Dihydropyridine *C*-glycoconjugates by organocatalytic Hantzsch cyclocondensation. Stereoselective synthesis of α-threofuranose *C*-nucleoside enantiomers†

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The Hantzsch reaction of *C*-glycosyl aldehyde/enamino ester/β-ketoester systems under L-proline catalysis to give dihydropyridine *C*-glycoconjugates is reported. Asymmetric cyclocondensations of differentially substituted enamine and β-dicarbonyl components with formyl α-L-*C*-threofuranoside and with the α-D-isomer were also carried out. Each reaction occurred with high yet opposite stereoselectivity (de >95%) so that the pair of α-threofuranose *C*-nucleoside enantiomers was prepared.

Introduction

Carbohydrate decoration of compounds possessing a firmly established pharmacological activity such as heterocycles with privileged structures[1] and bioactive natural products[2] is a well-established paradigm of the modern drug discovery process.[3] The introduction of carbohydrate fragments onto drug candidate scaffolds is typically envisaged to improve the pharmacokinetic and pharmacodynamic profiles of lead compounds[4] without altering their activity and selectivity. Even more significantly, this transformation may give rise to new classes of molecules with modified and unexpected pharmacological properties due to the unique functions exerted by carbohydrates at the molecular level.[5] Research in this field has been actively carried out in one of our laboratories over the last five years.[6] Efficient syntheses of pharmacologically active heterocycle *C*-glycoconjugates have been reported, including 1,4-dihydropyridines (DHPs),[7] pyridines,[8] 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs),[9] and β-lactams.[10] Towards this aim a set of one-pot multicomponent reactions (MCRs) employing *C*-glycosylated reagents were conveniently exploited. In particular, the Hantzsch three-component reaction (3CR), *i.e.* aldehyde/β-ketoester/enamino ester cyclocondensation, was utilized to generate a collection of structurally and stereochemically diversified 1,4-DHP *C*-glycoconjugates.[7] One of the goals of our synthetic efforts was the preparation of *C*-glycosylated analogues of medicinally relevant DHPs such as the C2-glycosylated Nifedipine analogue **1** (Fig. 1).[11] Interest in DHP *C*-glycosides arose also from the realization that these compounds were new *C*-nucleosides displaying the 1,4-dihydropyridine residue as the base. The C4-ribosyl derivative **2** is an example of this class of compounds (Fig. 1).[12]

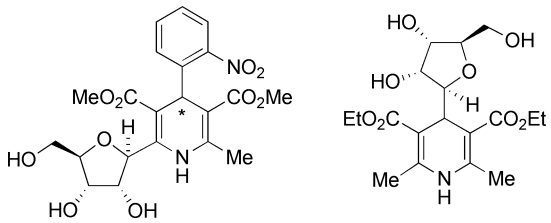

Fig. 1 The medicinally relevant C2-glycosylated Nifedipine analogue **1** and the artificial *C*-nucleoside **2**.

We also addressed the issue regarding the asymmetry of the DHP C4 stereocenter induced by the chiral sugar moiety in one of the reagents (β-ketoester or enamino ester). It is well known that C4 DHP epimers often display opposite pharmacological profiles.[11] Although modest degrees of asymmetric induction (de <50%) were registered under different conditions (thermal[7] and microwave dielectric heating,[8] and Yb(III)-catalysis[7]), the above asymmetric multicomponent reaction (AMCR) approach[13] allowed the synthesis of DHP *C*-glycoconjugates in a pure stereoisomeric form. In the present paper we report on the extension and improvement of the previous work. In particular, we have established a novel (organocatalytic) and mild procedure for the Hantzsch 3CR of different and rare *C*-glycosyl aldehydes. In addition, we have found conditions for its execution in a fully stereoselective manner (de >95%) to give biologically relevant *C*-nucleosides which were not accessible by the previously employed procedures.[7,8]

Results and discussion

The sugar derivatives to be employed in the planned Hantzsch reactions were the *C*-glycosyl aldehydes **3–7**, ***ent*-3**, and ***ent*-4** shown in Fig. 2. These carbohydrate building blocks (CBBs), all displaying the D- or L-threofuranosyl unit and one also displaying a sulfate group, were readily available in our laboratories by partial or complete depolymerization of red seaweed polysaccharides (Agarose and Kappa-carrageenan).[14] The presence of the sulfate

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† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra of compounds **11a–11e** and **13**, and ^{1}H NMR spectrum of *epi*-**11a**. See DOI: 10.1039/b900422j

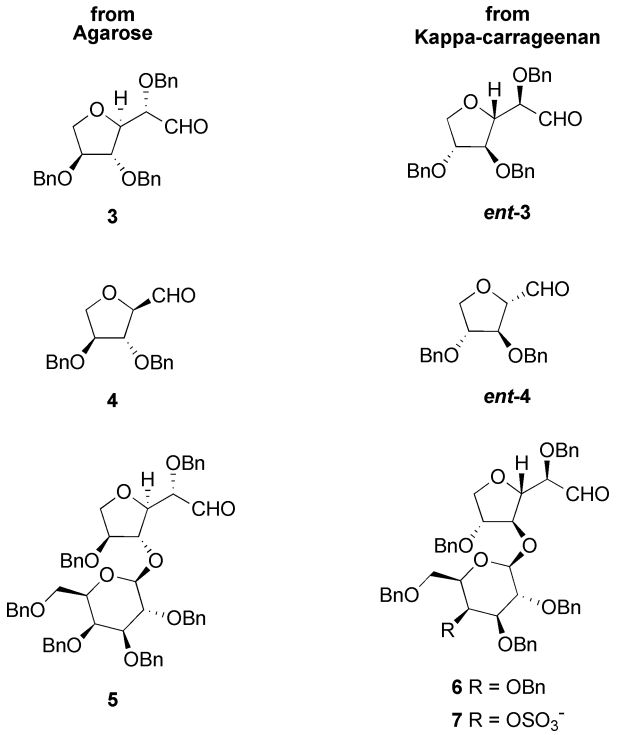
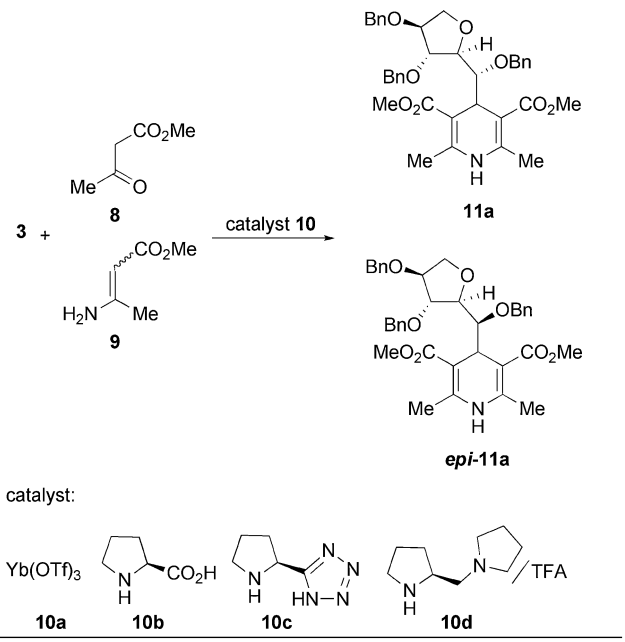


