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Intramolecular *C*-glycosylation of 2-*O*-benzylated pentenyl mannopyranosides: remarkable 1,2-*trans* stereoselectivity

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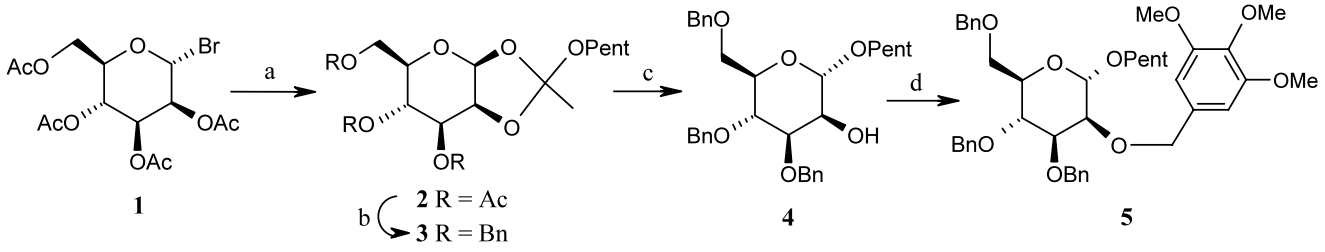
Abstract—The IDCP-promoted intramolecular *C*-glycosylation of pentenyl α-mannopyranosides carrying, at O-2, an activated benzyl group gave, unexpectedly, the 1,2-*trans*-fused bicyclic product which corresponds to an α-*C*-aryl mannopyranose derivative. This remarkable, strained *C*-glycosyl compound was rapidly epimerized to the more stable 1,2-*cis* product on treatment with $BF_3{\cdot}Et_2O$. The IDCP-reaction product could be elaborated into a 2-(α-*C*-mannopyranosyl)-3,4,5-trimethoxybenzyl alcohol derivative.

We have recently shown[1] that 4-pentenyl glucosides constituted useful substrates for the intramolecular *C*-arylation reactions of 2-*O*-benzylated glycosides,[2] particularly with Lewis-acid sensitive benzyl groups. Using this methodology, we were able to achieve the first synthesis of bergenin-related natural products by way of an intramolecular *C*-glycosylation process.[1] The chemoselective activation of pentenyl glycosides[3] combined with a sufficiently reactive benzyl group provide conditions for the intramolecular reaction that are much milder than the previously used hard Lewis acids such as $SnCl_4$, $BF_3{\cdot}Et_2O$, etc.[4] In order to investigate further the reactivity of benzylated pentenyl glycosides and generalize their use in such processes, we have examined the behavior of 4-pentenyl D-mannopyranosides carrying various benzyl groups at O-2. In this context, the interest in the *manno* series is the possibility of creating β-linked *C*-aryl glycosidic structures, which carry the anomeric configuration most commonly found in natural *C*-aryl glycosides. However, this expectation was not born out by experiment. We wish to report in this communication these unexpected results.

The required precursor, partially protected 4-pentenyl α-D-mannopyranoside **4**, was prepared from tetra-*O*-acetyl-α-D-mannopyranosyl bromide **1** (Scheme 1). The reaction of **1** with 4-pentenyl alcohol in the presence of tetrabutylammonium bromide in collidine[5] gave a good yield of the corresponding orthoester **2** (69%, 33 g-scale). Curiously, the formation of this compound under similar conditions had been reported to be unsuccessful;[6] the reactions of pentenyl orthoesters in the *manno* series have been performed so far most frequently from the phenyl-substituted orthoesters.[7] The acetyl groups of **2** were replaced by benzyl groups, and



Scheme 1. *Reagents and conditions*: (a) 4-penten-1-ol (3 equiv.), $n Bu_4NBr$ (0.3 equiv.), collidine, 69–71%; (b) KOH, BnBr, THF, Δ, 92%; (c) i. TMSOTf (cat.), CH_2Cl_2, 0°C, 2 h, ii. MeONa, MeOH, 75%; (d) $ArCH_2Cl$, NaH, DMF, 70%.

