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Studies Directed Toward the Total Synthesis of Acarbose: The Trisaccharide Domain

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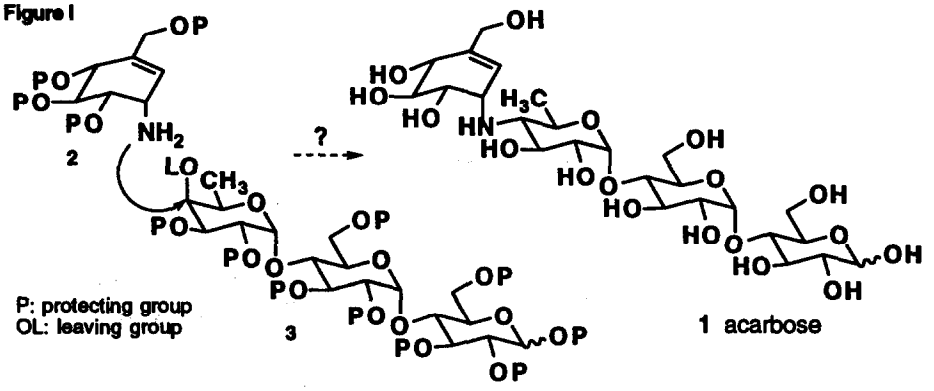
Abstract: The use of glycals in the construction of α-glycosides is illustrated in the synthesis of the trisaccharide domain of acarbose.

Acarbose is a very potent α-glycosidase inhibitor.[1] It was isolated from the strains of actinomycetales in 1977[2], and is currently undergoing evaluation in Europe as an orally active anti diabetic agent.[3] We have set for ourselves the goal of a total synthesis of acarbose. A construction of acarbose has been achieved by Ogawa,[4] however the carbohydrate domain has not been obtained by total synthesis. In the previous Letter we described a novel synthesis of the aglycone valienamine entity using an S_N2' displacement reaction of an allylic spiroepoxide. In this paper, we focus on the synthesis of the carbohydrate domain.

Figure I



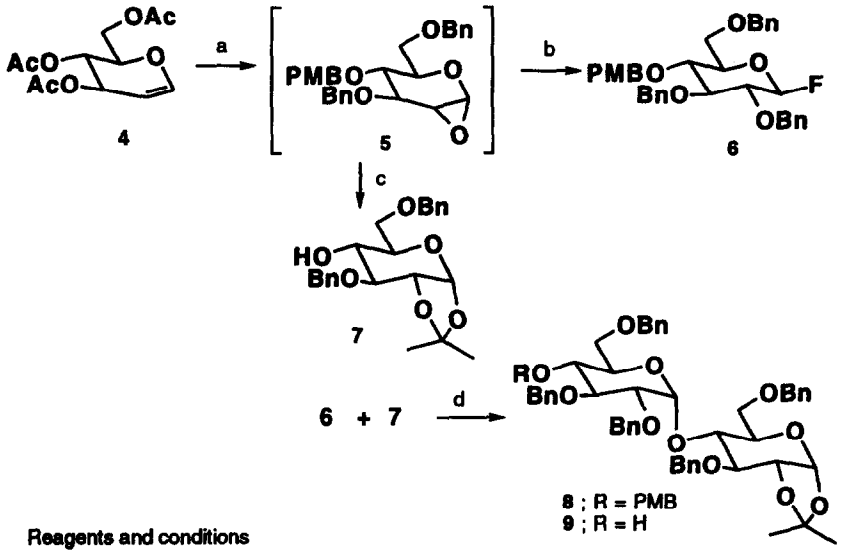
This problem held particular interest for us in view of the involvement of our laboratory with glycals as building blocks in the construction of oligosaccharides. The α-linked 1,2-anhydro sugars, available in one step from glycals, have been widely exploited as glycosyl donors to generate a variety of β-glycosides.[5]

We saw in the synthesis of the acarbose carbohydrate domain, the opportunity to confront the issue of utilizing α-glycal epoxides in the construction of oligosaccharides containing one or

more α linkages. Earlier an approach to this problem was described. Fluoridolysis of such an epoxide leads to 1β, 2α fluorohydrins.[6] Protection of the C_2 hydroxyl group with a non participating function allows for introduction of an α glycosidic bond by use of a 1β fluoro glycosyl donor.[7] The challenge of a synthesis of the oligosaccharide domain of acarbose provided us with a chance to study the implementation of this concept in a more functionalized setting. *We report herein the first total synthesis of the oligosaccharide domain of acarbose using glycal epoxides as building blocks.*

The program started with commercially available triacetyl glucal (**4**) which was converted by straightforward steps to epoxide (**5**). This epoxide was used for the introduction of a 1β fluoro function.[6] The resultant C2 hydroxyl group was protected as a "non-participating" benzyl ether (see compund **6**). Alternatively epoxide **5** was solvolyzed with aqueous acetone (see compound **7**) and the resulting 1,2 diol was protected as its 1α,2α isopropylidene derivative. Oxidative removal of the PMB group liberated the C4 hydroxyl group (see compound **5**). Coupling of **6** and **7** was carried out under standard Mukaiyama-Nicolaou[8,9] conditions providing disaccharide **8**. Once again, removal of the PMB group liberated a unique hydroxyl group at C4' (see compound **9**).

