methyl byproducts or toxic chromium(VI) oxidants for the preparation of ketonucleosides. Easy isolation of the 2-iodobenzoic acid byproducts and their reconversion to the periodinane reagent[19] (I) make this an economically feasible oxidant. Oxidation of 5′-*O*-tritylthymidine (**1c**) with I has provided the corresponding 2′-deoxy-3′-ketonucleoside (**2c**) in the highest yield (93%) presently reported. Preparation and characterization of 5′-*O*-TBDPS-2′-deoxy-3′-ketoadenosine (**2d**), the first "stable" purine 2′-deoxy-3′-ketonucleoside derivative, has been achieved by oxidation of 5′-*O*-TBDPS-2′-deoxyadenosine (**1d**) with I.

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A Concise Approach to β-(1→6)- and β,β-(1→1)-Linked *C*-Disaccharides. The Synthesis of *C*-β,β-Trehalose Peracetate

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Summary: The fluoride ion mediated condensation of the tetraacetate of β-*C*-glucopyranosylnitromethane with *aldehydo* sugars, followed by the elaboration of the resulting nitroaldol, provides an expeditious approach to β-(1→6)-linked (from hexodialdose derivatives) and β,β-(1→1)-linked (from *aldehydo*-hexoses) *C*-disaccharides. *C*-β,β-Trehalose peracetate, **13**, the first example of a *C*-disaccharide related to the trehaloses, was prepared using this methodology.

The replacement of the interglycosidic oxygen atom in disaccharides by a methylene group generates a class of extremely interesting, nonmetabolizable analogues of disaccharides, namely *C*-disaccharides. As chemically inert isosters of natural disaccharides, these pseudodisaccharides constitute potential inhibitors of glycosidases[1] and disaccharidases such as those present in the digestive tract.[2] The interest of these compounds is further supported by the recent discovery of the antiretroviral activity of certain glycosidase inhibitors (e.g., castanospermine).[3]

Since the first synthesis of a *C*-disaccharide by Sinaÿ and Rouzaud[4] (D-Glc-*C*-β-(1→6)-D-GlcOMe), several approaches to *C*-disaccharides have been investigated,[5,6] and the syntheses of such analogues as *C*-maltose,[5a] *C*-cellobiose,[5a] and others[5b-f] have been reported. Because of the difficulties inherent to the coupling of two sugar units by way of a carbon–carbon linkage, the first successful syntheses of *C*-disaccharides represent a major achievement. The long synthetic sequences involved limit, however, the availability of the final product. Our interest in *C*-disaccharides and derivatives as potential therapeutic agents for metabolic diseases prompted us to develop novel and short approaches to this type of pseudodisaccharides. We report, in this paper, a concise methodology for the synthesis of β-(1→6)- and β,β-(1→1)-linked *C*-disaccharides and its application to the preparation of two novel *C*-disaccharides, namely D-Glc-*C*-β-(1→6)-D-Gal (**7**) and *C*-β,β-trehalose peracetate (**13**).

Our approach is based on the utilization of *C*-glycosylnitromethane derivatives (e.g., **1**), available in two steps from the parent hexose,[7] as C-nucleophilic reaction partners. As suggested by the successful condensation of a 5-deoxy-5-*C*-nitroribofuranose derivative with *aldehydo* sugars,[8] and by the successful silylation of **1** to the corresponding silyl nitronates,[9] it was expected that the nitronate anion derived from **1** would be stable and could be used as a C-nucleophile *without concurrent β-elimination.* Indeed, the fluoride ion mediated[8,10] nitroaldol condensation of **1** with D-galactose-derived aldehyde **2** afforded the 7-deoxy-7-nitrotridecose derivative **3** in 52% yield[11] as one major diastereomer. The auxiliary functional groups of **3** were then removed in three steps (Scheme I): (1) acetylation–elimination of acetic acid, to give nitroalkene **4** [90%; *E*/*Z* mixture (~1:1), slowly isomerizing to *Z* only; *Z* isomer, δ H-6, 6.305; *E* isomer, δ H-6, 7.30]; (2) selective reduction of the double bond of **4** using $NaBH_4$,[12] to give 7-nitro derivative **5** (59%; ratio of epimers at C-7, 8:1); (3)

