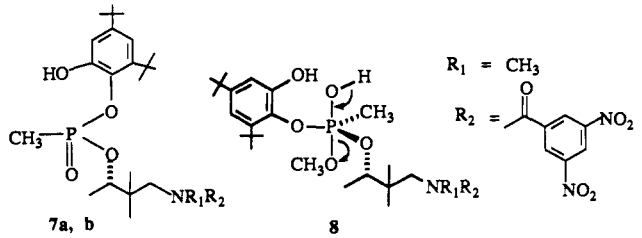
2b, respectively. These diastereomers were separated by silica gel column chromatography under basic conditions (**1a**, **1b**, and **2b**) or fractional crystallization (**2a**) (Table I).

The configuration of the crystalline phosphorane **2a** was determined by X-ray diffraction analysis. The distances and angles involving the pentacoordinated phosphorus atom are listed in Table II. The coordination is best described as an almost regular trigonal bipyramid (see Figure 1), with atoms O9 and O10 lying on the trigonal axis, and all angles falling within 10° of the ideal values (90, 120, and 180°). Knowledge of the absolute configuration of C(11) as (*S*)[6] reveals the configuration of the chiral pentacoordinated phosphorus. Another notable feature of these phosphoranes is that the configuration around the phosphorus is interconvertible between the two diastereomeric forms **2a** and **2b** by heating, although the configuration is stable enough to allow the isolation of each form at room temperature. The kinetics of the interconversion was the first order; **2a** was heated at 90 °C to give a 1:1 mixture of **2a** and **2b** with a first-order rate constant of 2.40×10^{-2} [min^{-1}].[7] The Gibbs energy of activation for the formation of **2b** was calculated to be 27.0 [Kcal mol^{-1}] at this temperature. This value is one of the highest energy barriers found for a pseudorotational process of phosphoranes.[8] As a dynamic aspect of chiral phosphoranes, the acid-catalyzed hydrolysis of **1** and **2** was examined.[9] Diastereomer **2a** reacted immediately with 0.1 N HCl to give a 1:1 mixture of two diastereomeric phosphonates **7a** and **7b**, but surprisingly the other diastereomer **2b** under the same conditions gave **7a** and **7b** in unequal amount (27:73).[10] Nucleophilic attack of water was at phosphorus, not



7a, b **8**

at the carbon of the methoxy group of **2b** during the hydrolysis, since ^{18}O was incorporated into the phosphoryl group (P=O) of the phosphonate **7** (*m/z* 610, $[M + 1]^+$) when **2b** was hydrolyzed in $H_2{}^{18}O$.[11] Upon the basis of the relative chemical shifts in phosphonates **7a** ($\delta^{31}P$, +33.85 ppm, $\delta^{13}C$, 10.85 ppm, J = 145.2 Hz) and **7b** ($\delta^{31}P$, +32.41, $\delta^{13}C$, 11.94 (J = 142.7 Hz) we assign the major stereoisomer **7b** as possessing the *R* configuration at phosphorus.[12] We believe the selectivity is based on the relative stabilities of two diastereomeric transition states which yield two diasteromeric hydroxyphosphoranes (**8** → **7a**, **7b**).

Acknowledgment. We thank the U.S. Army Medical Research and Development Command for support of the work under Contract No. DAMD 17-88-C-8021 and Dr. David Lenz, Biochemical Pharmacology Branch of the USAMRICD, for valuable discussions. The research of R.G. was supported in part by the Office of Naval Research.

Supplementary Material Available: Experimental details, molecular structure of **2a**, and tables of phosphorane epimerization, atomic coordinates, and bond lengths and angles (18 pages). Ordering information is given on any current masthead page.

(6) The alcohol **5** and **6** were synthesized from (*S*)-3-hydroxy-2,2-dimethylbutanenitrile prepared by yeast reduction of 2,2-dimethyl-3-oxobutanenitrile. The stereochemistry of the yeast reduction of unsymmetric ketones is well established: Prelog, V. *Pure Appl. Chem.* **1964**, *9*, 119. Zhou, B.-N.; Gopalan, A. S.; VanMiddlesworth, F.; Shieh, W.-R.; Sih, C. J. *J. Am. Chem. Soc.* **1983**, *105*, 5925.

(7) A solution of **2a** (15 mg) in $CDCl_3$ (600 μL) was placed in a sealed tube and heated at 90 °C for certain periods of time; the course of the reaction was determined with ^{31}P NMR.

