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Thermodynamics versus kinetics in hetero-Michael cyclizations: a highly stereoselective approach to access both epimers of a *C*-D-mannopyranoside

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ABSTRACT

A simple method for the stereocontrolled synthesis of both α and β pseudo-anomers of a thio-functionalized C-glycoside is described. A 2,3:4,6-di-*O*-isopropylidene *manno* scaffold is employed to allow a strict control of the diastereoselectivity of the base-catalyzed intramolecular hetero-Michael addition of an alcohol to a vinyl sulfone, by simply changing the temperature of the reaction.

Saccharidic lactols have been early recognized as intermediates of choice for the elaboration of complex, biologically-relevant C-glycosidic architectures.[1,2] The aldehyde species present in solution as a minor isomer in equilibrium with both α- and β-lactol anomers can undergo Wittig-type transformations to yield highly functionalized, acyclic γ- and/or δ-hydroxy substituted unsaturated building blocks.[3] These compounds can subsequently be converted into C-glycosides through electrophile-induced cyclizations whose regio- and stereoselectivities are usually determined by kinetics.[4] Olefins bearing electron-withdrawing groups can alternatively undergo base-catalyzed regioselective hetero-Michael cyclizations. Depending on the experimental conditions, the stereoselectivity of the ring closure can be controlled by either kinetic or thermodynamic factors: at relatively high temperature, an epimeric C-glycoside mixture can equilibrate through a retro-Michael/Michael process. As a consequence in the *pyrano* series, thermodynamic-controlled cyclizations often produce stereoselectively the β pseudo-anomers corresponding to a stabilizing equatorial substitution.[5] Low temperature, kinetically governed ring closures usually lead to mixtures of α- and β-*C*-glycopyranosides, whose composition mainly depends on the nature and stereochemistry of the C-2 substituent[6] and on the configuration of the double bond.[7]

Even if highly powerful, this two-step Wittig/hetero-Michael cyclization pathway to C-glycosides suffers from the difficulty to avoid concomitant uncontrolled ring closure during the olefin-forming reaction (Scheme 1). Slightly basic, stabilized phosphonium ylides sometimes afford cleanly the expected open-chain unsaturated compound,[8] but more commonly give a mixture of cyclic and open-chain isomers. The product distribution is strongly dependent on the substrate (sugar series, protective groups) and on the reaction conditions.[9] Making use of more basic Horner-Wadsworth-Emmons reagents usually results in the formation of a mixture of epimeric C-glycosides,[10] but the β-*C*-pyranoside can be obtained under appropriate equilibrating, thermodynamical conditions.[5a,11]

We recently proposed a general and efficient synthetic pathway to saccharidic vinyl sulfides involving the reaction of a semi-stabilized phosphonium ylide with protected sugar lactols.[12] These compounds are virtually unable to undergo hetero-Michael cyclization,[13] but can easily be oxidized into a variety of further-functionalized Michael acceptor moieties (i.e., vinyl sulfones, sulfoxides, sulfimides, and sulfoximines,...) under conditions that prevent any counterproductive cyclization. This method allows for the ability to access a wide range of open-chain saccharidic olefins for evaluation in the hetero-Michael reaction to form thio-functionalized C-glycosides under kinetic or thermodynamic conditions.

This preliminary report focuses on the model δ-hydroxy vinyl sulfide **1** which can potentially lead to biologically relevant *C*-D-mannopyranosides. *Z*-**1** can be obtained in high yield and

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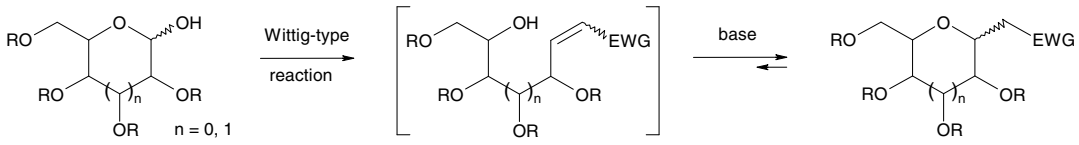