(1) Lalégerie, P.; Legler, G.; Yon, J. M. *Biochimie* **1982**, *64*, 977.
(2) Truscheit, E.; Frommer, W.; Junge, B.; Müller, L.; Schmidt, D. D.; Wingender, W. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 744.
(3) (a) Walker, B. D.; Kowalski, M.; Goh, W. C.; Kozarsky, K.; Krieger, M.; Rosen, C.; Rohrschneider, L.; Haseltine, W. A.; Sodroski, J. *Proc. Natl. Acad. Sci.* **1987**, *84*, 8210. (b) Sunkara, P. S.; Bowlin, T. L.; Liu, P. S.; Sjoerdsma, A. *Biochem. Biophys. Res. Commun.* **1987**, *148*, 206.
(4) Rouzaud, D.; Sinaÿ, P. *J. Chem. Soc., Chem. Commun.* **1983**, 1353.
(5) Syntheses of *C*-disaccharides: (a) Babirad, S. A.; Wang, Y.; Kishi, Y. *J. Org. Chem.* **1987**, *52*, 1370. (b) Giese, B.; Witzel, T. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 450. (c) Goekjian, P. G.; Wu, T. C.; Kang, H. Y.; Kishi, Y. *J. Org. Chem.* **1987**, *52*, 4823. (d) Giese, B.; Hoch, M.; Lamberth, C.; Schmidt, R. R. *Tetrahedron Lett.* **1988**, *29*, 1375. (e) Wang, Y.; Goekjian, P. G.; Ryckman, D. M.; Kishi, Y. *J. Org. Chem.* **1988**, *53*, 4153. (f) Dyer, U. C.; Kishi, Y. *J. Org. Chem.* **1988**, *53*, 3384.
(6) Syntheses of precursors or analogs of *C*-disaccharides: (a) Aebischer, B.; Bieri, J. H.; Prewo, R.; Vasella, A. *Helv. Chim. Acta* **1982**, *65*, 2251. (b) Beau, J. M.; Sinaÿ, P. *Tetrahedron Lett.* **1985**, *26*, 6189. (c) Danishefsky, S. J.; Pearson, W. H.; Harvey, D. F.; Maring, C. J.; Springer, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 1256. (d) Jarosz, S.; Mootoo, D.; Fraser-Reid, B. *Carbohydr. Res.* **1986**, *147*, 59. (e) Dawson, I. M.; Johnson, T.; Paton, R. M.; Rennie, R. A. *J. Chem. Soc., Chem. Commun.* **1988**, 1339. (f) Carcano, M.; Nicotra, F.; Panza, L.; Russo, G. *J. Chem. Soc., Chem. Commun.* **1989**, 642. (g) Boschetti, A.; Nicotra, F.; Panza, L.; Russo, G.; Zucchelli, L. *J. Chem. Soc., Chem. Commun.* **1989**, 1085. (h) Motherwell, W. B.; Ross, B. C.; Tozer, M. J. *Synlett* **1989**, 68. (i) Schmidt, R. R.; Preuss, R. *Tetrahedron Lett.* **1989**, *30*, 3409.
(7) (a) Petrus, L.; Bystricky, S.; Bilik, V. *Chem. zvesti* **1982**, *36*, 103. (b) Förtsch, A.; Kogelberg, H.; Köll, P. *Carbohydr. Res.* **1987**, *164*, 391.
(8) (a) Synthesis of a tunicamine derivative: Suami, T.; Sasai, H.; Matsuno, K. *Chem. Lett.* **1983**, 819. (b) Synthesis of octosyl acid A: Kozaki, S.; Sakanaka, O.; Yasuda, T.; Shimizu, T.; Ogawa, S.; Suami, T. *J. Org. Chem.* **1988**, *53*, 281.
(9) Martin, O. R.; Khamis, F. E.; Rao, S. P. *Tetrahedron Lett.* **1989**, *30*, 6143.
(10) (a) Sakanaka, O.; Ohmori, T.; Kozaki, S.; Suami, T.; Ishii, T.; Ohba, S.; Saito, Y. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1753. (b) Maguire, M. P.; Feldman, P. L.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 948 and references cited.
(11) All yields are for isolated products.
(12) See, for example: (a) Fukuda, Y.; Kitasato, H.; Sasai, H.; Suami, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 880. (b) Bhattacharjya, A.; Mukhopadhyay, R.; Pakrashi, S. C. *Synthesis* **1985**, 886.

