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AN EFFICIENT SYNTHESIS OF GLYCOSYL ESTERS EXPLOITING THE MITSUNOBU REACTION.

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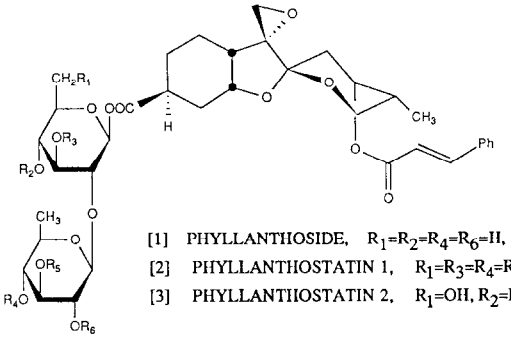
Summary: The anomeric hydroxyl group of various pyranose hemiacetals can be esterified with inversion of configuration, conveniently, mildly and on large-scale using triphenylphosphine (TPP), with either diisopropylazodicarboxylate (DIAD) or diethylazodicarboxylate (DEAD) and a carboxylic acid in THF at either -50° C or at room temperature.

Despite the considerable effort expended on developing practical methods for the synthesis of glycosyl esters,[2] their application to the construction of complex, multifunctional molecules is frequently unsuccessful. In connection with a program directed towards the total synthesis of the phyllanthostatin family[3] of antitumor agents (1-3), we investigated the glycosidation of reducing sugars with a range of carboxylic acids using the Mitsunobu protocol;[4] we find that extremely high stereoselectivity results when esterifications are conducted with anomerically pure glycosyl hemiacetals. To demonstrate the utility of this approach, we include here several examples from the phyllanthostatin area (see Table 1).



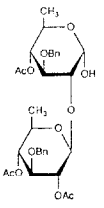
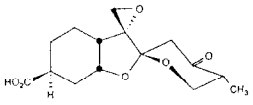
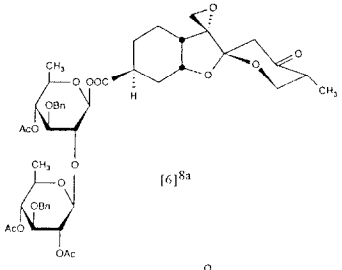
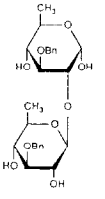
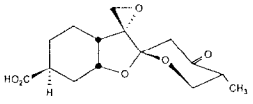
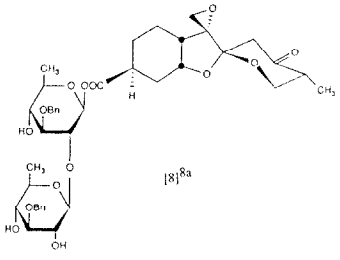
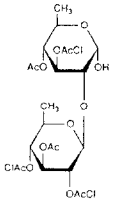
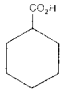
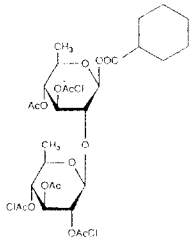
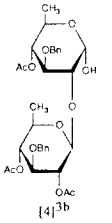
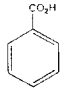
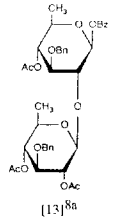
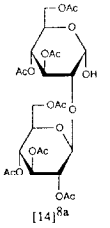
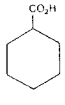
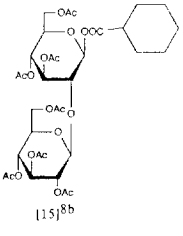
[1] PHYLLANTHOSIDE, $R_1=R_2=R_4=R_6=H$, $R_3=R_5=Ac$

[2] PHYLLANTHOSTATIN 1, $R_1=R_3=R_4=R_6=H$, $R_2=R_5=Ac$.

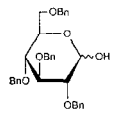
[3] PHYLLANTHOSTATIN 2, $R_1=OH$, $R_2=R_4=R_6=H$, $R_3=R_5=Ac$.