Fig. 2 *C*-Glycosyl aldehydes prepared from red seaweed polysaccharides.

group and threofuranosyl moiety were of great relevance for our program toward the identification of bioactive DHP glycoconjugates. In fact, sulfated carbohydrates have been demonstrated to be involved in many recognition processes,[15] while chiral hydroxylated tetrahydrofuran fragments have been identified in several bioactive natural products.[16]

The perbenzylated 3,6-anhydro-L-galactose aldehyde **3** was selected as a suitable substrate for an optimization study of the planned Hantzsch reaction. We felt that a successful approach with this aldehyde that contained an easily epimerizable α-stereocenter could be also applied to aldehydes **4–7**. Among the many reaction conditions that have been proposed for the execution of the Hantzsch cyclocondensation,[17] those that proved to be most efficient in our previous investigations[7,8] were selected for the benchmark reaction of aldehyde **3**, methyl acetoacetate **8**, and methyl aminocrotonate **9** (Table 1). Accordingly, this reaction was performed using equimolar amounts of all components (entry 1) under standard thermal conditions (MeOH, molecular sieves, 70 °C, 48 h) as previously reported.[7] Unexpectedly, evaporation of the solvent afforded a complex reaction mixture, from which the target symmetrically substituted DHP **11a** was isolated in low yield (15%). An even lower yield (5%) was obtained by microwave (MW) dielectric heating (110 °C) (entry 2),[8] very likely because of substantial decomposition of aldehyde **3**. Therefore, the cyclocondensation was next performed under milder conditions (MeOH, molecular sieves, rt, 48 h) using $Yb(OTf)_3$ as the promoter.[7] This metal-catalyzed procedure afforded **11a** in low yield (20%) along with its epimer ***epi*-11a** (5%, entry 3). At this stage, the use of L-proline **10b** organocatalyst was envisaged to increase the reaction output and, at the same time, preserve the configurational integrity of the aldehyde **3** α-stereocenter. This decision stemmed from an analysis of the original Hantzsch

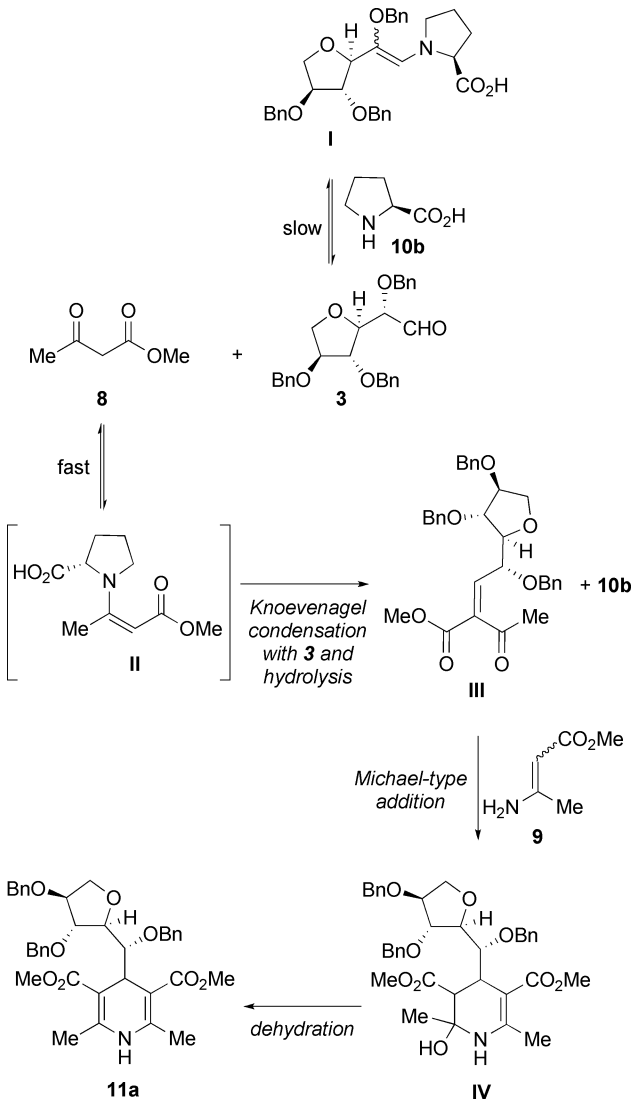
Table 1 Optimization of the reaction conditions for the three-component Hantzsch cyclocondensation of aldehyde **3**