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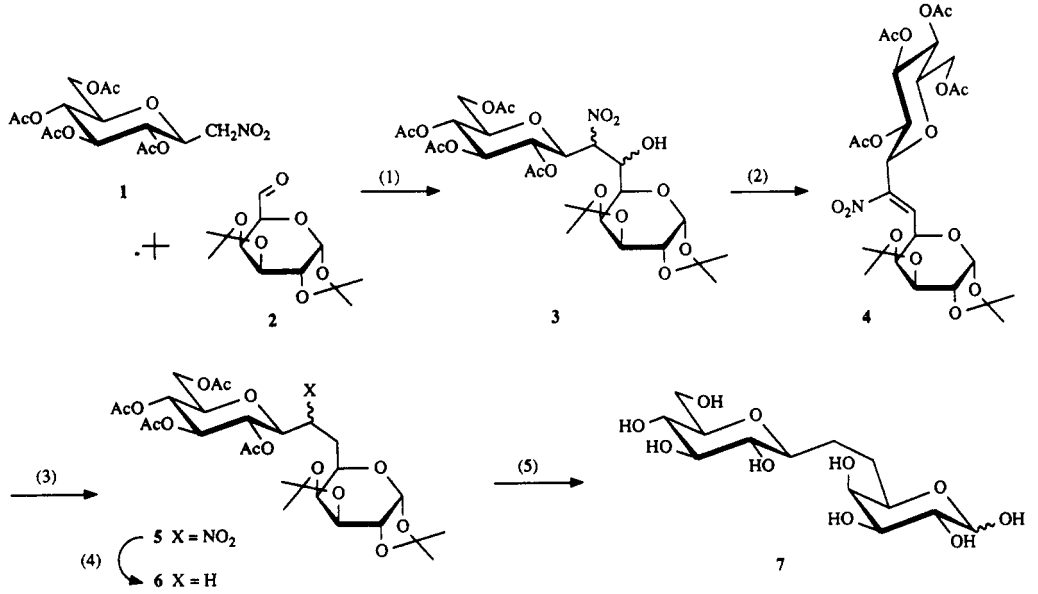
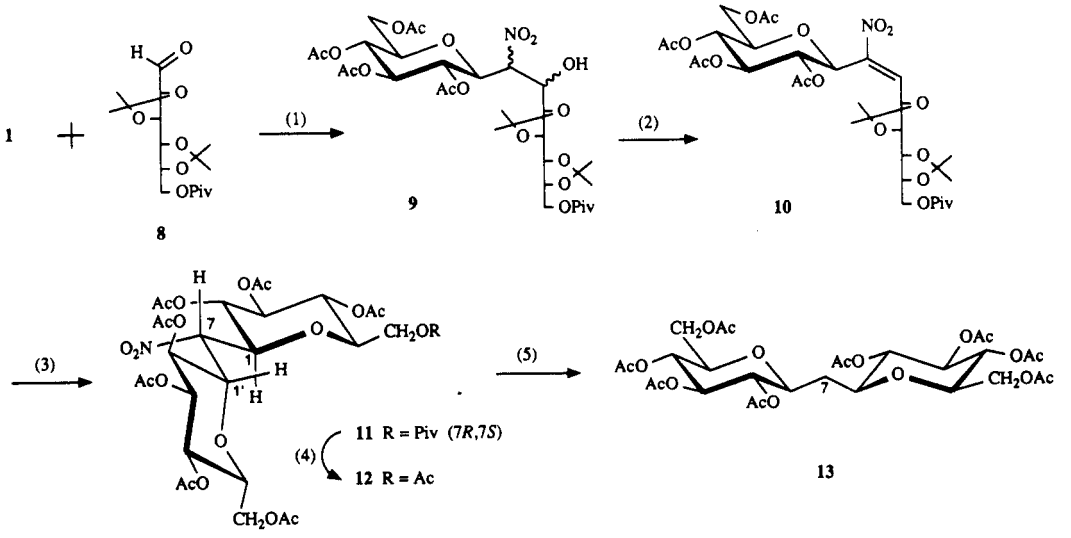
Scheme I[a]



