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C-glycosphingolipid precursors via iodocyclization of homoallylic trichloroacetimidates

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ABSTRACT

The iodocyclization of homoallylic trichloroacetimidates derived from α-*C*-allyl galactoside were investigated. In line with the stereochemical trend observed for less substituted non-glycosylated frameworks, *E* and Z substrates delivered stereoselectively the 1,3-*anti* and 1,3-*syn* amino alcohol motifs, respectively. These products are advanced precursors to *C*-glycosides of the potent immunostimulatory glycolipid KRN7000.

1. Introduction

The involvement of glycosphingolipids in a variety of biological pathways has created a demand for unnatural analogs for use as mechanistic probes.[1–8] A popular subset thereof are *C*-glycosides, which are of interest because of their greater hydrolytic stability and conformational mobility compared to their parent O-glycosides.[9–13] However, the synthesis of these materials are not trivial, with a major challenge being the stereoselective fabrication of the pseudoanomeric bond, which is exacerbated for structures with highly substituted aglycone segments, as in the case of *C*-glycosphingolipids. One solution to this problem is to elaborate simple *C*-glycosides in which the pseudoanomeric configuration is 'preset'.[14–24] In this vein *C*-allyl glycosides of a variety of different monosaccharides are available in either pseudoanomeric configuration,[25–29] and new approaches for their transformation to more functionalized *C*-glycosides are of interest.

Towards this end, we have recently reported a strategy in which *C*-allylglycosides **1** are converted to homoallylic alcohol derivatives **2**, which serve as templates to *C*-glycosphingolipids **5** via an intramolecular nitrogen delivery strategy (Scheme 1). Our initial execution of this plan utilized the iodocyclization of a homoallylic carboimidothioate **3**.[30] Herein, we describe our results on the cyclization of related trichloroacetimidates **4**. These studies were directed at *C*-glycosides of the potent immunostimulatory glycolipid KRN7000 **9** (Scheme 2).[31]

2. Results and discussion

2.1. Synthetic design

The specific templates **6** and **7**, chosen for this study were of interest because of their easily availability from known precursors, and their potential as versatile relay compounds to *C*-glycosides of KRN7000 and related sphingolipids (Scheme 2). Studies on the iodocyclization of simple homoallylic tricloroacetimidates suggest that the stereochemistry of this cyclization depends primarily on alkene geometry and the configuration at the allylic position.[32–34] Thus, the reaction of *E*-alkene **6** is expected to favor the 1,3-*anti* amino alcohol motif (cf. **22** vide infra), which would lead to the 'unnatural' stereochemistry in C-KRN7000 (i.e., **8a**), because of stereoelectronic factors due to the allylic oxygen. In contrast, the reaction of the *Z*-isomer **7** is predicted to give the 1,3-*syn* amino

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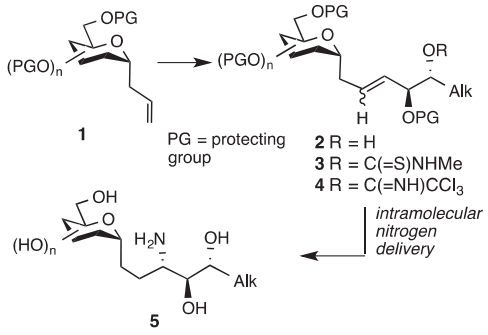


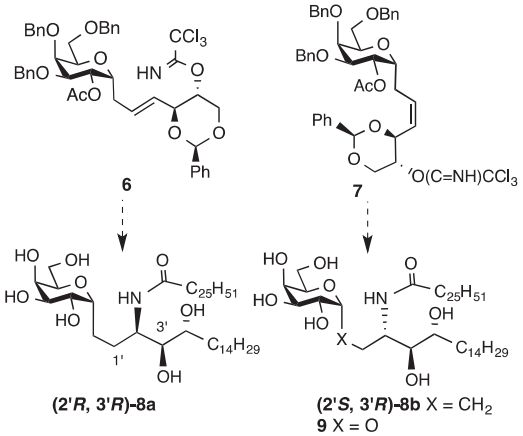
Scheme 1. *C*-glycosphingolipids via intramolecular nitrogen delivery.

alcohol derivative (cf. **23**, vide infra), because $A^{(1,3)}$ strain overrides the directing effect of the allylic substituent. However, because of the highly substituted nature of **6** and **7**, and the conformational rigidity imposed by the cyclic acetal framework, neither the expected stereoselectivity nor chemoselectivity in these reactions was assured. With regards to the latter, to reduce the likelihood of deleterious THF formation involving the C2-oxygen on the sugar ring, the 2-OH on the sugar segment was protected as an acetate[15,23,35] Schemes 3–5.