Entry	Catalyst (equiv.)	Solvent	Time (h)	Temp (°C)	Yield (%) **11a** [a]/***epi*-11a** [b]
1[c]	/	MeOH	48	70	15/-
2[c]	/	MeOH	1.5	110[d]	5/-
3[c]	**10a** (1.0)	MeOH	48	25	20/5
4[c]	**10b** (0.1)	MeOH	48	25	35/-
5[c]	**10b** (0.1)	THF	48	25	5/-
6[c]	**10b** (0.1)	CH_2Cl_2	48	25	19/10
7[c]	**10b** (0.1)	benzene	48	25	5/-
8[c]	**10b** (0.3)	MeOH	48	25	35/-
9[c]	**10b** (1.0)	MeOH	48	25	37/-
10[e]	**10b** (0.1)	MeOH	48	25	40/-
11[e]	**10b** (0.1)	MeOH	168	25	45/-
12[e]	**10b** (0.1)	MeOH	48	50	48/5
13[f]	**10b** (0.1)	MeOH	48	25	50/-
14[f]	**10b** (0.1)	MeOH	48	50	55/-
15[f]	**10b** (0.1)	MeOH	2	110[d]	35/5
16[f]	**10c** (0.1)	MeOH	48	25	40/-
17[f]	**10d** (0.1)	MeOH	48	25	44/-

[a] Isolated yield. [b] Estimated yield by ^{1}H NMR analysis. [c] Reactions performed with equimolar amounts of components in the presence of 4 Å MS. [d] Experiment run in a Biotage Initiator (temperature was measured externally by an IR sensor). [e] Reactions performed with equimolar amounts of components without MS. [f] Reactions performed with 1.5 equiv. of **8** and **9** without MS.

reaction mechanism (Scheme 1) and previous studies on proline catalytic activity. These demonstrated that proline is capable of efficiently promoting Hantzsch-type reactions of simple achiral substrates,[18] and can catalyze aldol reactions of chiral α-hydroxy aldehydes without producing α-epimerization.[19] Hence, we speculated that preferential β-ketoester **8** activation by proline *via* enamine **II** occurred in the aldol-type Knoevenagel condensation to give adduct **III** (Scheme 1). Indeed, performing the model cyclocondensation in MeOH at room temperature under L-proline **10b** catalysis (10 mol%) afforded the target DHP **11a** in 35% yield without any evident epimerization as judged by ^{1}H NMR analysis (entry 4). This result is in agreement with the hypothesis that enamine **II** is formed faster than aldehyde-derived enamine **I**.



Scheme 1 The proposed reaction pathway.

Then, according to the original Hantzsch cyclocondensation mechanism, the reaction proceeded *via* Michael-type addition of the enamino ester **9** to **III** to give **IV**, whose dehydration led to the final product **11a**.

The optimization study proceeded by considering other aspects of the reaction, such as the use of different solvents, a higher loading of proline catalyst, and the removal of the molecular sieves. While the replacement of MeOH as the solvent was detrimental (entries 5–7), the reaction was almost unaffected by increasing the amount of catalyst (entries 8–9). On the other hand, the absence of molecular sieves (entry 10) produced a slightly higher yield of **11a** (40% vs. 35%), which confirmed the importance of the hydrolysis step for the catalyst turnover. A longer reaction time (entry 11) as well as a higher temperature (entry 12) improved the reaction outcome, although some epimerization took place in the latter run. Thus, the best yield of **11a** (55%) was obtained by performing the reaction in MeOH at 50 °C for 48 h without molecular sieves under L-proline **10b** catalysis (10 mol%) and with an excess (1.5 equiv.) of methyl acetoacetate **8** and methyl aminocrotonate **9** (entry 14). Attempts to reducing the reaction time by means of MW irradiation were met with scarce success, with **11a** recovered in lower yields along with ***epi*-11a** (entry 15). Finally, (*S*)-5-(pyrrolidin-2-yl)-1*H*-tetrazole **10c** and (*S*)-1-(2-pyrroldinylmethyl)pyrrolidine/TFA **10d** organocatalysts proved to be suitable promoters of the model cyclocondensation although less effective than L-proline **10b** (entries 16–17).

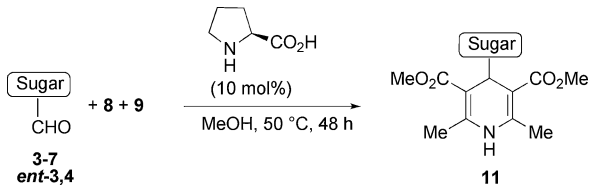
With the above information in hand, we extended the application of the optimized procedure to the Hantzsch 3CR of *C*-glycosyl aldehydes **4–7**, ***ent*-3**, and ***ent*-4** (Table 2). As a general trend, we observed that the higher the complexity of the starting aldehydes, the lower was the yield of the corresponding DHP *C*-glycoconjugate **11**. It is noteworthy that the availability of sugar components with opposite stereochemistry enabled access to both enantiomers of the target DHPs (pairs **11a**/***ent*-11a** and **11b**/***ent*-11b**). Notably, derivatives **11b** and ***ent*-11b** constitute a novel class of artificial *C*-nucleosides displaying the rare threofuranoside moiety anomerically linked to the unusual DHP heterocyclic base. The main interest in such compounds lies in the generation of modified sequences of (3′→2′)-α-L-threose oligonucleotides (TNA oligos).[20] These unnatural nucleic acid polymers feature a five-bond backbone in place of the six-bond backbone of DNA and RNA. Even with the shorter backbone, TNA oligos are capable of cross-hybridizing with complementary DNA and RNA sequences. Research on TNA oligos and their analogues is being actively pursued in biomedicinal chemistry, as demonstrated by the recent proposal concerning the role of TNA as an evolutionary progenitor of RNA.[21]

The scope of the L-proline-catalyzed Hantzsch 3CR was then extended to the preparation of unsymmetrically substituted C4-glycosylated DHPs. Crucial for this study was establishing the role of the carbohydrate residue and proline, *i.e.* the internal and external chiral inductors respectively, in the formation of the DHP C4 stereocenter. After some experimentation,[22] we found that the cyclocondensation of aldehyde **4** with 2,4-pentanedione **12** and methyl aminocrotonate **9** under L-proline **10b** catalysis (10 mol%) in MeOH at room temperature for five days afforded the target glycosylated DHP **13** in fair yield (50%) and excellent diastereoselectivity (de >95%; Table 3, entry 1). The same model reaction was then performed by using D-proline **10e** and pyrrolidine/acetic acid **10f** as the catalysts (entries 2–3). In both cases, the DHP **13** was again isolated as the sole stereoisomer. Hence, external asymmetric induction by the L-proline catalyst was reasonably excluded while the presence of the chiral glycoside moiety appeared to be crucial in the stereodefining step (Michael-type addition) of the Hantzsch reaction. This was unequivocally confirmed by the stereoselective formation of enantiomer ***ent*-13** from the L-proline-catalyzed cyclocondensation of aldehyde ***ent*-4** with diketone **12** and enamino ester **9** (entry 4). Unfortunately, we have been unable so far to obtain suitable crystals of **13** or ***ent*-13** for X-ray structural determination and therefore the absolute configuration at the C4 stereocenter of the DHP ring remains unassigned.