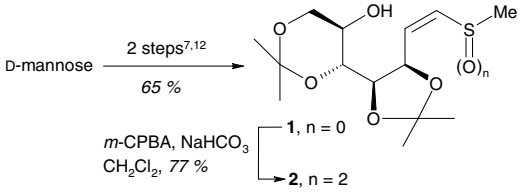
Scheme 1. Wittig/hetero-Michael pathway to C-glycosides.

stereochemical purity from readily available 2,3:4,6-di-*O*-isopropylidene-D-mannopyranose (Scheme 2).[17] We reasoned that the presence of the bulky 2,3-*O*-isopropylidene moiety on the β-face of the C-glycoside product could favor the kinetic formation of the α-compound due to a probable steric clash in the β-transition state, whereas not affecting dramatically the thermodynamic preference to the β equatorial product.

We first concentrated on sulfones: sulfonylmethyl C-glycosides are useful synthetic intermediates in the synthesis of sulfur-free C-glycosidic architectures through Ramberg–Bäcklund rearrangement[14] or reductive desulfonylation[15] and have been successfully employed as non-hydrolyzable mimics of glycosyl-phosphodiesters.[16]

When subjected to standard over-oxidizing conditions (excess *m*-CPBA, CH_2Cl_2),[18] **1** afforded the expected vinyl sulfone **2**[19] albeit in low yields due to partial deprotection of the highly acid-sensitive dioxane-type 4,6-*O*-isopropylidene group in the course of the reaction. Addition of solid sodium bicarbonate to the reaction mixture proved to be efficient enough to prevent any undesirable hydrolysis or acetal migration which could be induced by acidic side-products (Scheme 2).

We then focused on finding conditions for the selective formation of the thermodynamic product in the hetero-Michael reaction. We found that simple treatment of **2** with a catalytic amount (0.25 equiv) of freshly sublimed *t*-BuOK in THF for a few hours at room temperature quantitatively afforded a single epimer (**3** or **4**) of the expected C-glycoside (95% isolated yield).[20] Its pseudo-anomeric configuration was assigned as β(**4**) on the basis of ROESY 2D ^{1}H NMR experiments. No detectable amount of the α-epimer **3** can be observed in the ^{1}H NMR spectrum of the crude product mixture. This selectivity is attributed to a quick equilibrium between the two possible epimeric products, providing a strict thermodynamic control of the reaction. As anticipated, treating isolated **4** with excess *t*-BuOK at higher temperatures and for longer times did not affect its stereoisomeric integrity (Scheme 3).



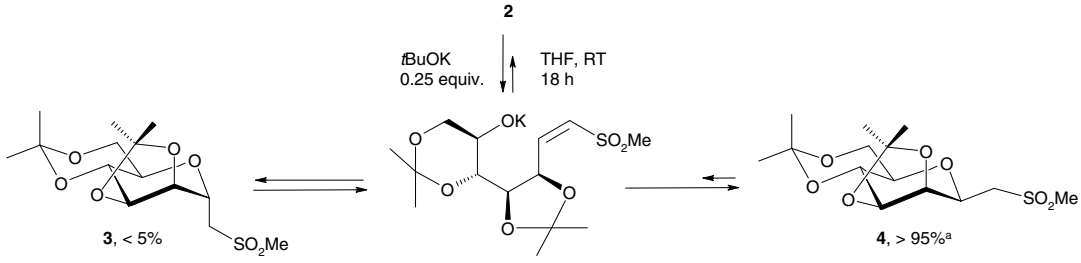
Scheme 2. Synthesis of a model saccharidic vinyl sulfone.

Having developed experimental conditions to produce selectively the β-*C*-mannopyranoside **4**, we started to investigate the effect of a lower reaction temperature on the product distribution and the retro-Michael/Michael epimerization process. We were delighted to find that simple treatment of **2** with 0.25 equiv *t*-BuOK in THF at −78 °C induced a smooth cyclization into the expected C-glycosides as a mixture dramatically enriched into the axial α-epimer **3** (**3**:**4** 9:1 ratio, ^{1}H NMR). When subjected to the same conditions, isolated **3** remained unchanged, while raising the temperature up to 25 °C caused a quick and irreversible epimerization to produce almost-pure **4**. This demonstrates that under our conditions, the retro-Michael process can be easily switched *on* and *off* through a simple temperature change, whereas the Michael cyclization remains a rather fast reaction.