[a] (1) KF, 18-crown-6; CH_3CN; (2) Ac_2O; pyridine–$CHCl_3$; (3) $NaBH_4$ (reverse addition mode); EtOH–CH_2Cl_2; (4) Bu_3SnH, AIBN; toluene, Δ; (5) (i) MeONa; MeOH; (ii) Amberlite IR-120 (H^+); H_2O, 70 °C. Yields in text.

Scheme II[a]



[a] (1) KF, 18-crown-6; CH_3CN; (2) Ac_2O; pyridine–$CHCl_3$; (3) (i) 80% AcOH, Δ; (ii) Ac_2O–pyridine; (4) (i) MeONa, MeOH; (ii) Ac_2O–BF_3·Et_2O; (5) Bu_3SnH, AIBN; toluene, Δ. Yields in text.

reductive denitration of **5** by way of a radical process,[13] to give protected *C*-disaccharide **6** [60%; $[\alpha]^{20}_D$ −45.6° (*c* 1.8, $CHCl_3$)]. Deprotection of **6** in two steps afforded the novel, free *C*-disaccharide **7**[14] [89%, β/α ratio: 2.4:1; $[\alpha]^{20}_D$ +11.9° (*c* 1.4, H_2O)], thereby concluding an eight-step synthesis[15] of the C-analogue of D-Glc-β-(1→6)-D-Gal from D-glucose and D-galactose.

Applied to open chain *aldehydo*-hexose derivatives as electrophilic reaction partners, the same methodology should give access to the extremely interesting and yet unknown C-analogues of (1→1)-linked disaccharides such as, for example, β,β-trehalose. It was anticipated that the open-chain fragment of the condensation product could be recyclized to a "C-pyranoside" by way of a thermodynamically controlled intramolecular Michael addition upon cleavage of the protecting groups. Thus, condensation of **1** with *aldehydo*-glucose derivative **8**[16] gave 7-deoxy-7-nitrotridecitol derivative **9** (Scheme II) as a mixture of diastereomers which were immediately converted into nitroalkene **10** (29% for three steps;[11] apparently only *E* isomer: δ H-6, 7.105). The treatment of **10** with 80% acetic acid at reflux temperature (30 min), followed by the acetylation and the separation of the resulting cyclized

(13) Ono, N.; Kaji, A. *Synthesis* **1986**, 693. For recent examples of reductive cleavage of secondary nitro groups, see: Yoshikawa, M.; Cha, B. C.; Nakae, T.; Kitagawa, I. *Chem. Pharm. Bull.* **1988**, *36*, 3714 and 3718.

(14) Selected ^{13}C NMR data (90 MHz, D_2O; reference δ Me_2CO 30.5 ppm): δ 96.59 (C-1β), 92.45 (C-1α), 61.33 (C-13), 26.10 and 27.47 (C-6,7). All data reported are for equilibrated aqueous solutions of **7**. For comparison, the specific rotation of equilibrated D-Glc-β-(1→6)-D-Gal is $[\alpha]^{18}_D$ +13.9° (H_2O) (Freudenberg,K.; Wolf, A.; Knopf, E.; Zaheer, S. H. *Ber.* **1928**, *61*, 1743).

(15) Overall unoptimized yield from *C*-glucosylnitromethane: 15%.

