Acknowledgment. We are grateful to the National Science Foundation (CHE 80-06495) for support of this research and use of the Southern California NMR Facility supported by NSF Grant CHE 79-16324.

Registry No. 1, 83487-43-8; 4, 21981-37-3; 5, 63819-70-5; 6, 83487-44-9; *tert*-butyl hypochlorite, 507-40-4.

(20) Authentic tetrazene **10** was synthesized by stirring the neat hydrazine **6** under an atmosphere of oxygen at 0 °C. Drying the resulting paste under vacuum afforded white needles: mp 49–50 °C; IR (mull) 2990, 1485, 1395, 1375, 1305, 1200, 1155, 930 cm^{-1}; UV (Et_2O) 230 nm (ϵ 1500); NMR ($CDCl_3$) δ 1.27 (s). Anal. Calcd for $C_{16}H_{36}N_4$: C, 67.55; H, 12.76; N, 19.69. Found: C, 67.29; H, 12.63; N, 19.44.

Synthesis of Saccharides and Related Polyhydroxylated Natural Products. 4. α-D- and β-D-*C*-Glycopyranosides (2,6-Dialkyl-Substituted Tetrahydropyrans)[1]

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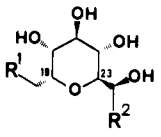
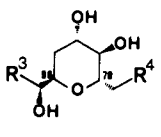
Received August 10, 1982

Polyhydroxylated tetrahydropyran rings with two alkyl (or oxygenated alkyl substituents at the 2- and 6-positions[2] of the pyran system represent a basic structural feature of many natural products, which may be regarded as α-D- or β-D-*C*-glycopyranoside derivatives in the context of carbohydrate chemistry. In addition to the synthesis of these natural products, a variety of C-analogues of saccharide phosphates[3] as well as C-linked oligosaccharides are now highly in demand for studies of sugar metabolism. Our attention was initially focused on the *C*-glycopyranosides by an interest in devising a means for stereoselectively constructing the four pyran moieties that constitute fragment A [C(19)–C(23)], B [C(66)–C(70)], C [C(75)–C(79)], and D [C(101)–C(105)] of palytoxin. The fragments are shown with the proposed stereochemistry.[4]


A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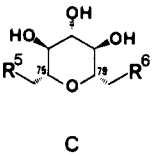
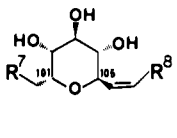

C


D

In recent years a variety of synthetic methods for construction of the *C*-glycopyranosides have been developed with *varying* degrees of success.[5] Unfortunately, most, if not all, of these methods did not appear to satisfy our synthetic objective in terms of efficiency, yield, and stereoselectivity, and there was a definite need for further improvement. The new method that we present herein constitutes a general solution for this problem and uses titanium-catalyzed asymmetric epoxidation with diethyl (+)- or (−)-tartrate (DET)[6] to create the crucial C(2) center of the tetrahydropyran system. Our process gives excellent stereoselection and provides the cis- and trans-C(2) and -C(6) substituents with versatile oxygen functionalities for further selective transformation.

Our approach is succinctly demonstrated in Scheme I for the α- and β-D-*C*-glucopyranosides (**1a**, **2a**), as well as their 2-deoxy analogues (**1b**, **2b**). The required starting pyranosides 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-glucopyranose (**3a**) and 3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-D-arabinohexopyranose (**3b**) are easily prepared in multigram quantities (five steps in each case)[7] from α-D-glucose pentaacetate and 2-deoxy-D-glucose, respectively. The synthetic process depicted in the scheme proceeds with remarkable facility in both the gluco and 2-deoxygluco series. There are, however, a few aspects worthy of comment. Protection of the free hydroxyl group in **4a** and **4b** was adopted as a conservative measure for these initial studies. All four asymmetric epoxidations (abreviated hereafter as AE) (**5a** → **6a**, **5a** → **7a**, **5b** → **6b**, **5b** → **7b**) proceed in high yield and with excellent (>30:1) diastereoselection under *modified* reaction conditions.[8] The α,β-unsaturated aldehyde corresponding to **5a** and **5b** emerged as a byproduct from AE under standard conditions. The probable culprit in this undesired side reaction is free $Ti(O\text{-}i\text{-}Pr)_4$,[9] and this problem is easily circumvented by increasing the tartrate/$Ti(OiPr)_4$ ratio.[10]

The scheme also reveals that all four intramolecular epoxide openings which provide the desired α- and β-*C*-glycopyranoside diols (**8a**, **8b**, **9a**, **9b**) proceed stereospecifically and in excellent yield. Not surprisingly, these cyclizations occur much more readily in the deoxy series, and both **6b** and **7b** are partially to completely cyclized under the conditions used to remove the silyl protecting group. All four epoxy diols are efficiently cyclized by treatment with sodium hydride in dimethylformamide.