Conclusions

In summary, we have presented the first organocatalytic aldehyde/β-ketoester/enamine three-component variant of the Hantzsch reaction, which potentially allows for variation in all positions of the DHP ring. Particularly, we have demonstrated

Table 2 DHP *C*-Glycoconjugates prepared[a]



3-7
ent-3,4

11

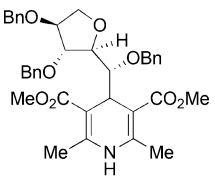
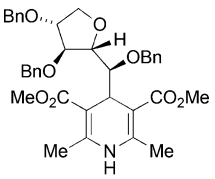
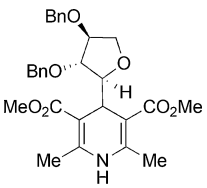
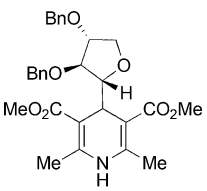
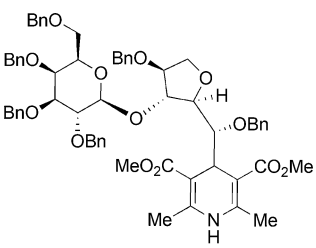
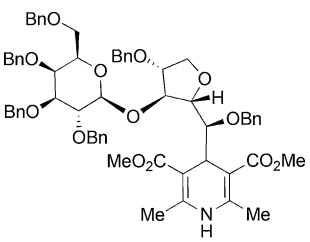
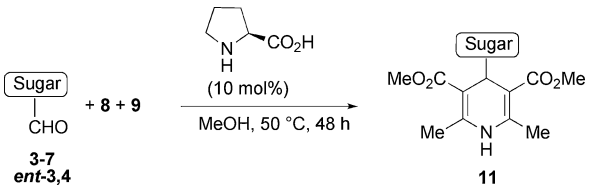
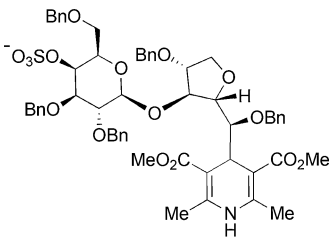
Entry	Aldehyde	Product (Yield)[b]
1	**3**	 **11a** (55%)
2	***ent*-3**	 ***ent*-11a** (52%)
3	**4**	 **11b** (67%)
4	***ent*-4**	 ***ent*-11b** (68%)
5	**5**	 **11c** (37%)
6	**6**	 **11d** (36%)

Table 2 *(Contd.)*



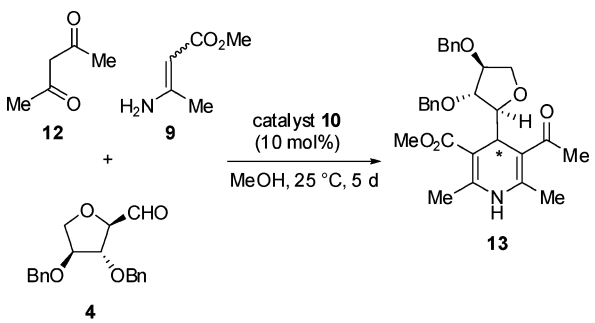
3-7
ent-3,4

11

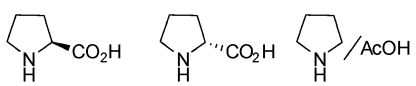
Entry	Aldehyde	Product (Yield)[b]
7	**7**	 **11e** (30%)

[a] Reactions performed with 0.28 mmol of aldehyde, **8** (1.5 equiv.) and **9** (1.5 equiv.) in 1.5 mL of MeOH. [b] Isolated yield.

Table 3 Study of the asymmetric induction[a]



catalyst:



10b **10e** **10f**

Entry	Aldehyde	Catalyst	Product	Yield (%)[b]	de (%)[c]
1	**4**	**10b**	**13**	50	>95
2	**4**	**10e**	**13**	48	>95
3	**4**	**10f**	**13**	50	>95
4	***ent*-4**	**10b**	***ent*-13**	47	>95

[a] Reactions performed with 0.28 mmol of aldehyde, **9** (1.5 equiv.), **12** (1.5 equiv.) in 1.5 mL of MeOH and in the presence of 4 Å MS. [b] Isolated yield. [c] Estimated by ^{1}H NMR analysis.

that the use of L-proline catalyst opened a suitable reaction window for the Hantzsch reaction of sensitive components such as sugar aldehydes **3–7**. The procedure disclosed has been applied to the synthesis of symmetrically and unsymmetrically substituted DHP *C*-glycoconjugates of biological relevance. It is noteworthy that the asymmetric variant occurred with high stereoselectivity (de >95%). This is a remarkable result in view of the strict

dependence of the biological properties of DHP-based drug candidates on the configuration at C4 of the heterocyclic ring.

Experimental section

Reactions were monitored by TLC on silica gel 60 F_{254} with detection by charring either with sulfuric acid (conc. H_2SO_4/EtOH 1:9) or 0.5% orcinol in conc. H_2SO_4/EtOH 1:20. Flash column chromatography was performed on silica gel 60 (230–400 mesh). Optical rotations were measured at 20 ± 2 °C in the stated solvent; $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded for $CDCl_3$ solutions at room temperature unless otherwise specified. Peak assignments were aided by ^{1}H–^{1}H COSY and gradient–HMQC experiments. MALDI-TOF mass spectra were acquired using α-cyano-4-hydroxycinnamic acid as the matrix. ESI MS analyses were performed in positive or negative-ion mode with samples dissolved in a mixture of MeCN/H_2O 1:1. Aldehydes **3–7**, ***ent*-3**, and ***ent*-4** are known compounds and were prepared as described.[14] The procedure for the preparation of aldehyde **3** is herein described as a representative example.