(16) Prepared from D-glucose diethyl dithioacetal as follows: (1) $(CH_3)_3CCOCl$, pyridine–$CHCl_3$, 0 °C (72%); (2) $(CH_3)_2C(OCH_3)_2$, cat. TsOH (73%); (3) $HgCl_2$, $CdCO_3$; $(CH_3)_2CO$–H_2O (90%). For a related example, see: Lorenz, K.; Lichtenthaler, F. W. *Tetrahedron Lett.* **1987**, *28*, 6437.

products by flash chromatography, afforded the desired, peracylated pseudodisaccharide **11** as well as a substantial amount of its *C*-pyranosyl/*C*-furanosyl isomer (ratio of ring-size isomers: 55:45, 49.5% overall yield); both were obtained as *R*/*S* mixtures at C-7. In order to get rid of the pivaloyl group, and thus convert **11** into a pseudosymmetric structure, compound **11** was deacylated and reacetylated (54% for both steps) to give the remarkable pseudodisaccharide **12** which bears two identical glucopyranosyl units [syrup; $[\alpha]^{20}_D$ -5.3° (*c* 1.5, $CHCl_3$)]; as a result of the presence of the nitro group at C-7 (pseudoasymmetric center), the two sugar units are, however, diastereotopic, and the ^1H NMR parameters of **12**[17] provide, thus, direct evidence on the conformation about the interglycosidic linkages: the magnitude of the $J_{7,1}$ and $J_{7,1'}$ coupling constants[17] indicates a nearly anti relationship between H-1 and H-7, and gauche between H-1′ and H-7, which is consistent with the sterically most favorable conformation of **12** about C-1–C-7 and C-1′–C-7 (see **12** in Scheme II); this conformation (equivalent to standard torsional angles in disaccharides[18] ϕ, ψ = -60°, -60°) is essentially the same as the one predicted to be the most stable for β,β-trehalose and model compounds.[19]

Removal of the nitro group of **12** using Bu_3SnH afforded the symmetric β,β-trehalose analogue **13**[20] [76%; mp 141.4–142.4 °C; $[\alpha]^{20}_D$ -17.2° (*c* 1.5, $CHCl_3$)], the first example of a (1→1)-linked *C*-disaccharide related to trehalose. Interestingly, the specific rotation of **13** was found to be identical with that measured and reported[21] in 1909 by E. Fischer for β,β-trehalose octaacetate! Detailed structural studies on these and related pseudodisaccharides are in progress and will be reported separately.

The results described in this paper demonstrate that the nitroaldol reaction of a β-*C*-glycosylnitromethane derivative wih *aldehydo* sugars provide a simple means of achieving the synthesis of β-(1→6)- and β,β-(1→1)-linked *C*-disaccharides with *minimal functional group manipulation*.

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(17) Selected ^1H NMR data ($CDCl_3$) δ 4.71 (dd, 1 H, $J_{7,1}$ = 8.2, $J_{7,1'}$ = 2.9 Hz, H-7), 4.41 (dd, 1 H, $J_{1,2}$ 9.7 Hz, H-1), 4.19 (dd, 1 H, $J_{1',2'}$ = 10.5 Hz, H-1′).

(18) Stoddart, J. F. *Stereochemisty of Carbohydrates*; Wiley-Interscience: New York, 1971.

(19) Tvaroska, I.; Vaclavic, L. *Carbohydr. Res.* **1987**, *160*, 137.

(20) ^{13}C NMR (90 MHz, $CDCl_3$): δ 20.54 (2 C), 20.63, 20.67 (CH_3CO's), 33.34 (0.5 C, C-7), 62.53 (C-6), 68.92, 71.96, 73.25, 74.38, 76.02 (C-1–C-5), 169.42, 169.63, 170.22, and 170.42 (CH_3CO's). ^1H NMR (360 MHz, $CDCl_3$): δ 1.60 (m, 1 H, apparent $J_{7,1}$ = 5.4 and 7.6 Hz, H-7's), 1.99, 2.03, 2.05, and 2.10 (4 s, 4 × 3 H, CH_3CO's), 3.60 (ddd, 1 H, $J_{4,5}$ = 10.0, $J_{5,6A}$ = 2.4, $J_{5,6B}$ = 5.35 Hz, H-5), 3.70 (ddd, 1 H, $J_{1,2}$ = 10.0 Hz, H-1), 4.10 (dd, 1 H, $J_{6A,6B}$ = 12.25 Hz, H-6A), 4.22 (dd, 1 H, H-6B), 4.85 (t, 1 H, $J_{2,3}$ = 9.2 Hz, H-2), 5.03 and 5.20 (2 t, 2 × 1 H, $J_{3,4}$ ~ 9.5 Hz, H-3 and H-4).

