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Stereospecific Ester Activation in Nitrite-Mediated Carbohydrate Epimerization

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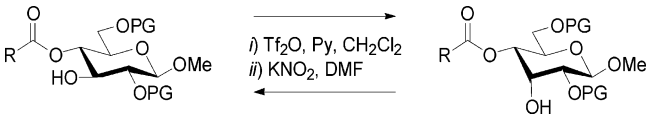
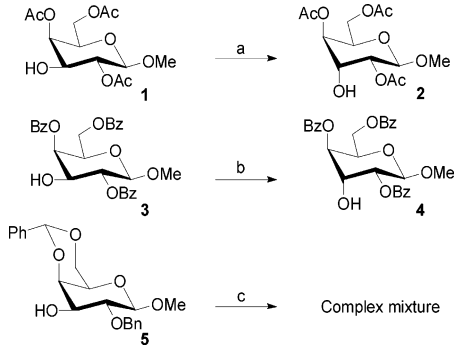
Received December 28, 2005



The Lattrell−Dax method of nitrite-mediated substitution of carbohydrate triflates is an efficient method to generate structures of inverse configuration. In the present study, epimerization of gluco- and galactopyranoside derivatives to the corresponding allo- and gulopyranoside structures by triflation/nitrite treatment has been investigated. It was found that a neighboring ester group was essential for the reactivity of the nitrite-mediated triflate inversion. Furthermore, a good inversion yield also depended on the relative configuration of the neighboring ester group to the triflate. Only with the ester group in the equatorial position, whatever the configuration of the triflate, did the reaction proceed smoothly, whereas a neighboring axial ester group proved largely inefficient. The results were subsequently used to predict the inversion of glucopyranoside derivatives to the mannopyranoside epimers.

Epimerization of carbohydrate structures to the corresponding epi-hydroxy stereoisomers is an efficient means to generate compounds with inverse configuration that may otherwise be cumbersome to prepare.[1] Several different synthetic methods have been developed, including protocols based on the Mitsunobu reaction,[2] sequential oxidation/reduction routes,[3] as well as enzymatic methods,[4] all of which with their respective advantages and shortcomings. A common route to stereocenter inversion in carbohydrate chemistry involves the triflation of a given hydroxyl group, followed by substitution using a variety of nucleophilic reagents. This method was used by Dax and co-workers who first reported that glycoside triflate displacement by nitrite ion, a reaction first found by Lattrell and Lohaus,[5] produced carbohydrates with inverse hydroxy configuration under very mild conditions.[6] Despite its reported efficiency,[7−10] the Lattrell−Dax method has unfortunately not been extensively adopted, likely because of difficulties in predicting the outcome for specific structures. This fact has been addressed in the present study, where it has been found that the protecting group pattern is an essential element in the reaction, both with regard to configuration and functionality.

SCHEME 1 [a]



[a] Reagents and conditions. (a) i: Tf_2O, pyridine, CH_2Cl_2, −20 to 10 °C, 2 h. ii: KNO_2, DMF, 50 °C, 3 h (**2**, 73%). (b) i: Tf_2O, pyridine, CH_2Cl_2, −20 to 10 °C, 2 h. ii: KNO_2, DMF, 50 °C, 6 h, (**4**, 77%). (c) i: Tf_2O, pyridine, CH_2Cl_2, −20 to 10 °C, 2 h. ii: KNO_2, DMF, 50 °C, 3 h.

Our first notion of the inversion reaction emanated from studies in thiosaccharide synthesis,[11−14] and whereas reported studies suggested certain reactivity patterns,[6,15−17] no detailed explanations were given. As a first approach to investigate the effect of the protecting group pattern to the inversion reaction, the epimerization of galactopyranosides, where the hydroxyl group in the 3-position was free and the other positions were separately protected with acetyl (**1**), benzoyl (**3**), and benzyl/benzylidene groups (**5**), respectively, was studied (Scheme 1). These compounds were subjected to conventional triflation by triflic anhydride, followed by treatment with potassium nitrite in DMF at 50 °C. As can be seen, good yields were in these cases obtained only on the condition that esters were chosen as protecting groups, benzoyl groups being slightly less activating than the acetyl counterparts. When the ester protecting groups were replaced by benzyl/benzylidene groups, a mixture of different products was instead obtained.