The α- and β-*C*-glycopyranosides (**8a**, **8b**, **9a**, **9b**) are rapidly cleaved by sodium metaperiodate to afford the corresponding (partially or fully) hydrated aldehydes (**1a**, **1b**, **2a**, **2b**), which are cleanly reduced by sodium borohydride to **10a**, **10b**, **11a**, and **11b** in high yield.

The structure of **10a** was unequivocally established by its conversion in two steps (reductive ring opening of the benzylidene

(1) Preceding communication of this series: Lee, A. W. M.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Walker, F. J. *J. am. Chem. Soc.* **1982**, *104*, 3515.

(2) The numbering is based on the tetrahydropyran system.

(3) Nicotra, F.; Ronchetti, F.; Russo, G. *J. Chem. Soc., Chem. Commun.* **1982**, 470 and references quoted therein.

(4) Moore, R. E.; Bartolini, G.; Barchi, J.; Botherner-By, A. A.; Dadok, J.; Ford, J. *J. Am. Chem. Soc.* **1982**, *104*, 3776. Some corrections are made on the proposed stereostructure.

(5) A summary of existing methods for synthesis of *C*-glycopyranosides (and also *C*-glycofuranosides) is given in the supplementary material.

(6) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Rossiter, B. E.; Katsuki, T.; Sharpless, K. B. *Ibid.* **1981**, *103*, 464. (c) Martin, V. S.; Woodward, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *Ibid.* **1981**, *103*, 6237. For the use of the epoxidation for a two-carbon extension, see: (d) Katsuki, T.; Lee, A. W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *J. Org. Chem.* **1982**, *47*, 1373. (e) Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Viti, S. M. *Ibid.* **1982**, *47*, 1378. (f) Minami, N.; Ko, S. S.; Kishi, Y. *Ibid.* **1982**, *104*, 1109.

(7) Detailed information concerning the synthesis of **3a** and **3b** is provided in the supplementary material.

(8) All reactions were performed at ca. −20 °C in CH_2Cl_2 (0.05–0.1 M in substrate). The "modified" conditions per mole of substrate are as follows: 5 mol of DET, 3.6 mol of $Ti(OiPr)_4$, and 2–4 mol of TBHP. For comparison, the "standard" conditions per mole of substrate are as follows: 1.5 mol of DET, 1.2 mol of $Ti(OiPr)_4$, and 1.5–4 mol of TBHP. We usually start with 2 equiv of TBHP, but when an epoxidation appears to have stopped and unreacted allylic alcohol remains, addition of 1 or 2 further equivalents of TBHP will often drive the reaction to completion. *Regardless of whether "standard" or "modified" AE conditions are employed, we now generally prefer the following new workup procedure* developed by Dr. D. Tuddenham: The reaction mixture (at ca. −20 °C) is diluted with roughly an equal volume of diethyl ether (at room temperature), then saturated sodium sulfate solution (1 mL/mL of $Ti(O\text{-}i\text{-}Pr)_4$ used) is added, and the mixture is stirred vigorously at room temperature for 1–2 h. The heavy precipitate formed is removed by filtration through a Celite pad, and the filtrate is concentrated. Several portions of toluene are added to aid in evaporation of the excess TBHP. Hydrolysis of the tartrate (as in ref 6a except that we now use a saturated brine solution that is 1–2 N in NaOH), or in most cases direct flash chromatography provides the pure epoxy alcohol.

(9) When **5a** was exposed to TBHP and free $Ti(O\text{-}i\text{-}Pr)_4$, it was rapidly and selectively oxidized to the α,β-unsaturated aldehyde.

(10) For a discussion of the effect of the tartrate/$Ti(O\text{-}i\text{-}Pr)_4$ ratio on the presence of "free $Ti(O\text{-}i\text{-}Pr)_4$", see ref 6c.