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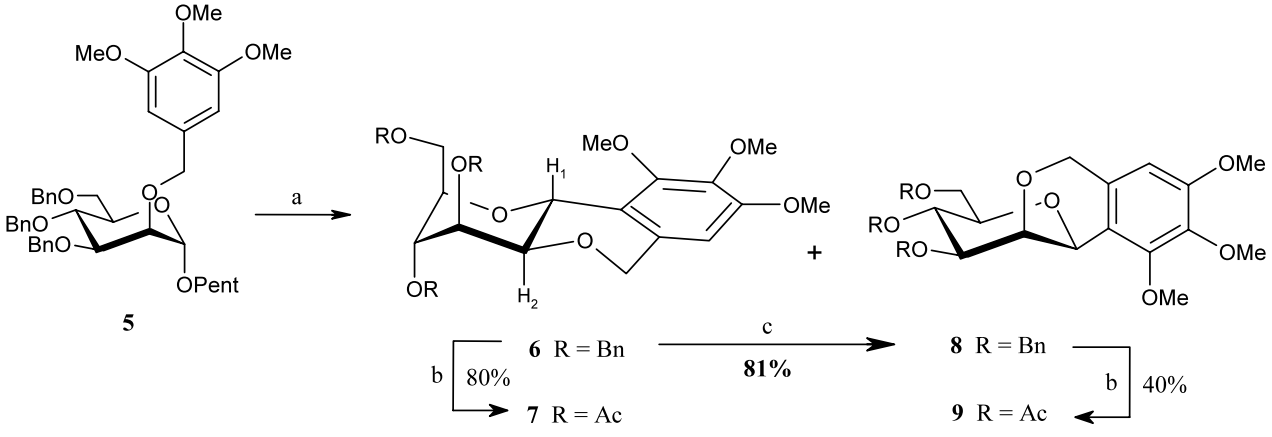
the resulting orthoester **3** was rearranged into the corresponding pentenyl α-mannoside **4** by treatment with trimethylsilyl triflate[8] followed by de-*O*-acetylation at O-2. Benzylation of **4** with 3,4,5-trimethoxybenzyl chloride (from 3,4,5-trimethoxybenzyl alcohol and $SOCl_2$) provided substrate **5** (58%).

Upon treatment with IDCP (iodonium dicollidine perchlorate),[9] compound **5** underwent rapid ring closure by an internal Friedel–Crafts type process; the clean reaction led however, to two products (**6** and **8**) in a ~5:1 ratio (Scheme 2). The two products could be readily separated by chromatography and isolated in 70 and 16% yields, respectively. The NMR analysis of the major product revealed that it had the unexpected 1,2-*trans* configuration (α-*C*-mannosyl arene), and existed in an inverted $^1C_4$-type conformation, and the minor product was the *cis*-fused structure **8** (β-*C*-mannosyl arene). Diagnostic NMR data[10] for the corresponding triacetates **7** and **9** are provided in Figure 1; in particular, the very large, $J_{1,2}$-coupling constant in **7** is characteristic of a nearly diaxial relationship between these two protons. This result is extremely surprising since it appeared that, for both steric and stereoelectronic reasons, the 1,2-*cis* product should have been favored in this intramolecular reaction. In order to evaluate the relative stability of the two products, the *trans* epimer **6** was treated with an equimolar amount of $BF_3{\cdot}Et_2O$; this promoted the essentially instantaneous epimerization at C-1 and the 1,2-*cis*-epimer **8** could be isolated in 81% yield.[11] This result established that compound **6** is the kinetic product and that it is, as expected, markedly less stable than the *cis* structure.

In order to be able to investigate the internal reaction of a 4-pentenyl glycoside under both soft and hard Lewis acidic conditions,[12] we prepared the 2-*O*-(3,5-dimethoxybenzyl) analog of **5**, compound **10**, by benzylation of **4** with 3,5-dimethoxybenzyl chloride (86%). Compound **10** was then reacted with IDCP (Scheme 3). Although the yield of the transformation was low because of extensive iodination of the starting material,[13] the reaction gave, again, a mixture of two products (**11** and **12**) in which the *trans* isomer (**11**) was predominant (ratio ~4/1). Both products also contained an iodine atom,[12] and were deiodinated in high yield with Zn in AcOH, to give **13** and **14**, respectively.