(8) (a) Holmes, R. R. Pentacoordinated Structures. In *Progress in Inorganic Chemistry*; Lippard, S. J., Ed.; John Wiley & Sons: New York, 1984; Vol. 32, p 119. (b) Holmes, R. R. *Pentacoordinated Phosphorus*; American Chemical Society: Washington, DC, 1980; Vol. I, pp 101-233.

(9) The phosphoranes **1** and **2** are extremely labile to aqueous acids but hydrolytically stable in neutral and basic conditions; they remained unchanged for at least 3 days in the presence of water or 0.1 N NaOH at room temperature. Also see ref 4.

(10) Similar results were obtained for the acid hydrolysis of **1**: the diastereomer **1a** gave a 63:36 mixture of the corresponding diasteromeric phosphonates, whereas **1b** afforded a 1:1 mixture. These phosphonates are configurationally stable, and no epimerization around phosphorus was observed in acidic conditions used for the hydrolysis.

(11) No oxygen of phosphonate **7b** was exchanged in the same reaction conditions as used for the hydrolysis (0.2 N HCl in $H_2{}^{18}O$, 25 °C, 20 min).

(12) For the four stereoisomers of a series of compounds $CH_3PO(OCH_3)[OCH(CH_3)C(CH_3)_2X]$ the P_R series has for $\delta^{31}P$, $\delta^{13}C$ (ppm) X = CN, 32.57, 10.87; NH_2, 32.26, 10.72; $NHCO(CH_2)_2CO_2H$, 34.98, 10.36; while in the P_S series X = CN, 31.64, 11.76; NH_2, 31.51, 12.97; $NHCO(CH_2)_2CO_2H$, 33.83, 11.44. The P_S chemical shift is invariably higher field, while the ^{13}C chemical shift is invariably lower field. The configuration of **7b** is therefore corresponding to P_S series but is designated *R* because of the sequence rule.

Synthesis of β-Mannopyranosides by Intramolecular Aglycon Delivery

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As the biological significance of glycosylation becomes increasingly evident,[1] the generation of reliable methods for the synthesis of complex oligosaccharides becomes even more important. Despite the great ingenuity applied in recent years to the development of new synthetic methods for stereospecific glycoside formation,[2] the construction of the 1,2-*cis*-β-D-mannopyranosidic linkage remains a particular problem.[3] We present here a new strategy for the construction of 1,2-*cis*-glycosidic linkages and the results obtained on its application to β-mannosides. This strategy (Scheme I) involves first the covalent attachment of the aglyconic alcohol (**1**) to a group on O-2 of a latent glycosyl donor (**2**) in a coupling reaction where stereospecificity is not a concern. Adduct **3** could conceivably be prepared in two ways as shown. Next, the aglycon is delivered *intra*molecularly in a concerted reaction to produce the intermediate **4**, which, on quenching with water, would give β-mannoside **5**. Quenching with other nucleophiles might yield β-mannosides protected at O-2. There are many possibilities for groups X, Y, and Z, and their selection will be critical to the success of this approach. We report here the results of initial experiments with one such set of groups.

Treatment of vinyl ether **6** (obtained in 83% yield by reaction of the 2-*O*-acetate with Tebbe's reagent[4]) with an equimolar

(1) (a) Hakomori, S. *Adv. Cancer Res.* **1989**, *52*, 257. (b) Paulsen, J. C. *Trends Biochem. Sci.* **1989**, 272. (c) Kobata, A. *Glycobiology* **1990**, *1*, 5. (d) Brandley, B. K.; Swiedler, S. J.; Robbins, P. W. *Cell* **1990**, *63*, 861. (e) Feizi, T. *Trends Biochem. Sci.* **1991**, *16*, 84. (f) Cumming, D. A. *Glycobiology* **1991**, *1*, 115.

(2) (a) Lemieux, R. U. *Chem. Soc. Rev.* **1978**, *7*, 423. (b) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 823. (c) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212. (d) Sinay, P. *Pure Appl. Chem.* **1991**, *63*, 519. (e) Nicolaou, K. C.; Caulfield, T. J.; Kataoka, H.; Stylianides, N. A. *J. Am. Chem. Soc.* **1990**, *112*, 3693. (f) Sugimoto, M.; Fujikura, K.; Nunomura, S.; Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1990**, *31*, 1435. (g) Mootoo, D. R.; Konradsson, P.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1989**, *111*, 8540. (h) Kahne, D.; Walker, S.; Cheng, Y.; Van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 6881. (i) Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661. (j) Friesen, R. W.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6656. (k) Kahne, D.; Yang, D.; Lim, J. J.; Miller, R.; Paguaga, E. *J. Am. Chem. Soc.* **1988**, *110*, 8716. (l) Nicolaou, K. C.; Caulfield, T.; Kataoka, H.; Kumazawa, T. *J. Am. Chem. Soc.* **1988**, *110*, 7910. (m) Mootoo, D. R.; Date, V.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 2662. (n) Sato, S.; Ito, Y.; Nukada, T.; Nakahara, Y.; Ogawa, T. *Carbohydr. Res.* **1987**, *167*, 197.