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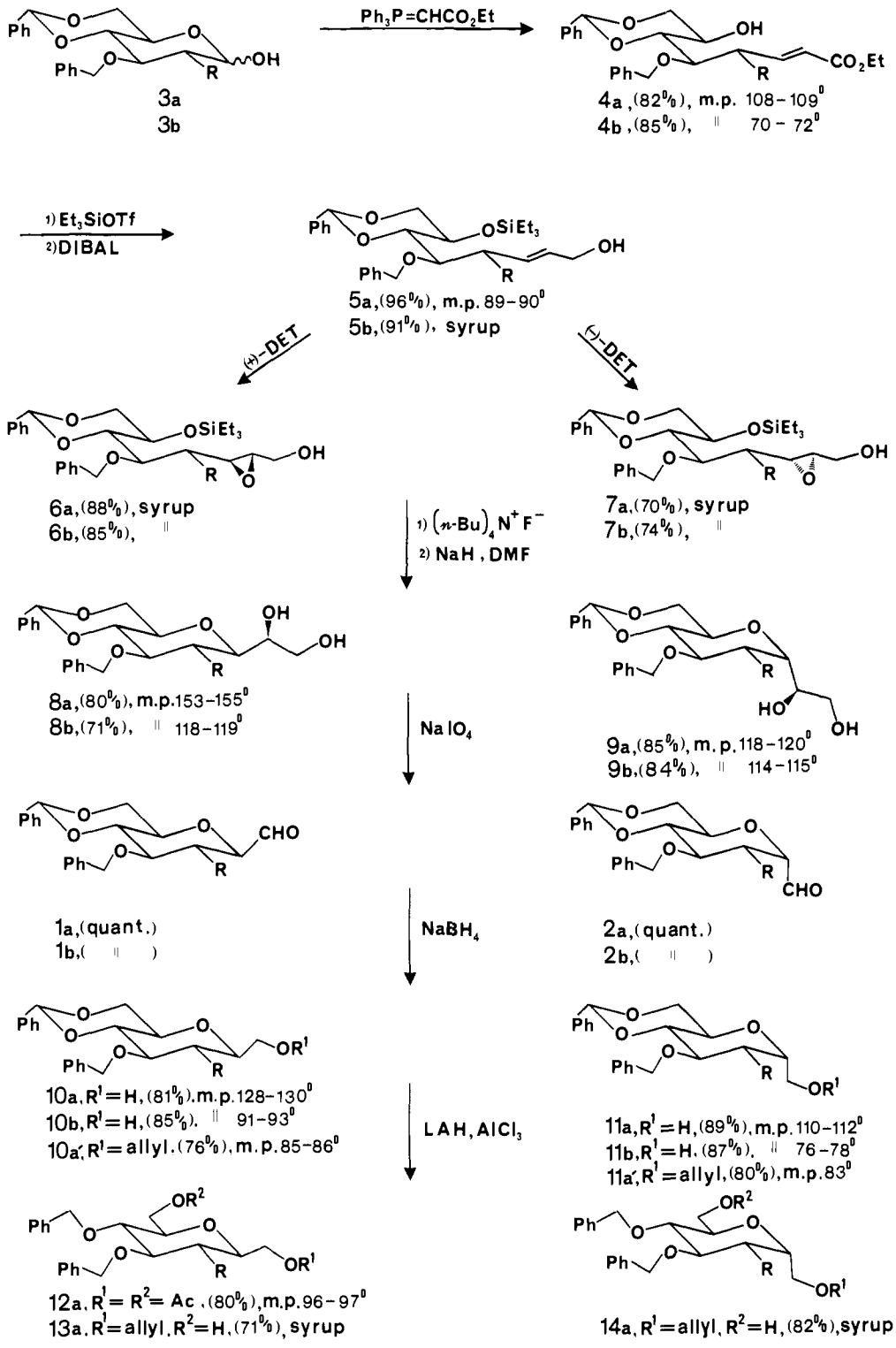
Scheme I[a]



[a] For series a: R = OCH_2Ph; for series b: R = H.

in **10a** with a mixture of lithium aluminum hydride and aluminum chloride,[11] followed by acetylation) to the *meso*-di-*O*-acetyltri-*O*-benzyl compound **12a**. The meso nature of this compound was confirmed by both ^1H and ^{13}C NMR spectroscopy (2-fold symmetry) and optical rotation; $[\alpha]_D = 0°$ (*c* 1.0, $CHCl_3$). This leaves no doubt about the structural assignments for the other isomers **10b**, **11a**, and **11b**.