With $BF_3{\cdot}Et_2O$ as the promoter, the glycoside **10** underwent a great deal of degradation, but the *cis*-fused structure **14** could be isolated in 17% yield as the only cyclization product. A better yield of the same product (43%) was obtained by treating **10** with sulfuric acid in AcOH.[2]

The surprising stereoselectivity of the internal *C*-glycosylation of **5** promoted by IDCP, which occurs with



Scheme 2. *Reagents and conditions*: (a) IDCP (2 equiv.), CH_2Cl_2, 3 h, rt, 86%; (b) i. H_2, Pd/C, AcOEt, ii. Ac_2O, pyr; (c) $BF_3{\cdot}Et_2O$, CH_2Cl_2.

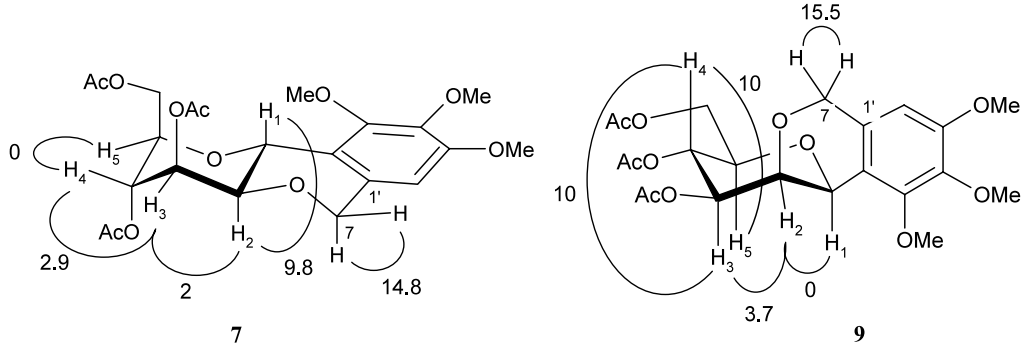
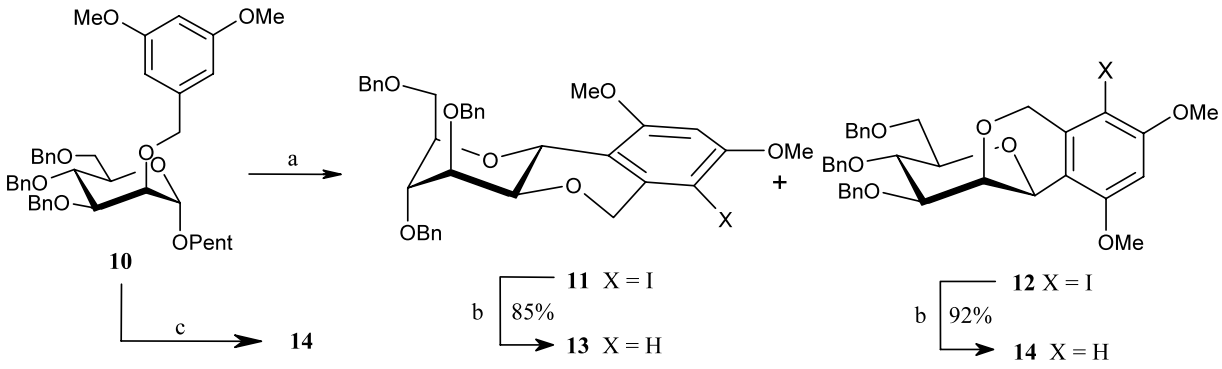
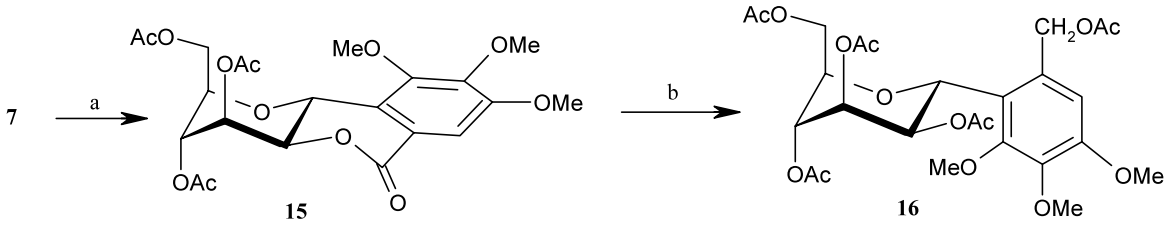


Figure 1. *J*-values (Hz).