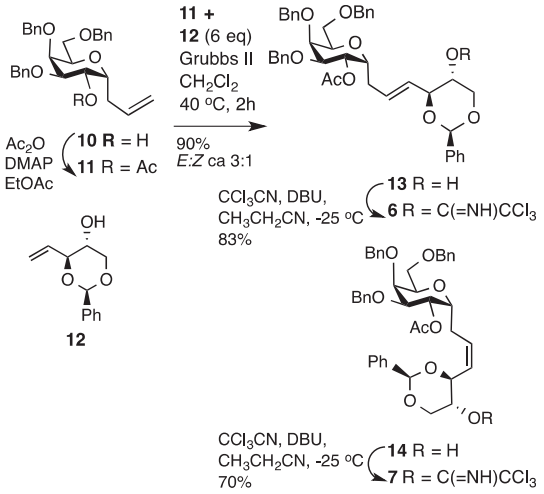
2.2. Synthesis

We envisaged that a cross metathesis (CM) strategy would provide the desired *E* and *Z* frameworks in a single step, with the former as the major isomer.[17,30,36] Accordingly, CM on known alkenes, *C*-allyl galactoside **11**[35] and the glucose derived alkene **12**[37] (6 equiv), using Grubbs II catalyst, produced an *E*:*Z* mixture of homoallylic alcohols **13** and **14** in 90% yield from **12**, as an approximately 3:1 *E*:*Z* mixture, as determined by ^{1}H NMR analysis. J_{vic} values of 15.7 and 11.0 Hz for **13** and **14**, respectively, supported the assigned alkene geometry. Treatment of **13** and **14** with DBU and trichloroacetonitrile provided the respective trichloroacetimidates **6** and **7**.

A more stereoselective synthesis of the *Z*-homoallylic alcohol **14** was performed using a Wittig olefination strategy. Thus, *C*-allyl glycoside **10** was converted to alcohol **16** through standard procedures for alcohol silylation and alkene processing. Transformation of **16** to the iodide **17** and reaction of the latter with triphenylphosphine provided phosphonium salt **18**. The use of the *tert*-butyldimethylsilyl protecting group was important for this

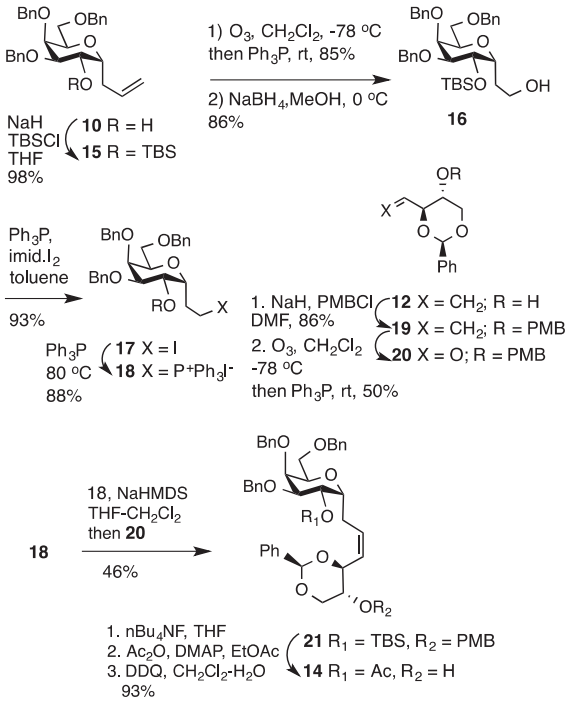


Scheme 2. Homoallylic trichloroacetimidate precursors for *C*-glycosides of KRN7000.

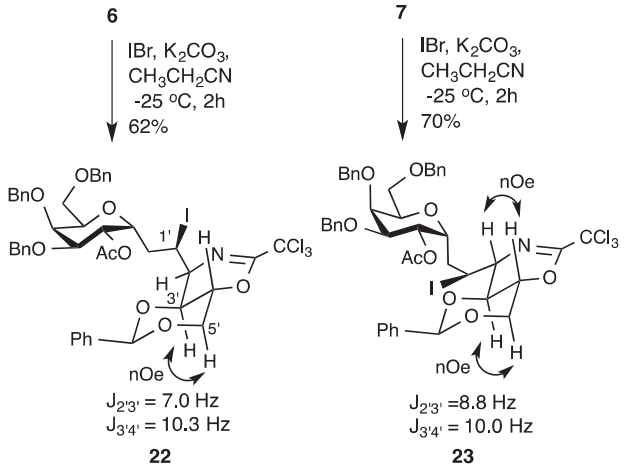


Scheme 3. Cross metathesis strategy for homoallylic trichloroacetimidates.

synthesis as benzyl and *p*-methoxybenzyl ethers were found to give appreciable amounts of the tetrahydrofuran product resulting from nucleophilic attack by the C2-oxygen, during the iodination step.[15,23] Aldehyde **20** was obtained from **12** after alcohol benzylation and ozonolysis of the alkene. Treatment of **18** in a mixture of THF and dichloromethane at −78 °C with NaHMDS, followed by addition of **20** to the resulting ylide, provided alkene **21** in 46% yield from **18**, as exclusively the *Z* isomer within the limits of ^{1}H NMR detection. The solvent mixture for this reaction was critical as pure THF gave lower *Z*:*E* ratios. This result may be due to a higher effective concentration of the metal cation in the reaction with pure THF, which facilitates oxaphosphetane reversion, and consequently stereochemical drift.[38,39] That the relative configuration at the α-carbon in **20** was unaffected by epimerization under the conditions of the Wittig reaction, was confirmed by correlation of the Wittig



Scheme 4. Wittig strategy for *Z*-homoallylic trichloroacetimidate.