With a view to improving the diastereoselectivity in the latter process by minimizing the activation energy and consequently favoring discrimination between the two possible transition states, an experiment was conducted at −95 °C. As expected, the selectivity of the addition in favor of **3** was further increased (>95:5, ^{1}H NMR). Guided by practical considerations, the *t*-BuOK ratio was then raised up to a nearly stoichiometric amount in order for the—otherwise rather lengthy-reaction to proceed within a few minutes while keeping the product distribution unchanged.[21]

We believe that this exceptionally high α-diastereoselectivity for a kinetically governed hetero-Michael C-glycoside formation originates in the combined effects of a 2-axial substituted *manno* scaffold with a *Z*-configuration of the vinyl sulfone double bond, thus maximizing the steric interactions in the transition state leading to the β-C-glycoside (Scheme 4). This observed 1,2-*trans*-selectivity is fully consistent with the empirical rule established by Martin et al.[7a] for the related kinetically governed hetero-Michael cyclization of γ-benzoyloxy-α,β-insaturated esters: *Z*-olefins always strongly favor the formation of 1,2-*trans* C-pyranosides while their *E*-stereomers produce more *cis*-configurated product.

Based on these findings, we tried to expand this methodology to vinyl sulfoxides. With this objective, **1** was readily converted into a *S*-epimeric mixture of sulfoxides,[22] from which a single major diastereomer **5**[23] was isolated in 58% yield (Scheme 5). Deceptively, under the low temperature conditions previously optimized for vinyl sulfone **2**, vinyl sulfoxide **5** remained unreacted. The temperature had to be raised up to 0 °C in order to observe (TLC) a slow cyclization process to produce a mixture of epimeric C-glycosides



Scheme 3. Hetero-Michael cyclization under thermodynamic control: production of a β-*C*-mannopyranoside. [a]: 95% isolated yield.

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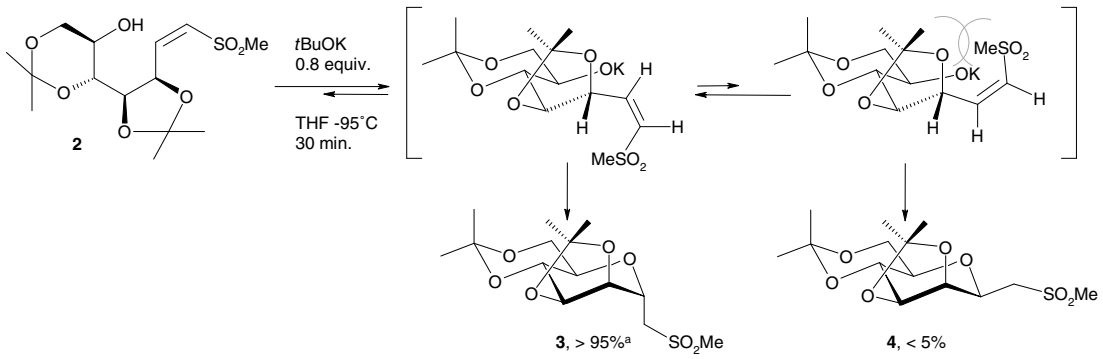
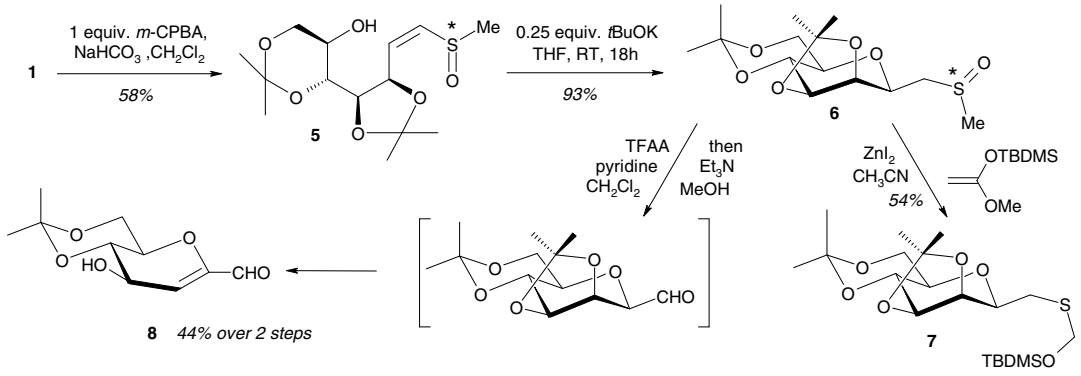


Scheme 4. Hetero-Michael cyclization under kinetic control: production of a α-*C*-mannopyranoside. [a]: 93% Isolated yield.