Similar results were obtained from the epimerization of glycopyranosides, where the hydroxyl group in the 4-position

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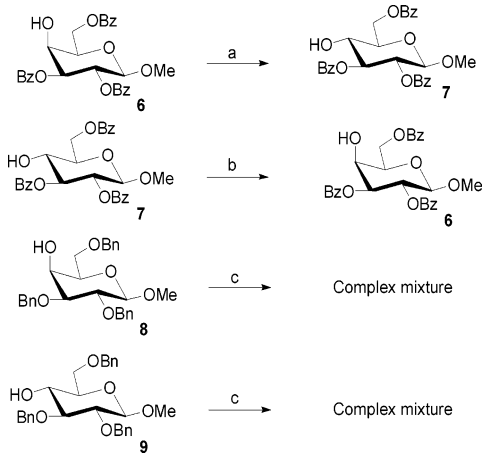
10.1021/jo052662i CCC: $33.50
Published on Web 03/15/2006

SCHEME 2 [a]



[a] Reagents and conditions. (a) i: Tf_2O, pyridine, CH_2Cl_2, −20 to 10 °C, 2 h. ii: KNO_2, DMF, 50 °C, 5 h, (**7**, 75%). (b) i: Tf_2O, pyridine, CH_2Cl_2, −20 to 10 °C, 2 h. ii: KNO_2, DMF, 50 °C, 2 h, (**6**, 70%). (c) i: Tf_2O, pyridine, CH_2Cl_2, −20 to 10 °C, 2 h. ii: KNO_2, DMF, 50 °C, 0.5 h.

was unprotected, and all other positions were protected with either benzoyl or benzyl groups (Scheme 2). Only when an ester group was present at the carbon adjacent to the carbon atom carrying the leaving triflate group did the reaction proceed smoothly, the axially oriented triflate being less reactive than the equatorial leaving group. In contrast to this effect, no efficient reaction occurred when benzyl groups were employed where compound mixtures were instead rapidly obtained. These results suggest that a neighboring ester group is able to induce or activate the inversion reaction, whereas an ether derivative is unable to produce this effect. The results also show that the inversion reaction proceeded smoothly regardless of the triflate configuration.

To further analyze these findings and explore the effect of neighboring ester group configurations of triflate to the reactivity, other inversion systems were designed (Table 1). To avoid the effects from the 2- and 6-positions and to isolate the effects arising from ester groups in the 3- and 4-positions, the 2- and 6-positions were protected with benzyl ether groups. Thus, a range of compounds where one of the hydroxyl groups in the 3- or 4-position was protected with an acetyl group were prepared and subsequently tested in the nitrite-mediated inversion reactions. The experimental results presented in Table 1 clearly indicate that the configuration of the neighboring ester group was decisive for the reactivity of the epimerization reaction. Good inversion yields depended mainly on the relative configurations between the two groups, and only with the ester group in the equatorial position, whatever the configuration of the triflate, did the reaction proceed smoothly, whereas a neighboring axial ester group proved inefficient.

Rapid internal triflate displacements by neighboring acetyl or benzoyl groups have been reported when the ester group and the leaving group have trans-diaxial relationships.[11] This leads to products where the configuration is retained, thus excluding these combinations from the present investigation. This internal displacement is indicative of the fast formation of an intermediate acyloxonium carbocation, stabilized by polar solvent. In our cases, compounds **11** and **14** hold 3,4-trans configurations in diequatorial relationships, where the internal triflate displacement by the neighboring ester group is considerably less efficient. Contrary to this situation, compounds **12** and **15** hold 3,4-cis configurations, where the ester groups are in the equatorial positions, a structural situation largely excluding the conventional neighboring group participation.[18,19]

The results obtained seem to point to the importance of a neighboring group (acyloxonium) effect, where compounds **11** and **14** (3,4-trans) expressed a higher reactivity as a result of activation from the neighboring ester group in inducing the inversion reaction compared to compounds **12** and **15** (3,4-cis). This is reflected in the longer reaction times for the 3,4-cis compounds, as displayed in Table 1. However, acyloxonium formation is still unlikely to be the sole explanation of the results, contradictory to the results for two reasons: first, starting compounds **6**, **12**, and **15** all have a cis relationship between the ester and the leaving group, which largely disqualifies acyloxonium formation;[18,19] and second, formation of a carbocation intermediate would result in a nucleophilic displacement from the triflate face of the compound leading to retention (double inversion) of configuration rather than single inversion.