2,4,5-Tri-*O*-benzyl-3,6-anhydro-*aldehydo*-L-galactose (3)

A mixture of commercial agar[23] (6.0 g), EtSH (9.0 mL), 37% HCl (3.0 mL), and MeOH (48 mL) was warmed to 60 °C and stirred at this temperature for 17 h. The mixture was then cooled to room temperature, neutralized with 1M NaOH solution, and kept under a nitrogen flow to remove unreacted EtSH. The mixture was then concentrated under vacuum to give a solid residue, which was suspended in H_2O (80 mL) and then extracted with Et_2O (5 × 100 mL). The combined organic phases were dried (Na_2SO_4) and concentrated to give a crude extract (3.18 g) containing the dithioacetal derivative of the hydroxy-free aldehyde **3**.

To a cooled (0 °C), stirred mixture of the above crude material and DMF (50 mL) was added NaH portionwise (1.92 g, 48.0 mmol of a 60% suspension in mineral oil) and, after 30 min, benzyl bromide (3.7 mL, 31.2 mmol). The mixture was stirred at room temperature for 40 min, then treated with MeOH (10 mL), stirred for an additional 10 min, diluted with H_2O (80 mL), and extracted with Et_2O (3 × 100 mL). The combined organic phases were dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with 15:1 cyclohexane–AcOEt to give the dithioacetal derivative of aldehyde **3** (3.8 g, 50% from starting agar)[23] as a colorless syrup.

To a cooled (0 °C), stirred mixture of the above dithioacetal derivative (1.22 g, 2.26 mmol), THF (4.5 mL) and Et_2O (11 mL), a solution of H_5IO_6 (1.03 g, 4.52 mmol) in THF (2.3 mL) was added dropwise. The resulting mixture was warmed to room temperature, stirred for 20 min, diluted with 1M phosphate buffer (75 mL), and extracted with Et_2O (200 mL). The organic phase was washed with 10% aqueous Na_2SO_3 solution (2 × 50 mL), dried (Na_2SO_4), and concentrated to give **3** (0.94 g, 95%) as a colorless syrup at least 95% pure as established by ^{1}H NMR analysis. An analytical sample was obtained by flash chromatography with 5:1 cyclohexane–AcOEt as the eluent; $[\alpha]_D = -24.4$ (*c* 1.0, $CHCl_3$); $R_f = 0.26$ (5:1 cyclohexane–AcOEt). ^{1}H NMR: $\delta = 9.68$ (d, 1 H, $J_{1,2} = 1.4$ Hz, H-1), 7.40–7.20 (m, 15 H, Ph), 4.74, 4.56, 4.48, 4.45, 4.43 (5 d, 6 H, $J = 12.0$ Hz, PhCH_2), 4.17–4.10 (m, 2 H, H-5, H-3), 4.07–4.01 (m, 2 H, H-4, H-6b), 3.97 (dd, 1 H, $J_{2,3} = 5.0$ Hz, H-2), 3.88 (dd, 1 H, $J_{5,6a} = 4.8$, $J_{6a,6b} = 10.5$ Hz, H-6a). ^{13}C NMR: $\delta = 202.0$, 137.5, 137.0, 128.5, 128.4, 128.3, 128.2 127.8, 127.7, 83.4, 83.0, 82.6, 82.3, 73.2, 71.9, 71.9, 71.1. MALDI-TOF MS: 471.3 (M^+ + K). Anal. Calcd for $C_{27}H_{28}O_5$ (432.19): C, 74.98; H, 6.53. Found: C, 75.00; H, 6.54.

Optimized procedure for the synthesis of symmetrically substituted DHPs 11a–e, and *ent*-11a,b

A screw-capped vial containing a magnetic bar was charged with the sugar aldehyde (0.28 mmol), **8** (45 μL, 0.42 mmol), **9** (48 mg, 0.42 mmol), L-proline **10b** (3 mg, 0.028 mmol) and anhydrous MeOH (1.5 mL). The mixture was vigorously stirred, degassed *in vacuo* and saturated with Ar (3 ×). The mixture was stirred at 50 °C for 48 h and then concentrated. The resulting residue was eluted from a column of silica gel with a suitable elution system to give the corresponding DHP derivative.

Dimethyl 4-((*R*)-benzyloxy((2*S*,3*R*,4*S*)-3,4-bis(benzyloxy) tetrahydrofuran-2-yl)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (11a)

Column chromatography with 2:1 cyclohexane-AcOEt afforded **11a** (97 mg, 55%) as a colorless syrup; $[\alpha]_D = -38.0$ (*c* 0.9, $CHCl_3$). $R_f = 0.16$ (2:1 cyclohexane–AcOEt). ^{1}H NMR: $\delta = 7.40$–7.20 (m, 15 H), 5.60 (br. s, 1 H), 4.50, 4.47 (2 d, $J = 12.0$ Hz, 2 H), 4.46 (s, 2 H), 4.45 (d, $J = 12.0$ Hz, 1 H), 4.43 (d, $J = 4.5$ Hz, 1 H), 4.36 (d, $J = 12.0$ Hz, 1 H), 4.03 (ddd, $J = 2.5$, $J = 3.0$, $J = 5.0$ Hz, 1 H), 4.00 (dd, $J = 4.5$, $J = 2.5$ Hz, 1 H), 3.96 (dd, $J = 3.0$, $J = 9.5$ Hz, 1 H), 3.83 (dd, $J = 5.0$, $J = 9.5$ Hz, 1 H), 3.81 (t, $J = 4.5$ Hz, 1 H), 3.62, 3.59 (2 s, 6 H), 3.36 (t, $J = 4.5$ Hz, 1 H), 2.30, 2.20 (2 s, 6 H); ^{13}C NMR: $\delta = 168.3$, 146.1, 145.6, 141.1, 139.0, 138.1, 128.3, 128.2, 128.0, 127.7, 127.5, 127.2, 100.3, 99.3, 85.0, 83.3, 81.4, 74.2, 71.9, 71.4, 71.2, 51.0, 36.0, 19.6, 19.4. ESI MS: 628.5 ($M + H^+$); 650.6 ($M + Na^+$). Anal. Calcd for $C_{37}H_{41}NO_8$ (627.28): C, 70.79; H, 6.58; N, 2.23. Found: C, 70.88; H, 6.50; N, 2.15.