(21) Fischer, E.; Delbrück, K. *Ber.* **1909**, *42*, 2776. See also: Birch, G. G. *Adv. Carbohydr. Chem.* **1963**, *18*, 201.

Reduction of β-Hydroxy Ketones with Catecholborane. A Stereoselective Approach to the Synthesis of Syn 1,3-Diols

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Summary: The stereoselective reduction of acyclic β-hydroxy ketones to syn 1,3-diols may be achieved with the mild reducing agent catecholborane. In certain instances reaction stereoselectivity may be enhanced through rhodium(I) catalysis.

The reduction of acyclic β-hydroxy ketones in a predictable and stereoselective manner is of considerable current interest, since syn and anti 1,3-diols are recurring units in a variety of polyacetate- and polypropionate-derived natural products. From the accumulated body of data, several generalizations have emerged. For example, when the reducing agent possesses the capacity to bind to the hydroxyl function with *intramolecular transfer of hydride*, the anti 1,3-diol is formed preferentially (eq 1).[1] In contrast, when an additive (e.g., Et_2B-X) is employed to preorganize the substrate prior to *intermolecular hydride addition* (e.g., by $NaBH_4$), the syn isomer becomes the major product (eq 2).[2] In the present paper, we report an operationally convenient method for the syn-selective reduction of β-hydroxy ketones which complements the existing methods. In these reactions, catecholborane (CB) apparently serves both to provide substrate organization through boron aldolate formation and to function as the hydride donor.[3]

Several representative experiments serve to illustrate the dual role which catecholborane might be assuming in these reactions. Treatment of the β-hydroxy ketone **1** (Table I, entry 1) with 2.2 equiv of catecholborane in THF[4] (-10 °C, 90 min) affords the syn diol **2** in 82% yield

(1) For anti-selective reductions of β-hydroxy ketones, see: (a) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.*, in press. (b) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560-3578. (c) Anwar, S.; Davis, A. P. *Tetrahedron* **1988**, *44*, 3761-3770.

(2) For syn-selective reductions of β-hydroxy ketones, see: (a) Hanamoto, T.; Hiyama, T. *Tetrahedron Lett.* **1988**, *29*, 6467-6470. (b) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Chem. Lett.* **1987**, 1923-1926. (c) Bonadies, F.; DiFabio, R.; Gubioti, A.; Mecozzi, S.; Bonini, C. *Tetrahedron Lett.* **1987**, *28*, 703-706. (d) Kiyooka, S.; Kuroda, H.; Shimasaki, Y. *Tetrahedron Lett.* **1986**, *27*, 3009-3112. (e) Kathawala, F. G.; Prager, B.; Prasad, K.; Repic, O.; Shapiro, M. J.; Stabler, R. S.; Widler, L. *Helv. Chim. Acta* **1986**, *69*, 803-805. (f) Narasaka, K.; Pai, F.-C. *Tetrahedron* **1984**, *40*, 2233-2238. (g) Narasaka, K.; Pai, F.-C. *Chem. Lett.* **1980**, 1415-1418.

(3) Kabalka, G. W.; Baker, J. D.; Neal, G. W. *J. Org. Chem.* **1977**, *42*, 512-517.

(4) Reductions may be performed in CH_2Cl_2 as well as THF. For example, **1** is reduced to the corresponding syn diol in CH_2Cl_2 (80% yield, syn:anti = 10:1).

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