Clearly, one of the main advantages offered by this glycosylation protocol lies in its compatibility with a wide variety of labile functionality, ranging from epoxides and spiroketals to many of the commonly utilised protecting groups. Furthermore, glycosidation proceeds with complete stereochemical inversion at C-1 of the starting sugar, as exemplified by entries (A) to (E). When an anomeric mixture of sugars is esterified, as for example with 2,3,4,6-tetra-O-benzyl D-glucose (Entry F) [α/β= 4:1],[5] complementary ratios of inverted products are formed. Interestingly, the stereochemical outcome of glycosidation is independant of anchimeric assistance from an O-acyl group at C-2. Thus, 2,3,4,6-tetra-O-acetyl D-mannose (Entry G) furnishes a mixture of 1-O-benzoates in which the β-anomer predominates, a result that is especially significant in view of the difficulties generally encountered in obtaining β-glycosides of D-mannose.[6] In systems where the presumed glycosyl phosphorane intermediates are thermally unstable, high stereoselectivities can only be obtained when the esterifications are conducted at low temperature. A good example of such behavior is provided by entry E; when this reaction

TABLE 1

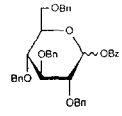
ENTRY	SUBSTRATE	REAGENTS AND CONDITIONS	PRODUCTS	ISOLATED YIELD / ANOMERIC RATIO (β/α)[9]
A	 [4][3b]	 [5] (1.0 equiv), TPP (1.5 equiv), DEAD (1.5 equiv), THF, PROCEDURE A.	 [6][8a]	90% β
B	 [7][8a]	 [5] (1.0 equiv), TPP (1.5 equiv), DIAD (1.5 equiv), THF, PROCEDURE A.	 [8][8a]	40% β
C	 [9][8a]	 [10] (2.0 equiv), TPP (1.5 equiv), DIAD (1.5 equiv), THF, PROCEDURE B.	 [11][8a]	64% β
D	 [4][3b]	 [12] (1.0 equiv), TPP (1.5 equiv), DIAD (1.5 equiv), THF, PROCEDURE A.	 [13][8a]	95% β
E	 [14][8a]	 [10] (1.3 equiv), TPP (1.5 equiv), DIAD (1.5 equiv), THF, PROCEDURE B.	 [15][8b]	85% β

F



[16][10]

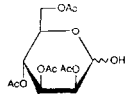
[12] (1.3 equiv), TPP (1.5 equiv), DIAD (1.5 equiv), THF, PROCEDURE B.



[17][8a]

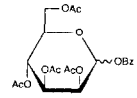
54% (4:1)

G



[18][11]

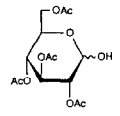
[12] (1.3 equiv), TPP (1.3 equiv), DIAD (1.3 equiv), THF, PROCEDURE B.



[19][8b]

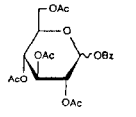
62% (4:1)

H



[20][12]

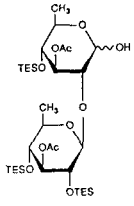
[12] (1.3 equiv), TPP (1.3 equiv), DIAD (1.3 equiv), THF, PROCEDURE B.



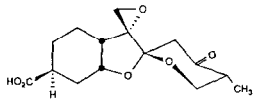
[21][8b]

80% (2:1)

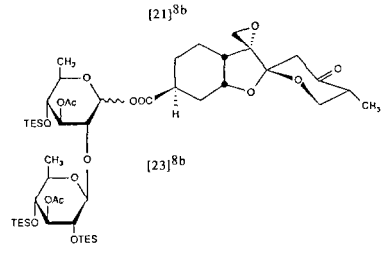
I



[22][3b]



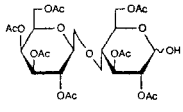
[5] (1.5 equiv), TPP (1.5 equiv), DIAD (1.5 equiv), THF, PROCEDURE A.