Dimethyl 4-((*S*)-benzyloxy((2*R*,3*S*,4*R*)-3,4-bis(benzyloxy) tetrahydrofuran-2-yl)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (*ent*-11a)

Column chromatography with 2:1 cyclohexane–AcOEt afforded ***ent*-11a** (91 mg, 52%) as a colorless syrup; $[\alpha]_D = +38.5$ (*c* 1.0, $CHCl_3$). $R_f = 0.16$ (2:1 cyclohexane–AcOEt). ^{1}H and ^{13}C NMR as **11a**. ESI MS: 628.6 ($M + H^+$); 650.4 ($M + Na^+$). Anal. Calcd for $C_{37}H_{41}NO_8$ (627.28): C, 70.79; H, 6.58; N, 2.23. Found: C, 70.65; H, 6.66; N, 2.30.

Dimethyl 4-(2′,3′-di-*O*-benzyl-α-L-threofuranosyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (11b)

Column chromatography with 3:1 cyclohexane–AcOEt afforded **11b** (95 mg, 67%) as a colorless syrup; $[\alpha]_D = +5.6$ (*c* 1.9, $CHCl_3$). $R_f = 0.33$ (3:1 cyclohexane–AcOEt). ^{1}H NMR ($CDCl_3$): $\delta = 7.40$–7.20 (m, 10 H, Ph), 6.00 (br., s, 1 H, NH), 4.49, (d, $J = 11.5$ Hz, 1 H, PhCH_2), 4.45 (s, 1 H, PhCH_2), 4.44 (d, $J = 11.5$ Hz, 1 H, PhCH_2), 4.43 (d, $J_{1'4} = 7.5$ Hz, 1 H, H-4), 4.42 (d, $J = 11.5$ Hz, 1 H, PhCH_2), 4.06 (dd, $J_{1',2'} = 3.5$, $J_{2',3'} = 2.0$ Hz, 1 H, H-2′), 4.03

(ddd, 1 H, H-3′), 3.86, 3.85 (2 s, 2 H, H-4a′, H-4b′), 3.69 (dd, 1 H, H-1′), 3.65, 3.60 (2 s, 6 H, OCH_3), 2.34, 2.30 (2 s, 6 H, CH_3); ^{13}C NMR: $\delta = 168.7, 168.3, 146.9, 145.6, 138.5, 138.4, 128.6, 128.5, 127.9, 127.8, 127.7, 100.6, 99.5, 86.6, 84.4, 84.1, 71.7, 71.2, 52.6, 51.2, 35.9, 19.9, 19.8$. ESI MS: 508.7 (M + H^+); 530.6 (M + Na^+). Anal. Calcd for $C_{29}H_{33}NO_7$ (507.23): C, 68.62; H, 6.55; N, 2.76. Found: C, 68.75; H, 6.48; N, 2.71.

Dimethyl 4-(2′,3′-di-*O*-benzyl-α-D-threofuranosyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (*ent*-11b)

Column chromatography with 3:1 cyclohexane–AcOEt afforded **11b** (97 mg, 68%) as a colorless syrup; $[\alpha]_D = -5.4$ (*c* 0.8, $CHCl_3$). $R_f = 0.33$ (3:1 cyclohexane–AcOEt). ^1H and ^{13}C NMR as **11b**. ESI MS: 508.9 (M + H^+); 530.8 (M + Na^+). Anal. Calcd for $C_{29}H_{33}NO_7$ (507.23): C, 68.62; H, 6.55; N, 2.76. Found: C, 68.55; H, 6.62; N, 2.83.

Dimethyl 4-((*R*)-benzyloxy((2*S*,3*R*,4*S*)-4-(benzyloxy)-3-((2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl) tetrahydro-2*H*-pyran-2-yloxy)tetrahydrofuran-2-yl)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (11c)

Column chromatography with 2.5:1 cyclohexane–AcOEt afforded **11c** (110 mg, 37%) as a colorless syrup; $[\alpha]_D = -11.7$ (*c* 1.2, $CHCl_3$). $R_f = 0.15$ (2.5:1 cyclohexane–AcOEt). ^1H NMR: $\delta = 7.40–7.15$ (m, 30 H), 6.00 (br. s, 1 H), 4.98, 4.84, 4.79, 4.75, 4.74, 4.66, 4.58, 4.55 (8 d, $J = 12.0$ Hz, 8 H), 4.49–4.42 (m, 4 H), 4.40 (d, $J = 12.0$ Hz, 1 H), 4.38 (d, $J = 7.5$ Hz, 1 H), 4.37 (d, $J = 12.0$ Hz, 1 H), 4.08 (ddd, $J = 2.5$, $J = 3.5$, $J = 5.0$ Hz, 1 H), 3.91 (dd, $J = 2.0$, $J = 3.5$ Hz, 1 H), 3.90 (dd, $J = 4.5$, $J = 4.0$ Hz, 1 H), 3.89 (dd, $J = 3.5$, $J = 9.5$ Hz, 1 H), 3.81 (dd, $J = 5.0$, $J = 9.5$ Hz, 1 H), 3.76 (dd, $J = 7.5$, $J = 9.5$ Hz, 1 H), 3.59, 3.56 (2 s, 6 H), 3.58–3.52 (m, 3 H), 3.49 (dd, $J = 3.5$, $J = 9.5$ Hz, 1 H), 3.43 (dd, $J = 4.5$, $J = 6.0$ Hz, 1 H), 2.25, 2.17 (2 s, 6 H);^{13}C NMR: $\delta = 168.6. 168.4, 146.2, 145.0, 139.3, 138.6, 138.5, 138.4, 138.1, 137.5, 128.5, 128.4, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.5, 127.4, 127.3, 127.0, 102.0, 100.0, 99.4, 83.8, 83.2, 82.9, 82.2, 81.4, 79.1, 75.1, 74.7, 74.0, 73.7, 73.5, 73.3, 73.0, 71.0, 68.7, 51.0, 50.9, 35.8, 19.2, 19.0$. ESI MS: 1060.7 (M + H^+) 1082.8 (M + Na^+). Anal. Calcd for $C_{64}H_{69}NO_{13}$ (1059.48): C, 72.50; H, 6.56; N, 1.32. Found: C, 72.63; H, 6.49; N, 1.27.