Figure II

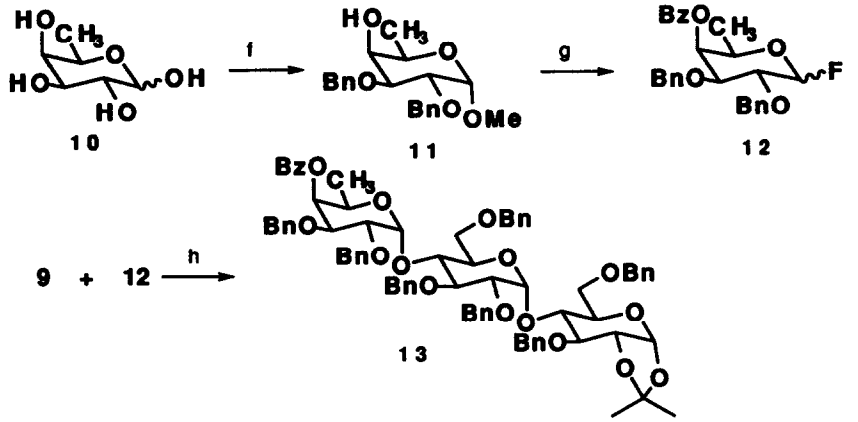


Reagents and conditions

a) NaOMe, MeOH, 97 %; $(Bu_3Sn)_2O$, benzene, reflux, BnBr, $(n\text{-}Bu)_4NBr$, reflux, 73%; NaH, PMBCl, DMF, 82%; dimethyl dioxirane, acetone, quant., b) TBAF, THF, overnight, 66%; NaH, BnBr, DMF, 72%, c) aq-acetone, reflux, >90 %; acetone, p- TsOH, $CuSO_4$, 73 %; DDQ, wet CH_2Cl_2, 86%, d) $SnCl_2$, $AgClO_4$, 2,6-di-t-butylpyridine, 4 Å MS, Et_2O, 73 % (8:1 = α:β)

In a parallel sequence, D-fucose (**10**) was converted via its methyl glycoside, to its 2,3 dibenzyl derivative **11**.[10] Protection of the C4 hydroxyl group of **11** as a benzoate occurred uneventfully as did conversion of the methyl glycoside at C_1 to the anomeric mixture of fluorosugars, shown as **12**.[10] Coupling of **9** + **12** was, again, conducted under Mukaiyama-Nicolaou [8,9] conditions to provide **13**. There was also generated the C1" epimer of **13** (**13**: C1" epimer=~6:1). Compound **13**[11] was fully purified by HPLC.

Figure III



Reagents and conditions
f) MeOH, H^+- resin, reflux, 45%; $(Bu_3Sn)_2O$, toluene, reflux; BnBr, $(n\text{-}Bu)_4NBr$, toluene, reflux, 45 % g) BzCl, DMAP, Py, 89 %; HCl-aq-AcOH, reflux, 71 %; DAST, THF, -30 °, 15 min, 94 %; h) $SnCl_2$, $AgClO_4$, di-t-butylpyridine, 4Å MS, Et_2O

It will be noted that in **13** the axial hydroxyl of the fucose domain is uniquely protected as a benzoate. The possibility of coupling suitably equipped versions of valienamine with a leaving group derived from this accessible C4" hydroxyl group constitutes a central element of the total synthesis plan.

Clearly, much remains to be learned before a fully pleasing total synthesis of acarbose is achieved by this methodology. However, the synthesis of trisaccharide **13** already demonstrates the value of glycal epoxides in providing simplified access to α-glycosides including a system with two such consecutive linkages. The potential of using this reiteratable logic in the synthesis of cyclodextrins[12] is apparent.

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11 ^{1}H-NMR data for **9** (400 MHz, $CDCl_3$) δ 7.32-7.20 (m, 25H), 5.67 (d, 1H, J = 4.9 Hz), 5.20 (d, 1H, J = 3.6 Hz), 4.92 (d, 1H, J = 11.3 Hz), 4.71 (d, 1H, J = 11.3 Hz), 4.65 (d, 1H, J = 12.0 Hz), 4.56-4.52 (m, 5H), 4.49 (d, 1H, J = 12.3 Hz), 4.39 (d, 1H, J = 12.2 Hz), 4.28 (m, 1H), 4.12-4.09 (m, 1H), 4.04-3.98 (m, 2H), 3.79-3.61 (m, 6H), 3.56-3.53 (m, 1H), 3.49-3.44 (m, 2H), 1.57 (s, 3H), 1.37 (s, 3H); for **13** (400 MHz, $CDCl_3$) δ 7.99 (d, 2H, J = 8.4, 1.4 Hz), 7.56 (m, 1H), 7.42 (t, 2H, J = 8.0 Hz), 7.32-7.10 (m, 35H), 5.69-5.67 (m, 2H), 5.45 (d, 1H, J = 1.9 Hz), 5.16 (d, 1H, J = 3.7 Hz), 4.92 (d, 1H, J = 11.7 Hz), 4.84 (d, 1H, J = 11.6 Hz), 4.72 (d, 1H, J = 11.2 Hz), 4.67 -4.64 (m, 2H), 4.59-4.52 (m, 4H), 4.48-4.42 (m, 5H), 4.40-4.28 (m, 1H), 4.15-3.90 (m, 7H), 3.84-3.75 (m, 3H), 3.62-3.48 (m, 3H), 1.59 (s, 3H), 1.37 (s, 3H), 0.99 (d, 3H, J = 6.5 Hz)

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