Scheme 3. *Reagents and conditions*: (a) IDCP (2 equiv.), CH_2Cl_2, 3 h, rt; (b) Zn, AcOH; (c) H_2SO_4/AcOH, 43%.



Scheme 4. *Reagents and conditions*: (a) $RuCl_3$, $NaIO_4/CCl_4$–CH_3CN–H_2O, 41%; (b) $LiAlH_4$, THF, then Ac_2O, py, 40%.

retention of configuration, is probably best explained by a double displacement mechanism. Possible nucleophiles to promote the first substitution include collidine and the perchlorate anion which are liberated upon I^+ consumption; however, an intermediate β-*N*-glycosylated collidinium ion would have a very strong propensity to exist in an equatorial disposition (formerly known as reverse anomeric effect)[14] thus making the 1,2-*trans* attack difficult. Alternatively, a β-perchlorate[15] might force the mannopyranose ring to adopt the inverted $^1C_4$ chair conformation present in the final product and thus occupy the axial position favored by its strong anomeric effect; this would provide the highly reactive 1,2-*cis* intermediate necessary for the alkylation of the electron-rich 2-*O*-arylmethyl group by a 1,2-*trans* trajectory. Clearly, the reaction does not occur by way of a 'free' oxocarbenium ion since a 1,2-*cis* attack on such a species would be much more favorable than the 1,2-*trans* process. These observations may have important repercussions on the interpretation of the mechanism of other reactions of 4-pentenyl glycosides.

The synthetic usefulness of the intramolecular *C*-arylation process described above was demonstrated by the elaboration of **7** into an α-*C*-mannosylated benzene derivative (Scheme 4): oxidation of the primary benzylic position in **7** using catalytic ruthenium tetroxide[16] afforded the bergenin-related lactone **15**.[17] The lactone was then cleaved reductively with $LiAlH_4$ to provide, after reacetylation, the α-*C*-mannosyl trimethoxybenzyl acetate **16**, a compound whose structure is related to that of the chaetiacandins.[18] The sugar substituent of the *C*-aryl glycoside **16** remains for steric reasons in the $^1C_4$ conformation.[19] It is important to note that the internal *C*-arylation of 4-pentenyl glucosides[1,4c] as well as mannosides give access stereoselectively to α-*C*-aryl glycosides whereas equivalent intermolecular processes generally lead to the thermodynamically more favorable β-epimers.[20,21]

In conclusion, 4-pentenyl mannopyranosides carrying an activated benzyl group at O-2 revealed unusual behavior in the intramolecular *C*-arylations promoted by IDCP, by giving the kinetically favored *trans*-fused product. Further work is in progress to determine the origin of this unexpected stereoselectivity.

