloroacetate was filtered off, washed with CH_2Cl_2 (2×5 mL), the filtrate and washings were combined and washed by ice-water, aqueous $NaHCO_3$ and ice-water to neutrality, dried, and concentrated under reduced pressure to give a colorless syrup, 1.37 g (quantitative yield). ^1H NMR (90 MHz, $CDCl_3$) δ (ppm): 3.60-5.10 (m, 14H, H-2,3,4,5,6, 4×$PhCH_2$), 6.36 (d, 1H, J=2.20Hz, H-1,α), 7.20-7.60 (m, 20H, ArH). ^{13}C NMR chemical shifts are listed in Table 2. Anal. Calcd for $C_{36}H_{35}O_7Cl_3$: C, 63.14; H, 5.16; Cl, 15.33. Found: C, 63.03; H, 5.30; Cl, 15.32.

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10. Selected $^2J_{C1\text{-}H1}$ data (Hz, measured by broadening band decoupling technique): **6**: 173.0 (α); **7**: 171.6 (α); **8**: 171.7 (α); **9**: 171.6 (α); **12**: 168.5 (α); **13**:170.3 (α); **15**: 169.6 (α).
11. FAB-MS for selected compounds:
2: 644 (M^+); **4**: 658 (M^+); **6**: 610 (M^+); **9**: 647 $(M+1)^+$; **11**: 695 (M^+); **13**: 712 (M^+); **14**: 757 $(M+Na)^+$; **15**: 987 $(M+1)^+$; **16**: 934 (M^+); **17**: 724 (M^+).
12. Elemental analysis:
2: Anal. Calcd for $C_{41}H_{40}O_7$: C, 76.38; H, 6.25. Found: C, 76.32; H, 6.34.
3: Anal. Calcd for $C_{45}H_{42}O_7$: C, 77.78; H, 6.10. Found: C, 77.77; H, 6.00.
4: Anal. Calcd for $C_{42}H_{42}O_7$: C, 76.57; H, 6.43. Found: C, 76.70; H, 6.50.
5: Anal. Calcd for $C_{36}H_{37}O_7Br$: C, 65.36; H, 5.64; Br, 12.08. Found: C, 65.31; H, 5.70; Br, 12.02.
6: Anal. Calcd for $C_{38}H_{42}O_7$: C, 74.73; H, 6.93. Found: C, 74.80; H, 7.00.
7: Anal. Calcd for $C_{41}H_{39}O_9N$: C, 71.39; H, 5.70; N, 2.03. Found: C, 71.20; H, 5.70; N, 2.05.
8: Anal. Calcd for $C_{41}H_{40}O_7$: C, 76.38; H, 6.25. Found: C, 76.35; H, 6.30.
9: Anal. Calcd for $C_{41}H_{42}O_5S$: C, 76.13; H, 6.54. Found: C, 76.14; H, 6.50.
10: Anal. Calcd for $C_{40}H_{39}O_8N$: C, 72.60; H, 5.94; N, 2.12. Found: C, 72.71; H, 5.91; N, 2.11.
11: Anal. Calcd for $C_{40}H_{39}O_6Br$: C, 69.09; H, 5.65; Br, 11.49. Found: C, 69.00; H, 5.72; Br, 11.50.
12: Anal. Calcd for $C_{50}H_{68}O_6$: C, 78.49; H, 8.96. Found: C, 78.23; H, 8.95.
13: Anal. Calcd for $C_{45}H_{44}O_8$: C, 75.82; H, 6.22. Found: C, 75.90; H, 6.23.
14: Anal. Calcd for $C_{45}H_{44}O_8$: C, 75.82; H, 6.86. Found: C, 73.56; H, 6.92.
15: Anal. Calcd for $C_{62}H_{66}O_{11}$: C, 75.43; H, 6.74. Found: C, 75.13; H, 6.91.
16: Anal. Calcd for $C_{57}H_{58}O_{12}$: C, 73.22; H, 6.25. Found: C, 73.21; H, 6.25.
17: Anal. Calcd for $C_{43}H_{48}O_{10}$: C, 71.25; H, 6.67. Found: C, 71.05; H, 6.50.