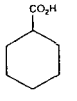
[23][8b]

55% (2:1)

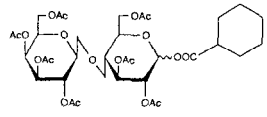
J



[24][8a]



[10] (1.3 equiv), TPP (1.5 equiv), DIAD (1.5 equiv), THF, PROCEDURE B.



[25][8b]

63% (4.5:1)

was carried out at room temperature, a 1:1 mixture of anomers was obtained, whereas at -50° C, only the β–isomer was formed. Finally, entry B indicates that selective activation of the anomeric position is possible, even when a multiplicity of other hydroxyl groups are present in the sugar component. This observation augments the earlier work of Grynkiewicz[7] on the selective glycosidation of free aldoses with phenols via the Mitsunobu procedure.

EXPERIMENTAL METHODS

Procedure A: To a solution containing 4 [35 mg, 0.0568 mmol], acid 5 [25 mg, 1.5 eq] and triphenylphosphine (TPP) [23 mg, 1.5 eq] in dry THF [0.75 mL] was added diisopropyl-azodicarboxylate (DIAD) [0.014 mL, 1.5 eq] under an argon atmosphere. After stirring the reactants at room temperature for 20 min, the solvent was evaporated under reduced pressure and the resultant mixture purified by flash chromatography (EtOAc/hexane, 1:4) to give pure 6 [46 mg, 90%; [α] +37.5° (c 0.82 , $CHCl_3$)].

Procedure B: To a solution of TPP [0.98 g, 3.7 mmol.] in dry THF [6 mL] at -50°C, under an argon atmosphere, was added DIAD [0.74 mL, 3.7 mmol]. The mixture was stirred at this temperature for 10 min, whereupon a thick yellow precipitate formed. The hemiacetal 20 [1.0 g, 2.9 mmol] was added and the stirring continued at -50° C for a further 10 min before benzoic acid 12 [0.46g,

3.8 mmol] was added. The mixture was allowed to warm slowly to room temperature over a period of 2 h, the solvent removed in vacuo, and the residue purified by flash chromatography (EtOAc/hexane 1:4) to furnish 21 [1.04 g, 80%] as a 2:1 mixture of anomers. Crystallization from ether gave the pure β–anomer [mp 143-144° C (Lit.[2c] mp 143.5-144° C); $[\alpha]_D$-27.6° (c 1.0 $CHCl_3$); Lit.[2c] $[\alpha]_D$ -28.2° (c 2.0 $CHCl_3$)].

In conclusion, we expect that the many advantages offered by the present technology will make the Mitsunobu protocol an attractive choice for the synthesis of 1-O-acyl aldoses. Further progress on the synthesis of potentially important biologically active analogs of phyllanthoside will be reported in due course.

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3. (a) For a comprehensive account of the phyllanthostatin glycosides see: Pettit, G. R., Cragg, G. M. and Suffness, M., J. Org. Chem., 1985, 50, 5060, and references cited therein; (b) For the synthesis of phyllanthoside, see Smith III, A. B. and Rivero, R., (Submitted for publication); (c) For recent syntheses of the aglycone (phyllanthocin) see: McGuirk, P. R., and Collum, D. B., J. Am. Chem. Soc., 1982, 104, 4496; Williams, D. R. and Sit, S. Y., J. Am. Chem. Soc., 1984, 106, 2949; McGuirk, P. R., and Collum, D. B., J. Org. Chem., 1984, 49, 843; Burke, S. D. , Cobb, J. E. and Takeuchi, K., J. Org. Chem., 1985, 50, 3420.
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8. a) The structure assigned to this compound is in accord with its infrared, 250-MHz ^1H NMR and high resolution mass spectra. b) In addition, an analytical of this compound, obtained by recrystallization or chromatography (LC or TLC) gave satisfactory C and H combustion analysis within 0.4%.
9. Anomeric ratios were determined by 250 MHz ^1H NMR spectroscopy.
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