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10. NMR data for **7**: ^{1}H NMR (250 MHz, $CDCl_3$, attributions verified by H,H-COSY): δ 2.06, 2.11, 2.12 (3s, 3×3H, 3 $COCH_3$), 3.78, 3.80, 3.88 (3s, 3×3H, 3 OMe), 3.81 (m, 1H, H-2), 4.24 (t, 1H, $J=7.2$, H-5), 4.53 (dd, 1H, $J_{5,6a}=6.7$, $J_{6a,6b}=11.6$ Hz, H-6a), 4.71 (dd, 1H, $J_{5,6b}=7.8$ Hz, H-6b), 4.71 (d, 1H, $J_{7a,7b}=14.8$ Hz, H-7a), 4.92 (d, 1H, H-7b), 5.00 (d, 1H, $J_{3,4}=2.9$ Hz, H-4), 5.11 (d, 1H, $J_{1,2}=9.8$ Hz, H-1), 5.42 (t, 1H, $J=2.3$ Hz, H-3), 6.33 (s, 1H, H_{Ar}); ^{13}C NMR (62.9 MHz, $CDCl_3$, attributions verified by H,C-correlation): δ 21.2, 21.3 (Ac), 56.5 (OMe), 61.0 (C-6), 61.1 (OMe), 61.6 (OMe), 62.6 (C-1), 69.0 (C-3), 69.7 (2C, C-4, C-7), 73.6 (C-2), 75.1 (C-5), 103.1 (C-6′), 119.7 (C-2′), 131,7 (C-1′), 142.2, 153.8, 154.1 (C-3′,4′,5′), 169.7, 169.8, 171.0 (MeCOO). For **9**: ^{1}H NMR (250 MHz, $CDCl_3$, attributions verified by H,H-COSY): δ 2.02, 2.06, 2.14 (3s, 3×3H, 3 $COCH_3$), 3.83, 3.86, 3.96 (3s, 3×3H, 3 OMe), 3.78–3.99 (m, 2H, H-2, H-5), 4.15 (dd, 1H, $J_{5,6a}=2.5$, $J_{6a,6b}=12.2$ Hz, H-6a), 4.23 (dd, 1H, $J_{5,6b}=5.9$ Hz, H-6b), 4.62 (s, 1H, H-1), 4.66 (d, 1H, $J_{7a,7b}=15.5$ Hz, H-7a), 4.96 (d, 1H, H-7b), 5.18 (dd, 1H, $J_{2,3}=3.7$, $J_{3,4}=10.2$ Hz, H-3), 5.39 (t, 1H, $J=9.8$ Hz, H-4), 6.34 (s, 1H, H-6′).
11. For the related epimerization of an α-*C*-mannosylated phloroacetophenone derivative, see: Kumazawa, T.; Sato, S.; Matsuba, S.; Onodera, J.-I. *Carbohydr. Res*. **2001**, *332*, 103–108.
12. Compound **5** undergoes rapid 2-*O*-debenzylation in the presence of hard, oxophilic Lewis acids.
13. The reaction gave iodinated starting material as the major product, an indication that the reaction of the aromatic residue with IDCP is faster than that of the pentenyl group. Iodination took place at C-2 of the 3,5-dimethoxybenzyl group. Isolated yields: iodinated starting material: 37%, **11**: 18%, **12**: 5%.
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17. NMR data for **15**: ^{1}H NMR (250 MHz, C_6D_6, attributions verified by H,H-COSY): δ 1.56, 1.71, 1.82 (3s, 3×3H, 3 $COCH_3$), 3.26, 3.69, 3.75 (3s, 3×3H, 3 OMe), 4.09 (dd, 1H, $J_{5,6a}=5.7$, $J_{6a,6b}=11.9$ Hz, H-6a), 4.34 (dd, 1H, $J=5.7$, 9 Hz, H-5), 4.58 (dd, 1H, $J_{1,2}=10.7$, $J_{2,3}=2.8$ Hz, H-2), 4.93 (dd, 1H, $J_{5,6b}=9.1$ Hz, H-6b), 5.08 (d, 1H, $J_{3,4}=3.1$ Hz, H-4), 5.30 (d, 1H, $J_{1,2}=10.7$ Hz, H-1), 5.61 (t, 1H, $J=2.7$ Hz, H-3), 7.52 (s, 1H, H-6′); ^{13}C NMR (62.9 MHz, C_6D_6, attributions verified by H,C-correlation): δ 20.8. 21.0 (Ac), 56.1, 61.2, 62.2 (3 OMe), 60.2 (C-6), 63.8 (C-1), 67.8 (C-3), 69.3 (C-4), 74.9 (C-2), 75.6 (C-5), 110.7 (C-6′), 120.5 (C-2′), 127.4 (C-1′), 149.9, 152.8, 154.8 (C-3′,4′,5′), 163.9 (C-7), 169.4, 169.6 (MeCOO).
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