However, that acyloxonium formation is important in the trans-configuration cases was further supported by studies with added water. Thus, compounds **11** and **14**, both with 3,4-trans-diequatorial relationships, mainly yielded compounds **12** and **15** from reaction with potassium nitrite in dry DMF. If on the other hand wet DMF was used, compounds **10** and **13** were instead obtained as the main products (Table 2). This suggests acyloxonium formation to the five-membered-ring intermediate, which rapidly collapses in the presence of water to produce the axial ester and the equatorial hydroxyl group. These results are indicative of (partial) acyloxonium formation in the trans-configuration cases, but that the nitrite ion is unable to open the five-membered ring from either the triflate face or from attacking the carbonyl cation, as has been suggested for water.[15] More importantly, the ester group is, therefore, likely to induce or stabilize the attacking nitrite ion regardless of the trans- or cis-configurational relationships.

The effects observed for the ether-protected carbohydrates are likely a result of their lower degree of positive charge destabilization than the corresponding ester groups, leading to side reactions such as ring contraction and elimination.[20,21]

To further test the hypothesis of ester activation in the nitrite-mediated inversion reaction, glucopyranoside compounds **16** and **18** were synthesized (Scheme 3). Instead of observing the inversion behavior in the 3- and 4-positions of the hexopyranosides, the 2- and 3-positions were probed (2,3-trans). If the induction argument would hold valid, the ester-protecting group would prove efficient in inducing the inversion, whereas the corresponding ether protecting group would fail to produce this effect. The results are displayed in Scheme 3, and as can be seen, the hypothesis was valid also for these compounds. The ester-protected glucopyranoside compound **16** afforded the inversion mannopyranoside product **17** in good yield, whereas the ether-protected compound **18** proved inefficient. In this case, slightly longer reaction times were, however, necessary due to the lower reactivity of the 2-OTf derivative.

In conclusion, it has been demonstrated that esters play highly important roles in the Lattrell−Dax reaction, facilitating nitrite-

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TABLE 1. Epimerization Reactions Studied

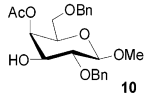
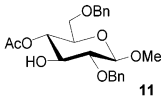
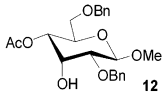
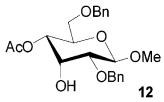
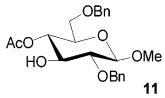
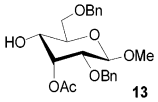
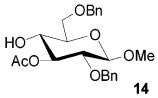
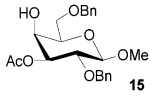
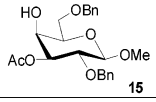
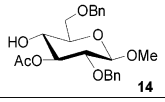
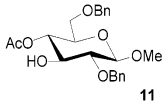
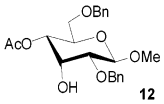
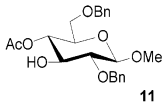
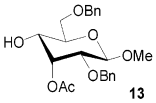
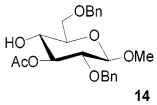
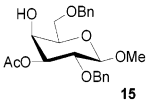
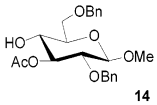
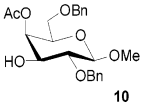
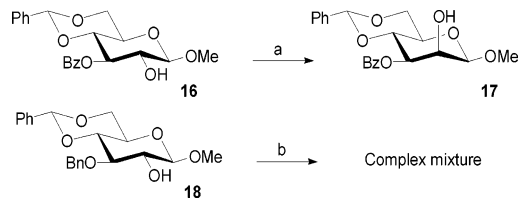
Reactant	Time/h	Product	Yield/%
 **10**	3	Complex mixture	-
 **11**	0.5	 **12**	69
 **12**	4	 **11**	73
 **13**	3	Complex mixture	-
 **14**	1.5	 **15**	72
 **15**	4	 **14**	75

TABLE 2. Water Effects in Studied Nitrite-Mediated Inversion Reactions

Reactant	Nucleophile[a]	Product	Yield/%
 **11**	KNO_2	 **12**	69
 **11**	H_2O	 **13**	70
 **14**	KNO_2	 **15**	72
 **14**	H_2O	 **10**	70

[a] i: Tf_2O, pyridine, CH_2Cl_2, −20 to 10 °C, 2 h. ii: KNO_2, 50 °C, DMF, 0.5−1.5 h or H_2O, rt, DMF, 6 h.