Dimethyl 4-((*S*)-benzyloxy((2*R*,3*S*,4*R*)-4-(benzyloxy)-3-((2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl) tetrahydro-2*H*-pyran-2-yloxy)tetrahydrofuran-2-yl)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (11d)

Column chromatography with 2.5:1 cyclohexane–AcOEt afforded **11d** (106 mg, 36%) as a colorless syrup; $[\alpha]_D = +8.8$ (*c* 1.2, $CHCl_3$). $R_f = 0.15$ (2.5:1 cyclohexane–AcOEt).^1H NMR: $\delta = 7.50–7.10$ (m, 30 H), 5.38 (br. s, 1 H), 4.91, 4.83, 4.69, (3 d, $J = 11.5$ Hz, 3 H), 4.67 (s, 2 H), 4.60, 4.56, 4.52, 4.50, (4 d, $J = 11.5$ Hz, 4 H), 4.47 (d, $J = 6.0$ Hz, 1H), 4.41 (d, $J = 11.5$ Hz, 1 H), 4.32 (s, 2 H), 4.28 (d, $J = 7.5$ Hz, 1 H), 4.25 (ddd, $J = 1.5$, $J = 2.5$, $J = 5.0$ Hz, 1 H) 4.20 (dd, $J = 5.0$, $J = 1.5$ Hz, 1 H), 3.95 (dd, $J = 2.5$, $J = 9.5$ Hz, 1 H), 3.86 (dd, $J = 2.0$, $J = 3.0$ Hz, 1 H), 3.81 (dd, $J = 5.0$, $J = 9.5$ Hz, 1 H), 3.80 (dd, $J = 3.5$, $J = 5.0$ Hz, 1 H), 3.73 (dd, $J = 7.5$, $J = 10.0$ Hz, 1 H), 3.55, 3.52 (2 s, 6 H), 3.50 (dd, $J = 6.5$, $J = 12.0$ Hz, 1 H), 3.46–3.39 (m, 3 H), 3.36 (dd, $J = 3.5$, $J = 6.0$ Hz, 1 H), 2.18, 2.07 (2 s, 6 H); ^{13}C NMR: $\delta = 168.5, 168.4, 145.8, 145.0, 139.2, 139.1, 138.7, 138.5, 137.7, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.6, 127.4, 127.3, 127.2, 103.9, 100.3, 100.1, 86.0, 84.4, 83.1, 81.9, 80.7, 79.2, 74.7, 74.6, 74.1, 73.5, 73.4, 73.2, 73.0, 72.1, 71.1, 68.7, 51.1, 36.0, 19.5, 19.1$. ESI MS: 1060.6 (M + H^+) 1082.6 (M + Na^+). Anal. Calcd for $C_{64}H_{69}NO_{13}$ (1059.48): C, 72.50; H, 6.56; N, 1.32. Found: C, 72.63; H, 6.49; N, 1.28.

Dimethyl 4-((*S*)-benzyloxy((2*R*,3*S*,4*R*)-4-(benzyloxy)-3-((2*S*,3*R*,4*R*,5*S*,6*R*)-3,4-bis(benzyloxy)-6-(benzyloxymethyl)-5-sulfate-tetrahydro-2*H*-pyran-2-yloxy)tetrahydrofuran-2-yl)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (11e)

Column chromatography with 15:1 AcOEt–MeOH afforded **11e** (88 mg, 30%) at least 90% pure as established by ^1H NMR analysis. $R_f = 0.27$ (15:1 AcOEt–MeOH). ^1H NMR (acetone-d_6): $\delta = 7.90$ (s, 1 H), 7.60–7.10 (m, 25 H), 5.08, (d, $J = 12.0$ Hz, 1 H), 5.00 (dd, $J = 2.0$, $J = 3.1$, Hz, 1 H), 4.80, 4.70, 4.60, 4.59, 4.58 (5 d, $J = 12.0$ Hz, 5 H), 4.52 (d, $J = 7.5$, Hz, 1 H), 4.51 (d, $J = 6.0$, Hz, 1 H), 4.50 (d, $J = 12.0$ Hz, 1 H), 4.48 (s, 1 H), 4.47, 4.46 (2 d, $J = 12.0$ Hz, 1 H), 4.40 (dd, $J = 4.5$, $J = 1.7$ Hz, 1 H), 4.30 (ddd, $J = 1.7$, $J = 2.5$, $J = 5.0$ Hz, 1 H), 4.00 (dd, $J = 4.2$, $J = 10.0$ Hz, 1 H), 3.87 (dd, $J = 2.5$, $J = 9.5$ Hz, 1 H), 3.86 (t, $J = 4.5$ Hz, 1 H), 3.81–3.70 (m, 3 H), 3.63 (dd, $J = 3.1$, $J = 9.5$ Hz, 1 H), 3.54 (dd, $J = 7.5$, $J = 9.5$ Hz, 1 H), 3.50, 3.48 (2 s, 6 H), 3.42 (dd, $J = 4.0$, $J = 6.0$ Hz, 1 H), 2.30, 2.20 (2 s, 6 H); ^{13}C NMR (acetone-d_6): $\delta = 168.1, 146.4, 145.9, 139.3, 139.1, 139.0, 128.3, 128.1, 128.0, 127.9, 127.8 127.7, 127.6, 127.5, 127.1, 127.0, 126.8, 103.2, 99.5, 99.1, 85.0, 84.4, 81.7, 79.8, 78.7, 74.3 74.2, 73.6, 72.6, 71.8, 71.5, 70.9, 70.8, 70.4, 50.1, 50.0, 36.1, 17.9, 17.6$. ESI MS: 1049.4 (M − H).