A variety of acetal ring-opening reactions[11] are available for further elaboration of our versatile synthons (**10a**, **10b**, **11a**, **11b**). We have chosen to demonstrate this point by effecting a simple "end-switching" procedure that provides either the free C(2) or C(6) oxygenated alkyl substituents attached to the pyran system and hence the α- and β-D- as well as β-L-*C*-glucopyranosides. Thus **10a**, and **11a** are protected as the allyl ether derivatives **10a'** and

(11) The use of $LiAlH_4$ and $AlCl_3$ in ether affords the "4-*O*-benzyl-6-OH free" derivative with excellent selectivity: Liptăk, A.; Jodăl, I.; Nanăsi, P. *Carbohydr. Res.* **1975**, *44*, 1. Opposite selectivity can be achieved with $NaCNBH_3$, HCl, and MeOH: Garegg, P. J.; Hultberg, H. *Ibid.* **1981**, *93*, C-10. Cleavage of the benzylidine (H^+ or H_2/catalyst) followed by selective protection represents a third option. The "4-*O*-benzoyl-6-bromo" derivative is also available by reaction of the benzylidene with NBS: Hanessian, S. *Ibid.* **1966**, *2*, 86.

11a', respectively. Reductive ring opening of the benzylidene acetal with a mixture of lithium aluminum hydride and aluminum chloride efficiently produces the 2,3,4-tri-*O*-benzyl-substituted derivatives **13a** and **14a** in excellent overall yield. Further operations required to achieve a specific aim (e.g., the synthesis of any of fragments A–D of palytoxin) are obvious.[1,6d-f,12]

Acknowledgment. We are greateful to the National Institutes of Health (GM 31124) and to the National Science Foundation for financial support. We also thank Mary A. Blanchette for her assistance at a late stage in this work. High-resolution mass spectra were provided by the facility, supported by the National Institutes of Health (Grant RR 00317; principal investigator, Professor K. Biemann), from the Biotechnology Resources Branch, Division of Research Resources.

Registry No. **1a**, 83416-93-7; **1b**, 83416-94-8; **2a**, 83416-95-9; **2b**, 83416-96-0; **3a**, 83461-73-8; **3b**, 83416-97-1; **4a**, 83416-98-2; **4b**, 83416-99-3; **5a**, 83417-00-9; **5b**, 83417-01-0; **6a**, 83417-02-1; **6b**, 83417-03-2; **7a**, 83461-74-9; **7b**, 83461-75-0; **8a**, 83417-04-3; **8b**, 83417-05-4; **9a**, 53461-76-1; **9b**, 83461-77-2; **10a**, 83417-06-5; **10a'**, 83417-08-7; **10b**, 83417-07-6; **11a**, 83461-78-3; **11a'**, 83461-80-7; **11b**, 83461-79-4; **12a**, 83417-09-8; **13a**, 83417-10-1; **14a**, 83461-81-8; Ti(O-*i*-Pr)$_4$, 546-68-9; $Ph_3P{=}CHCO_2Et$, 1099-45-2.

Supplementary Material Available: Listings of physical properties of new compounds, a summary of known methods for synthesis of *C*-glycopyranosides, and synthesis of **3a** and **3b** (10 pages). Ordering information is given on any current masthead page.

(12) **Note Added in Proof**: We (M. A. Blanchette and S. Masamune) now find that the three precautionary steps that were incorporated in the above reaction sequence are no longer necessary and thus can be eliminated. These steps are as follows: (1) protection of the free OH group of an unsaturated ester (typically **4b**), (2) liberation of the same OH group after epoxidation, and (3) pyrano-ring closure. The resulting simplified sequence (involving the Wittig reaction of **3b**, Dibal reduction, and epoxidation) directly provides **8b** or **9b** with (near-) perfect stereoselection and excellent overall yield. The ring closure is effected with titanium during the epoxidation reaction.

Photonitration of Phenols by Tetranitromethane under Visible Light[1]

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Tetranitromethane (TNM) is a reagent commonly used for protein modification.[2] In aqueous media at pH 8, TNM converts tyrosyl to 3-nitrotyrosyl residues. Bruice and co-workers[3] showed that the substituted phenolate anion is the kinetically active form in this reaction while the undissociated substituted phenol is unreactive toward TNM. On the basis of the ability of olefins to form complexes with TNM[4] and because irradiation of these complexes yield free radicals,[5] Bruice et al. proposed that substituted phenolate anions form charge-transfer complexes (CTC) with TNM in aqueous solution (eq 1), which then undergo electron