SCHEME 3 [a]



[a] Reagents and conditions. (a) i: Tf_2O, pyridine, CH_2Cl_2, −20 to 10 °C, 2 h. ii: KNO_2, DMF, 50 °C, 6 h, (**17**, 74%). (b) i: Tf_2O, pyridine, CH_2Cl_2, −20 to 10 °C, 2 h. ii: KNO_2, DMF, 50 °C, 3 h.

mediated carbohydrate epimerizations. Despite the higher reactivity of carbohydrate triflates protected with ether functionalities, these compounds proved inefficient in these reactions, where mixtures of compounds were rapidly obtained. Neighboring ester groups, on the other hand, could induce the formation of inversion compounds in good yields. The reactions further demonstrated stereospecificity, inasmuch as axially oriented neighboring ester groups were unproductive and only equatorial ester groups induced the nucleophilic displacement reaction. These findings expand the utility of this highly useful reaction in carbohydrate synthesis as well as for other compound classes.

Experimental Section

General Synthesis of Triflate Derivatives. To a solution of the suitably O-protected methyl β-D-glycoside, carrying an unprotected OH at C3 or C4 (0.3 g, 0.94 mmol), in CH_2Cl_2 (5 mL) was added pyridine (0.65 mL) at −20 °C. Trifluoromethanesulfonic anhydride (0.53 g, 1.88 mol) in CH_2Cl_2 (2 mL) was added dropwise, and the mixture was stirred while allowing to warm from −20 °C to 10 °C over 2 h. The resulting mixture was subsequently diluted with CH_2Cl_2 and washed with 1 M HCl, aqueous $NaHCO_3$, water, and brine. The organic phase was dried over Na_2SO_4 and concen-

trated in vacuo at low temperature. The residue was used directly in the next step without further purification.

General Inversion of Triflate Derivatives. KNO_2 (5 equiv) was added to a solution of the protected triflate residue (20 mg) in dry DMF (2.0 mL). After stirring at 50 °C for 1−6 h, the mixture was diluted with CH_2Cl_2 and washed with brine. The organic phase was dried with $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash column chromatography (5:2, hexanes−ethyl acetate) afforded the inversion products.

Methyl 2,4,6-Tri-*O*-acetyl-*β*-D-gulopyranoside (2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.98 (dd, 1H, $J_{3,4}$ = 3.9 Hz, $J_{4,5}$ = 1.6 Hz, H_4), 4.93 (dd, 1H, $J_{1,2}$ = 8.1 Hz, $J_{2,3}$ = 3.1 Hz, H_2), 4.74 (d, 1H, $J_{1,2}$ = 8.1 Hz, H_1), 4.30 (td, 1H, $J_{4,5}$ = 1.6 Hz, $J_{5,6}$ = 6.5 Hz, H_5), 4.14−4.33 (m, 3H, H_3, H_{6a}, H_{6b}), 3.51 (s, 3H, OMe.), 2.13 (s, 3H, OAc), 2.12 (s, 3H, OAc), 2.05 (s, 3H, OAc). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.6, 170.2, 169.5, 99.1, 70.5, 69.9, 69.5, 67.6, 61.9, 56.8, 21.0, 20.8, 20.7. $[\alpha]^{20}_D$ = −103 (*c* 2.0, $CHCl_3$). Anal. Calcd for $C_{13}H_{20}O_9$·1/2H_2O: C, 47.42; H, 6.43. Found: C, 47.49; H, 6.42.