Scheme 5. Hetero-Michael cyclization of vinyl sulfoxide **5** and further Pummerer rearrangement of the β-C-glycosidic product **6**.

which, in our hands, was not easily separable using conventional preparative methods. Such dramatically reduced reactivity of **5** as compared to **2** can be explained by the large difference in Michael-acceptor ability between α,β-unsaturated sulfones and the related sulfoxides. This considerably raises up the activation energy to access both α- and β-transition states and, as a consequence, weakens the kinetic discrimination between the two epimeric C-glycosides.[24] A more rewarding result was reached when using the thermodynamically controlled conditions previously optimized for sulfone **2**: within decent time, sulfoxide **5** was almost quantitatively converted into the β-*C*-mannopyranoside sulfoxide **6** (93% isolated yield).[25]

In order to illustrate the potency and versatility of sulfinylmethyl C-glycosides as synthons for the production of biologically relevant carbohydrate mimics, the sulfoxide **6** was subjected to a range of Pummerer rearrangement-inducing conditions (Scheme 5). Treating **6** in acetonitrile with Kita's reagent (*O*-methyl-*O*-*tert*-butyldimethylsilyl ketene acetal) in the presence of a catalytic amount of zinc iodide[26] led to the formation of the C-glycosidic sulfide **7**[27] as a major product. Treatment of **6** with trifluoroacetic anhydride, followed by methanolysis,[28] afforded C-formyl glucal **8**.[29]

In summary, we have demonstrated the utility of a three-step Wittig/vinyl sulfide oxidation/intramolecular hetero-Michael addition pathway to biologically relevant C-glycosides. The promising 2,3:4,6-di-*O*-isopropylidene *manno* scaffold allows a strict control of the diastereoselectivity of the hetero-Michael cyclization on a vinyl sulfone by simply changing the temperature of the reaction.