Dimethyl 4-((*S*)-benzyloxy((2*S*,3*R*,4*S*)-3,4-bis(benzyloxy)-tetrahydrofuran-2-yl)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (*epi*-11a)

A screw-capped vial containing a magnetic bar was charged with the sugar aldehyde **3** (121 mg, 0.28 mmol), **8** (30 μL, 0.28 mmol), **9** (35 mg, 0.28 mmol), L-proline **10b** (3 mg, 0.028 mmol), molecular sieves (~100 mg) and anhydrous CH_2Cl_2 (1.5 mL). The mixture was vigorously stirred, degassed *in vacuo* and saturated with Ar (3 ×). The mixture was stirred at 25 °C for 48 h, filtered through a pad of Celite, and washed thoroughly with MeOH. The combined filtrates were concentrated and the resulting residue was eluted from a column of silica gel with 2:1 cyclohexane–AcOEt to give first ***epi*-11a** (16 mg, 10%) at least 70% pure as established by ^1H NMR analysis. $R_f = 0.24$ (2:1 cyclohexane-AcOEt). ^1H NMR: $\delta = 7.40–7.20$ (m, 15 H), 5.59 (br. s, 1 H), 4.61, 4.60 (2 d, $J = 12.0$ Hz, 2 H), 4.54 (d, $J = 5.0$ Hz, 1 H), 4.51, 4.48 (2 d, $J = 12.0$ Hz, 2 H), 4.40 (s, 2 H), 4.25 (dd, $J = 1.3$, $J = 3.0$ Hz, 1 H), 4.04 (ddd, $J = 1.3$, $J = 3.0$, $J = 5.0$ Hz, 1 H), 3.94 (dd, $J = 3.0$, $J = 5.5$ Hz, 1 H), 3.89 (dd, $J = 5.0$, $J = 10.0$, 1 H), 3.87 (dd, $J = 3.0$, $J = 10.0$ Hz, 1 H), 3.69, 3.52 (2 s, 6 H), 3.49 (dd, $J = 5.0$, $J = 5.5$ Hz, 1 H), 2.29, 2.19 (2 s, 6 H). ESI MS: 628.4 (M + H^+); 650.5 (M + Na^+).

Eluted second was **11a** (33 mg, 19%).

Methyl 4-(2′,3′-di-*O*-benzyl-α-L-threofuranosyl)-1,4-dihydro-2, 6-dimethylpyridine-3-acetyl-5-carboxylate (13)

A screw-capped vial containing a magnetic bar was charged with the sugar aldehyde **4** (88 mg, 0.28 mmol), **12** (45 μL, 0.42 mmol), **9** (48 mg, 0.42 mmol), L-proline **10b** (3 mg, 0.028 mmol), molecular sieves (~100 mg) and anhydrous MeOH (1.5 mL). The mixture was vigorously stirred, degassed *in vacuo* and saturated with Ar (3×). The mixture was stirred at 25 °C for 5 days, filtered through a pad of Celite, and washed thoroughly with MeOH. The combined filtrates were concentrated and the resulting residue was eluted from a column of silica gel with 15:1 *i*-Pr_2O–MeCN to give **13** (68 mg, 50%) as a colorless syrup. $[\alpha]_D = +31.3$ (*c* 0.5, $CHCl_3$). $R_f = 0.35$ (15:1 *i*-Pr_2O–MeCN).^{1}H NMR: ^{1}H NMR (benzene-d_6): δ = 7.33–7.00 (m, 10 H, Ph), 4.73 (d, $J_{1'4}$ = 6.0 Hz, 1 H, H-4), 4.54 (br., s, 1 H, NH), 4.45, 4.40, 4.18, 4.12 (4 d, J = 11.7 Hz, 1 H, PhCH_2), 4.06 (dd, $J_{1',2'}$ = 4.3 Hz, 1 H, H-1′), 4.00 (dd, $J_{2',3'}$ = 1.5 Hz, 1 H, H-2′), 3.88–3.84 (m, 2 H, H-3′, H-4b′), 3.70 (dd, $J_{3',4a'}$ = 5.6, $J_{4a',4b'}$ = 10.5 Hz, 1 H, H-4a′), 3.45 (s, 3 H, OCH_3), 2.34 (s, 3 H, $COCH_3$), 1.92, 1.84 (2 s, 6 H, CH_3); ^{13}C NMR (benzene-d_6): δ = 198.3, 167.6, 145.3, 142.0, 138.5, 138.4, 128.2, 127.9, 127.7, 127.4, 109.2, 99.8, 86.6, 85.1, 83.9, 71.7, 70.8, 70.3, 50.5, 37.3, 28.9, 19.0, 18.8. ESI MS: 492.6 (M + H^+); 514.7 (M + Na^+). Anal. Calcd for $C_{29}H_{33}NO_6$ (491.23): C, 70.86; H, 6.77; N, 2.85. Found: C, 70.92; H, 6.85; N, 2.80.

Methyl 4-(2′,3′-di-*O*-benzyl-α-D-threofuranosyl)-1,4-dihydro-2, 6-dimethylpyridine-3-acetyl-5-carboxylate (*ent*-13)

Treatment of ***ent*-4** (88 mg, 0.28 mmol) as described for the preparation of **13** gave ***ent*-13** (64 mg, 47%) as a colorless syrup. $[\alpha]_D = -31.1$ (*c* 0.5, $CHCl_3$). $R_f = 0.35$ (15:1 *i*-Pr_2O-MeCN). ^{1}H and ^{13}C NMR as **13**. ESI MS: 492.8 (M + H^+); 514.8 (M + Na^+). Anal. Calcd for $C_{29}H_{33}NO_6$ (491.23): C, 70.86; H, 6.77; N, 2.85. Found: C, 70.78; H, 6.60; N, 2.79.

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22 The presence in the reaction mixture of molecular sieves proved to be crucial to avoid the formation of large amounts of the symmetrically substituted DHP **11b**. This compound resulted from partial hydrolysis of enamine **9** to β-ketoester **8** and their subsequent three-component condensation with aldehyde **4**.

23 One gram of commercial agar that has been used for this project contains 2.38 mmol of 3,6-anhydro-L-galactose units as estimated by GC-MS analysis. See: T. T. Stevenson and R. H. Furneaux, *Carbohydr. Res.*, 1991, **210**, 277–298.