Methyl 2,4,6-Tri-*O*-benzoyl-*β*-D-gulopyranoside (4). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38−8.14 (m, 15H, 3 × OBz), 5.43 (dd, 1H, *J* = 4.0 Hz, *J* = 1.0 Hz, H_4), 5.30 (dd, 1H, $J_{1,2}$ = 8.0 Hz, $J_{2,3}$ = 3.1 Hz, H_2), 5.03 (d, 1H, $J_{1,2}$ = 8.0 Hz, H_1), 4.59−4.68 (m, 2H, H_{6a}, H_{6b}), 4.44−4.52 (m, 2H, H_3, H_5), 3.58 (s, 3H, OMe). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.1 165.5 165.2, 133.6, 133.5, 133.1, 130.0, 129.8, 129.7, 129.6, 129.5, 129.0, 128.6, 128.5, 128.4, 99.5, 71.3, 70.7, 70.1, 68.0, 62.6, 57.0. $[\alpha]^{20}_D$ = +20 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{28}H_{26}O_9$: C, 66.40; H, 5.17. Found: C, 66.22; H, 5.08.

Methyl 4-*O*-Acetyl-2,6-di-*O*-benzyl-*β*-D-glucopyranoside (11). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.25−7.36 (m, 10H, 2 × OBn), 4.79−4.86 (m, 1H, H_4), 4.85, 4.59, 4.50, 4.45 (d, 4H, $J_{a,b}$ = 12.0 Hz, 2 × OCH_aH_bC$_6$H$_5$), 4.25 (d, 1H, $J_{1,2}$ = 7.6 Hz, H_1), 3.60 (td, 1H, $J_{2,3}$ = 9.2 Hz, $J_{3,4}$ = 2.8 Hz, H_3), 3.45−3.55 (m, 3H, H_5, H_{6a}, H_{6b}), 3.57 (s, 3H, OMe), 3.22 (dd, 1H, $J_{1,2}$ = 7.6 Hz, $J_{2,3}$ = 9.2 Hz, H_2), 2.33 (d, 1H, *J* = 2.8 Hz, OH), 1.98 (s, 3 H, OAc). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.4, 138.2, 137.8, 128.5, 128.4, 128.1, 127.9, 127.8, 127.7, 104.2, 81.2, 74.4, 74.2, 73.6, 73.4, 71.1, 69.2, 57.1, 20.9. $[\alpha]^{20}_D$ = +66 (*c* 0.5, $CHCl_3$). Anal. Calcd for $C_{23}H_{28}O_7$·1/2H_2O: C, 64.93; H, 6.87. Found: C, 64.85; H, 6.87.

Methyl 4-*O*-Acetyl-2,6-di-*O*-benzyl-*β*-D-gulopyranoside (12). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.25−7.36 (m, 10H, 2 × OBn), 4.83 (dd, 1H, $J_{3,4}$ = 2.8 Hz, $J_{4,5}$ = 9.7 Hz, H_4), 4.81, 4.65, 4.61, 4.47 (d, 4H, $J_{a,b}$ = 12.0 Hz, 2 × OCH_aH_bC$_6$H$_5$), 4.68 (d, 1H, $J_{1,2}$ = 7.6 Hz, H_1), 4.34 (t, 1H, $J_{2,3}$, $J_{3,4}$ = 2.8 Hz, H_3), 4.08 (m, 1H, H_5), 3.51−3.64 (m, 2H, H_{6a}, H_{6b}), 3.56 (s, 3H, OMe), 3.34 (dd, 1H, $J_{1,2}$ = 7.6 Hz, $J_{2,3}$ = 2.8 Hz, H_2), 2.48 (s, 1H, OH), 1.97 (s, 3H, OAc). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.9, 138.1, 137.7, 128.5, 128.3, 128.0, 127.9, 127.8, 127.6, 101.6, 77.1, 73.4, 73.0, 70.4, 69.1, 68.7, 68.0, 57.1, 20.9. $[\alpha]^{20}_D$ = +106 (*c* 0.5, $CHCl_3$). Anal. Calcd for $C_{23}H_{28}O_7$·1/2H_2O: C, 64.93; H, 6.87. Found: C, 64.98; H, 7.08.