(3) (a) Paulsen, H.; Lebuhn, R.; Lockhoff, O. *Carbohydr. Res.* **1982**, *103*, C7. (b) Ogawa, T.; Kitajima, T.; Nukada, T. *Carbohydr. Res.* **1983**, *123*, C5. (c) Garegg, P. J.; Ossowski, P. *Acta Chem. Scand.* **1983**, *B37*, 249. (d) David, S.; Malleron, A.; Dini, C. *Carbohydr. Res.* **1989**, *188*, 193. (e) Gunther, W.; Kunz, H. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1050. (f) Auge, C.; Warren, C. D.; Jeanloz, R. W. *Carbohydr. Res.* **1980**, *82*, 85. (g) Ekborg, G.; Lindberg, B.; Lonngren, J. *Acta Chem. Scand.* **1972**, *26*, 3287.

(4) (a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611. (b) Ali, M. H.; Collins, P. M.; Overend, W. G. *Carbohydr. Res.* **1990**, *205*, 428.

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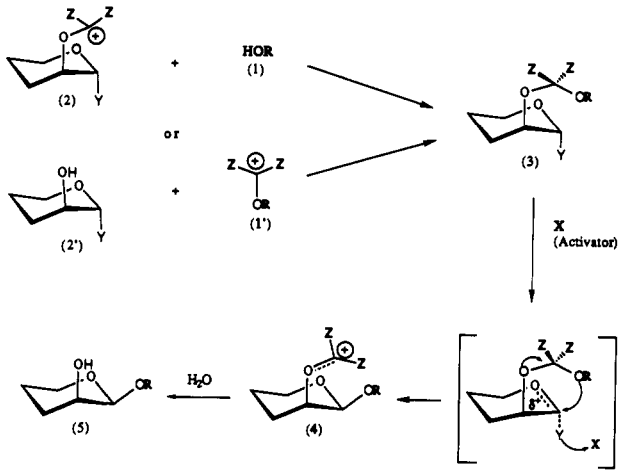
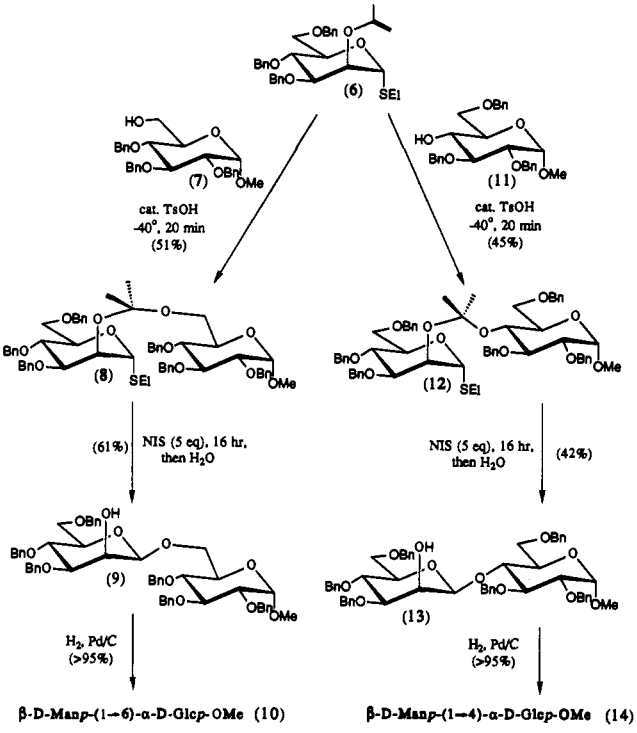
Scheme I



Scheme II



amount of either **7** or **11** produced adduct **8** (51%) or **12** (45%) (Scheme II). No attempt was made to improve these yields since the objective of this work was to evaluate the potential of **8** and **12** to undergo intramolecular rearrangements to β-glycosides. Reaction of **8** or **12** with *N*-iodosuccinimide (NIS, 5 equiv) in dichloromethane was initiated at −5 °C, and the mixture was warmed to room temperature overnight. After aqueous workup and chromatography, the β-linked disaccharide **9** or **13** was obtained in 61% or 42% yield, respectively. The yields were lower when less NIS was used. No α-linked disaccharides could be detected in any of the chromatographic fractions.