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18. see for example Marot, C.; Rollin, P. *Tetrahedron Lett.* **1994**, *35*, 8377–8380.
19. *Selected spectroscopy data for* **2**: ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.36 (s, 3H, Me_2C), 1.39 (s, 3H, Me_2C), 1.40 (s, 3H, Me_2C), 1.53 (s, 3H, Me_2C), 2.86 (br s, 1H, OH), 3.03 (s, 3H, $MeSO_2$), 3.48–3.67 (m, 2H, H-5 and H-7b), 3.77–3.93 (m, 2H, H-6 and H-7a), 4.75 (dd, 1H, J_{3-4} = 7.7, J_{4-5} = 1.3, H-4), 5.62 (ddd, 1H, J_{1-3} = 1.9, J_{2-3} = 7.2, H-3), 6.32 (dd, 1H, J_{1-2} = 11.5, H-1), 6.63 (dd, 1H, H-2). ^{13}C NMR (62.89 MHz, $CDCl_3$): δ 19.2, 25.8, 26.7, 28.7 (2 * Me_2C), 43.4 ($MeSO_2$), 63.0 (C-6), 64.8 (C-7), 72.6 (C-5), 73.1 (C-3), 77.4 (C-4), 98.6, 110.3 (2 * CMe_2), 128.3 (C-1), 146.4 (C-2). MS (IS+): *m/z* 337 $[MH]^+$.
20. Vinyl sulfone **2** (336 mg, 1 mmol) was dissolved in THF (10 mL), and *t*-BuOK (28 mg, 0.25 equiv) was added. The reaction mixture was stirred for 18 h at rt, then quenched with a saturated NH_4Cl aqueous solution (10 mL) and extracted with CH_2Cl_2 (3 * 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The resulting oil was purified by flash column chromatography (petroleum ether/AcOEt 7:3) to give pure **4** as a colorless oil (319 mg, 95%). Selected spectroscopy data for **4**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.35 (s, 3H, Me_2C), 1.42 (s, 3H, Me_2C), 1.51 (s, 3H, Me_2C), 1.55 (s, 3H, Me_2C), 2.98 (s, 3H, $MeSO_2$), 3.16 (dd, 1H, $J_{1'a-1'b}$ = 15.6, $J_{1'b-1}$ = 2.6, H-1′b), 3.23 (ddd, 1H, J_{4-5} = 5.5, J_{5-6a} = 5.5, J_{5-6b} = 10.0 H-5), 3.56 (dd, 1H, $J_{1'a-1}$ = 9.8, H-1′a), 3.65–3.77 (m, 2H, H-4 and H-6b), 3.91 (dd, 1H, J_{6a-6b} = 10.7, H-6a), 4.10 (dd, 1H, J_{2-3} = 7.4, J_{3-4} = 5.3, H-3), 4.17 (dd, 1H, J_{1-2} = 2.6, H-2), 4.39 (ddd, 1H, H-1). ^{13}C NMR (62.89 MHz, $CDCl_3$): δ 18.8, 26.4, 28.4, 29.0 (2 * Me_2C), 43.3 ($MeSO_2$), 56.6 (C-1′), 61.6 (C-6), 69.7 (C-5), 72.0 (C-1), 72.6 (C-4), 75.3 (C-2), 76.0 (C-3), 99.9, 110.2 (2 * CMe_2). MS (IS+): *m/z* 337 $[MH]^+$.
21. Compound **2** (336 mg, 1 mmol) was dissolved in THF (10 mL) and cooled to −95 °C in a acetone/liquid nitrogen bath, then tBuOK (90 mg, 0.8 equiv) was added. The mixture was stirred for 30 min at −95 °C, then quenched by adding solid NH_4Cl (268 mg, 5 equiv) under vigorous stirring. After warming up to rt, water (10 mL) was added and the same protocol as described for **4** was followed to give pure **3** as a colorless oil (312 mg, 93%). Selected data for **3**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.35 (s, 3H, Me_2C), 1.43 (s, 3H, Me_2C), 1.49 (s, 3H, Me_2C), 1.54 (s, 3H, Me_2C), 2.98 (s, 3H, $MeSO_2$), 3.17 (dd, 1H, $J_{1'a-1'b}$ = 14.5, $J_{1'b-1}$ = 8.6, H-1′b), 3.29 (bd, 1H, H-1′a), 3.50 (ddd, 1H, J_{4-5} = 5.1, J_{5-6a} = 5.1, J_{5-6b} = 11.1, H-5), 3.73 (dd, 1H, J_{6a-6b} = 11.1, H-6b), 3.88 (dd, 1H, H-6a), 4.08–4.23 (m, 3H, H-1, H-2 and H-4), 4.32 (dd, 1H, J_{2-3} = 6.8, J_{3-4} = 6.8, H-3). ^{13}C NMR (62.89 MHz, $CDCl_3$): δ 19.1, 24.9, 27.2, 29.0 (2 * Me_2C), 43.5 ($MeSO_2$), 57.6 (C-1′), 63.0 (C-6), 65.4 (C-5), 69.6 (C-1), 71.7 (C-4), 74.5 (C-2), 76.2 (C-3), 99.8, 111.2 (2 * CMe_2). MS (IS+): *m/z* 337 $[MH]^+$.