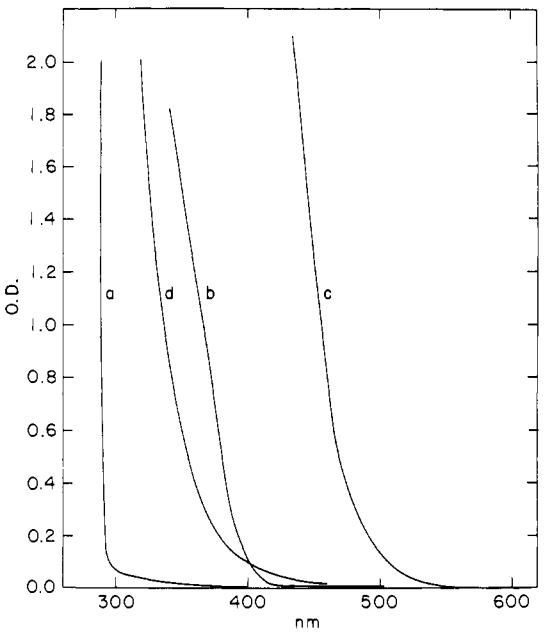

Figure 1. UV-visible spectra of tetranitromethane and phenol alone and in combination in cyclohexane: (a) 0.167 M phenol; (b) 0.167 M tetranitromethane; (c) 0.167 M phenol + 0.167 M tetranitromethane; (d) 0.0167 M phenol + 0.0167 M tetranitromethane.

$$X\text{-}PhO^- + TNM \rightleftharpoons CTC \quad (1)$$

$$CTC \xrightarrow{e^- \text{ transfer}} \overline{X\text{-}PhO\cdot + NO_2\cdot + C(NO_2)_3^-} \quad (2)$$

transfer in a slow step (eq 2) to provide the substituted phenoxy radical, the NO_2 radical, and the nitroform anion in a solvent cage. Radical–radical addition within the solvent cage provide nitrated phenoxy anions. NO_2 radicals that escape, however, yield nitrite ion.

Recent studies in our laboratories with bacteriorhodopsin (bR) have uncovered a different type of TNM-nitration reaction of phenols. Nitration of a tyrosine residue of bR by TNM has been found recently to be light dependent ($\lambda \geq 530$ nm) at pH 5.5.[6] This observation prompted a study of model systems. We report our observations here because of the possible synthetic utility that they may have in the nitration of labile systems and because of the mechanistic information that they provide.

Since TNM photonitration of bR occurs in aqueous media, *N*-acetyl-L-tyrosine ethyl ester was subjected to the same conditions (pH 5.5, $\lambda \geq 530$ nm). No apparent nitration could be detected as evidenced by the lack of nitroform anion absorption (λ_{max} 350 nm). Bacteriorhodopsin, however, is a membrane protein that is almost completely surrounded by a lipid bilayer. Hence TNM photonitration of substituted phenols in cyclohexane was attempted to mimic the nitration of a bR–tyrosine in a presumably lipophilic environment. An equimolar mixture of phenol and TNM in cyclohexane was found to absorb at considerably longer wavelength then either reactant alone at the same concentration in the same solvent (Figure 1). Upon 10-fold dilution of that solution, absorption decreases by about a factor of 100 (Figure 1), suggesting that a ground-state donor–acceptor (D–A) complex is formed by combination of TNM and phenol. Similar complexes are observed for *o*- and *p*-cresol and *o*- and *p*-chlorophenol.

In the dark these complexes in solvent cyclohexane are unreactive but react to form nitroform and ortho- and para-nitrated

(1) Research carried out at Brookhaven National Laboratory was supported by the Basic Energy Sciences Division of the Department of Energy. Research carried out at the Lawrence Berkeley Laboratory and the University of California was supported by the Office of Biological Energy Research of the Department of Energy. E.L. acknowledges support for an NIH Training Grant (No. T32 GMO7379).

(2) Sokolovsky, M.; Riordan, J. R.; Vallee, B. L. *Biochemistry* **1966**, *5*, 3582. Riordan, J. F.; Vallee, B. L. *Methods Enzymol.* **1972**, *25*, 515.

(3) Bruice, T. C.; Gregory, M. J.; Walters, S. L. *J. Am. Chem. Soc.* **1968**, *90*, 1612. Walters, S. L.; Bruice, T. C. *Ibid.* **1971**, *93*, 2269.

(4) Heilbronner, E. *Helv. Chem. Acta* **1953**, *36*, 1121.

(5) Lagercrantz, C.; Yhland, M. *Acta Chem. Scand.* **1962**, *16*, 1807.

(6) Katsura, T.; Lam, E.; Packer, L.; Seltzer, S. *Biochem. Int.* **1982**, *5*, 445.

(7) Beens, H.; Weller, A. In "Organic Molecular Photophysics"; Birks, J. B., Ed.; Wiley: New York, 1975; Vol. 2, p 159.

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