We believe that the formation of the β-linked disaccharides occurs intramolecularly for the following reasons. When the rearrangement of **8** to **9** was carried out in the presence of added methanol (1 equiv), the yield of **9** was unchanged. This speaks against a free anomeric carbocation as an intermediate. When the rearrangement of **12** to **13** was performed in the presence of added methanol (1 equiv), the yield of **13** was diminished to 11%, reflecting the well-known lower reactivity of O-4 of glucopyranosides. It is noteworthy that no α-methyl glycoside was formed, only methyl 3,4,6-tri-*O*-benzyl-β-D-mannopyranoside (40%), this latter product probably derived by trans-acetalation of **12** with methanol. The methyl aglycon was then delivered intramolecularly as shown in Scheme I (R = CH_3). Compounds **9** and **13** were deprotected to produce disaccharides **10** and **14**.[5]

In conclusion, intramolecular aglycon delivery appears to be a promising new method for the stereospecific synthesis of β-mannosides which can probably also be extended to the formation of other 1,2-*cis*-glycosides. The yields reported have not been optimized, and we expect that a careful study to define groups X, Y, and Z in Scheme I will yield an important new synthetic method for oligosaccharide synthesis.

Acknowledgment. We acknowledge the support of the Alberta Heritage Foundation for Medical Research for a scholarship (F.B.) and the Natural Sciences and Engineering Research Council of Canada.

(5) **10**: ^{1}H NMR (D_2O, 300 MHz) H-1 4.80 (d, J = 3.7 Hz), H-1′ 4.68 (s), H-2′ 4.03 (d, $J_{2',3'}$ = 3.0 Hz), OCH_3 3.41 (s, 3 H); ^{13}C NMR (D_2O, 75 MHz) C-1′ 101.4 ($J_{C1',H1'}$ = 160 Hz), C-1 100.1 ($J_{C1,H1}$ = 170 Hz), OCH_3 56.0. **14**: ^{1}H NMR (D_2O, 300 MHz) H-1 4.80 (d, J = 4.0 Hz), H-1′ 4.74 (s), H-2′ 4.05 (d, $J_{2',3'}$ = 3.0 Hz), OCH_3 3.41 (s, 3 H); ^{13}C NMR (D_2O, 75 MHz), C-1′ 100.8 ($J_{C1',H1'}$ = 160 Hz), C-1 99.9 ($J_{C1,H1}$ = 171 Hz), OCH_3 56.0.

In Situ Complexation Directs the Stereochemistry of N-Glycosylation in the Synthesis of Oxathiolanyl and Dioxolanyl Nucleoside Analogues

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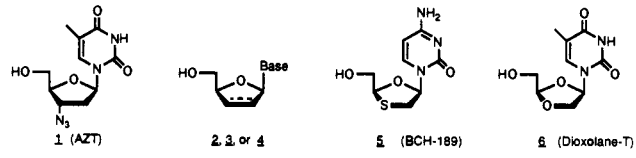
The emergence of 3′-azido-3′-deoxythymidine (AZT, **1**) as an anti-HIV agent has demonstrated the biological importance of nucleosides lacking a 3′-hydroxyl function.[1] Moreover, the discovery that other 2′,3′-dideoxynucleosides inhibit the replication and infectivity of HIV has spurred both the search for superior therapeutic agents and the development of different synthetic approaches to nucleosides.[2] As the result of extensive structure-function studies on nucleoside analogues, a number of 2′,3′-dideoxynucleoside derivatives have been selected for clinical evaluation.[3] These include D4T (2′,3′-didehydro-3′-deoxythymidine, **2**), DDC (2′,3′-dideoxycytidine, **3**), and DDI (2′,3′-dideoxyinosine, **4**).



Recently, the unnatural 3′-heteronucleosides 3′-thia-2′,3′-dideoxycytidine (**5**, BCH-189)[4] and 3′-oxa-3′-deoxythymidine (**6**,

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(4) (a) Belleau, B.; et al. *Abstracts of Papers*, Fifth International Conference on AIDS, Montreal; Abstract No. T.C.O.1, Ottawa, Ontario, 1989. (b) Belleau, B.; Belleau, P.; Nguyen-Ba, N. European Patent Office 90301335.7, 1990. (c) Liotta, D. C.; Choi, W. B. Patent Cooperation Treaty WO 91/11186, 1991.

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