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23. *Selected spectroscopy data for* **5**: ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.38 (s, 3H, Me_2C), 1.44 (s, 3H, Me_2C), 1.50 (s, 3H, Me_2C), 1.53 (s, 3H, Me_2C), 2.71 (s, 3H, MeSO), 3.49–3.67 (m, 3H, OH, H-5 and H-7b), 3.73-3.94 (m, 2H, H-6 and H-7b), 4.63 (dd, 1H, J_{3-4} = 7.1, J_{4-5} = 2.0, H-4), 5.33 (dd, 1H, J_{2-3} = 7.3, H-3), 6.37 (d, 1H, J_{1-2} = 10.2, H-1), 6.45 (dd, 1H, H-2). ^{13}C NMR (62.89 MHz, $CDCl_3$): δ 19.4, 25.9, 26.8, 28.6 (2 * Me_2C), 40.4 (MeSO), 63.1 (C-6), 65.0 (C-7), 72.8 (C-5), 73.7 (C-3), 77.0 (C-4), 98.6, 110.2 (2 * CMe_2), 136.6 (C-1), 139.2 (C-2). MS (IS+): *m/z* 321 $[MH]^+$.
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25. *Selected spectroscopy data for* **6**: ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.36 (s, 3H, Me_2C),1.43 (s, 3H, Me_2C), 1.50 (s, 3H, Me_2C), 1.54 (s, 3H, Me_2C), 2.63 (s, 3H, MeSO), 2.75 (dd, 1H, $J_{1'a-1'b}$ = 12.5, $J_{1'a-1}$ = 9.5, H-1′a), 3.08 (dd, 1H, $J_{1'b-1}$ = 2.2, H-1′b), 3.47 (ddd, 1H, J_{4-5} = 10.5, J_{5-6a} = 10.5, J_{5-6b} = 5.6, H-5), 3.76 (dd, 1H, J_{6a-6b} = 11.0, H-6b), 3.91 (dd, 1H, H-6a), 4.08–4.35 (m, 4H, H-1, H-2, H-3 and H-4). ^{13}C NMR (62.89 MHz, $CDCl_3$): δ19.1, 25.0, 27.3, 29.1 (2 * Me_2C), 39.84 (MeSO), 58.5 (C-1′), 63.0 (C-6), 65.3 (C-5), 67.9, 71.8, 75.5, 76.1 (C-1, C-2, C-3 and C-4), 99.7, 110.9 (2 * CMe_2). MS (IS+): *m/z* 321 $[MH]^+$.
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27. *Selected spectroscopy data for* **7**: ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.12 (s, 6H, Me_2Si), 0.89 (s, 9H, Me_3CSi), 1.34 (s, 3H, Me_2C), 1.41 (s, 3H, Me_2C), 1.51 (s, 3H, Me_2C), 1.52 (s, 3H, Me_2C), 2.84 (dd, 1H, $J_{1'a-1'b}$ = 13.7, $J_{1'a-1}$ = 6.9, H-1′a), 2.91 (dd, 1H, $J_{1'b-1}$ = 5.9, H-1′b), 3.47 (ddd, 1H, J_{4-5} = 10.3, J_{5-6a} = 10.3, J_{5-6b} = 5.6, H-5), 3.83–3.99 (m, 2H, H-4 and H-6b), 4.03–4.13 (m, 1H, H-1), 4.18 (dd, 1H, J_{2-3} = 6.5, J_{4-5} = 7.3, H-3), 4.29 (dd, 1H, J_{1-2} = 5.4, H-2), 4.78 (d, 1H, J_{gem} = 10.8, SCH_2O), 4.83 (d, 1H, SCH_2O). ^{13}C NMR ($CDCl_3$): δ 5.0 (Me_2Si), 18.3 (CMe_3), 19.0, 25.6 (2 * Me_2C), 25.9 (Me_3C), 27.8, 29.1 (2 * Me_2C), 32.5 (C-1′), 63.0 (C-6), 64.5 (C-5), 66.9 (SCH_2O), 72.5 (C-4), 74.1 (C-1), 75.2 (C-2), 75.5 (C-3), 99.6, 109.9 (2 * CMe_2). MS (IS+): *m/z* 435 $[MH]^+$.
28. Sugiharo, H.; Tanikoga, R.; Kaji, A. *Synthesis* **1978**, 881–885.
29. *Selected spectroscopy data for* **8**: ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.45 (s, 3H, Me_2C), 1.55 (s, 3H, Me_2C), 2.85 (br s, 1H, OH), 3.80–4.16 (m, 4H, H-4, H-5, H-6a and H-6b), 4.55–4.62 (m, 1H, H-3), 5.79 (d, 1H, J_{2-3} = 1.5, H-2), 9.21 (s, 1H, CHO). ^{13}C NMR (62.89 MHz, $CDCl_3$): δ 19.1, 29.0 (Me_2C), 61.5 (C-6), 67.5 (C-3), 70.0, 72.4 (C-4 and C-5), 100.3 (CMe_2), 121.9 (C-1), 185.9 (CHO). MS (IS+): *m/z* 215 $[MH]^+$.