Methyl 3-*O*-Acetyl-2,6-di-*O*-benzyl-*β*-D-gulopyranoside (13). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.25−7.36 (m, 10H, 2 × OBn), 5.61 (t, 1H, $J_{2,3}$, $J_{3,4}$ = 3.1 Hz, H_3), 4.65 (s, 2H, OCH_2C$_6$H$_5$), 4.64 (d, 1H, $J_{1,2}$ = 7.6 Hz, H_1), 4.61, 4.51 (d, 2H, $J_{a,b}$ = 12.1 Hz, OCH_aH_bC$_6$H$_5$), 3.70−3.86 (m, 4H, H_4, H_5, H_{6a}, H_{6b}), 3.53 (s, 3H, OMe), 3.34 (dd, 1H, $J_{1,2}$ = 7.6 Hz, $J_{2,3}$ = 3.1 Hz, H_2), 2.62 (d, 1H, *J* = 4.53 Hz, OH), 2.14 (s, 3H, OAc). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.0, 137.7, 137.6, 128.5, 128.4, 127.9, 127.8, 127.7, 101.4, 75.8, 73.7, 72.5, 72.3, 70.6, 70.5, 68.8, 56.9, 21.0. $[\alpha]^{20}_D$ = −116 (*c* 0.5, $CHCl_3$). HRMS for $C_{23}H_{28}O_7$·Na, 439.1733; found, 439.1723.

Methyl 3-*O*-Acetyl-2,6-di-*O*-benzyl-*β*-D-glucopyranoside (14). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.25−7.36 (m, 10H, 2 × OBn), 4.97 (t, 1H, $J_{2,3}$, $J_{3,4}$ = 9.3 Hz, H_3), 4.83, 4.60, 4.59, 4.56 (d, 4H, $J_{a,b}$ = 12.1 Hz, 2 × OCH_aH_bC$_6$H$_5$), 4.36 (d, 1H, $J_{1,2}$ = 7.9 Hz, H_1), 3.76 (dd, 2H, *J* = 4.57 Hz, *J* = 3.0 Hz, H_6), 3.61 (td, 1H, $J_{4,3}$ = 9.3 Hz, *J* = 3.8 Hz, H_4), 3.56 (s, 3H, OMe), 3.46−3.51 (m, 1H, H_5), 3.33 (dd, 1H, $J_{2,1}$ = 7.9 Hz, $J_{2,3}$ = 9.3 Hz, H_2), 2.92 (d, 1H, *J* = 3.8 Hz, OH), 2.00 (s, 3H, OAc). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.8, 138.3, 137.7, 128.4, 128.3, 127.9, 127.8, 127.7, 127.6, 104.5, 78.7, 77.2, 74.2, 74.1, 73.7, 71.0, 70.1, 57.2, 21.0. $[\alpha]^{20}_D$ = +21 (*c* 4.0, $CHCl_3$). Anal. Calcd for $C_{23}H_{28}O_7$·1/2H_2O: C, 64.93; H, 6.87. Found: C, 65.42; H, 7.01.

Methyl 3-*O*-Acetyl-2,6-di-*O*-benzyl-*β*-D-galactopyranoside (15). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.26−7.36 (m, 10H, 2 × OBn), 4.88 (dd, 1H, $J_{2,3}$ = 10.20 Hz, $J_{3,4}$ = 3.2 Hz, H_3), 4.84, 4.61, 4.59, 4.55 (d, 4H, $J_{a,b}$ = 12.0 Hz, 2 × OCH_aH_bC$_6$H$_5$), 4.35 (d, 1H, $J_{1,2}$ = 7.8 Hz, H_1), 4.11 (t, 1H, $J_{3,4}$, $J_{4,5}$ = 3.25 Hz, H_4), 3.61−3.81 (m, 4H, H_2, H_5, H_{6a}, H_{6b}), 3.58 (s, 3H, OMe), 2.65 (d, 1H, *J* = 4.3 Hz, OH), 2.04 (s, 3H, OAc). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.3, 138.3, 137.5, 128.5, 128.3, 127.9, 127.8, 127.6, 105.0, 76.6, 74.7, 73.8, 72.6, 69.5, 68.4, 57.2, 21.0. $[\alpha]^{20}_D$ = +88 (*c* 0.5, $CHCl_3$). Anal. Calcd for $C_{23}H_{28}O_7$: C, 66.33; H, 6.78. Found: C, 66.11; H, 7.02.

Acknowledgment. This study was supported by the Swedish Research Council, the Swedish Foundation for International Cooperation in Research and Higher Education, the Royal Institute of Technology, and the Carl Trygger Foundation.

Supporting Information Available: General methods, ^{1}H and ^{13}C spectra of compound **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO052662I