Scheme 5. Iodocyclization of *E*- and *Z*-homoallylic trichloroacetimidates.

product **21** with the Z-alkene **14** from the CM route, and by NMR analysis of **23**, the oxazine subsequently obtained from **14** (vide infra). Thus, exchange of the protecting group at the C2–OH of the sugar residue in **21** from the silyl ether to the acetate, followed by DDQ promoted removal of the *p*-methoxybenzyl ether afforded **14** in 93% overall yield from **21**.

Treatment of a solution of the *E*-homoallylic trichloroacetimidate **6** in dry propionitrile with IBr, in the presence of anhydrous K_2CO_3 at −78 → −25 °C, gave oxazine **22** in approximately 62% yield. Under similar conditions the *Z*-trichloroacetimidate **7** gave oxazine **23** in 70% yield. In contrast to the iodocyclizations of related carboimidothioate substrates where iodonium dicollidine perchlorate (IDCP) was favored as the promoter over IBr, the more reactive IBr was preferred here because of the apparently lower reactivity of the trichloroacetimidate substrates. The structures of **22** and **23** were assigned from 2D COSY, HSQC and NOESY experiments. The stereochemistry of the newly formed oxazine ring in **22** was deduced from $J_{2',3'}$ and $J_{3'4'}$ values of 7.0 and 10.3 Hz, respectively, and a H3′/5′ NOE. That the $J_{2'3'}$ is 7.0 Hz and not much lower, suggests that six membered ring adopts a distorted half chair conformation. Similarly, $J_{2',3'}$ and $J_{3'4'}$ values of 8.8 and 10 Hz, respectively, and H2′/H4′ and H3′/5′ nOes supported the structure of **23**. In this case the relatively large $J_{2'3'}$ of 8.8 Hz suggests a less distorted conformation of the oxazine ring.

3. Conclusion

Thus, the iodocyclizations of homoallylic trichloroacetimidates **6** and **7** showed opposite facial selectivity, resulting in the 1,3-*syn* and 1,3-*anti* aminoalcohol motifs, respectively. This stereochemical trend is line with results reported for less substituted non-glycosylated substrates, but differs to our earlier result for related carboimidothioates, in which the *E* and *Z* substrates showed the same facial selectivity.[30,32,33] However, since the trichloroacetimidates in the present study are conformationally restrained by the cyclic acetal framework, whereas the analogous carboimidothioates were not, it is unclear whether the contrasting stereochemical trends are a consequence of the different imidate nucleophiles or the greater rigidity of the trichloroacetimidate substrates. It is also unclear whether highly substituted sugar ring impacts on the stereoselectivity of these iodocyclizations. More systematic are needed for a clearer understanding of the stereochemistry of these complex imidate cyclizations. These and applications to the synthesis of *C*-glycosides of KRN7000 and related glycosphingolipids are underway.

4. Experimental

4.1. Synthesis–general

Solvents were purified by standard procedures or used from commercial sources as appropriate. Petroleum ether refers to the fraction of petroleum ether boiling between 40 and 60 °C. Ether refers to diethyl ether. Unless otherwise stated thin layer chromatography (TLC) was done on 0.25 mm thick precoated silica gel 60 (HF-254, Whatman) aluminium sheets and flash column chromatography (FCC) was performed using Kieselgel 60 (32–63 mesh, Scientific Adsorbents). Elution for FCC usually employed a stepwise solvent polarity gradient, correlated with TLC mobility. Chromatograms were observed under UV (short and long wavelength) light, and/or were visualized by heating plates that were dipped in a solution of ammonium (VI) molybdate tetrahydrate (12.5 g) and cerium (IV) sulfate tetrahydrate (5.0 g) in 10% aqueous sulphuric acid (500 mL), or a solution of 20% sulfuric acid in ethanol. NMR spectra were recorded using a Varian Unity Plus 500 instrument. ^1H and ^{13}C spectra were recorded at 500 and 125 MHz, respectively in $CDCl_3$ or C_6D_6 solutions with residual $CHCl_3$ or C_6H_6 as internal standard (δ_H 7.27, 7.16 and δ_C 77.2, 128.4 ppm). Optical rotations ($[\alpha]_D$ were recorded using a Jasco P-1020 polarimeter and are given in units of 10^{-1} degcm^{2}g at 589 nm (sodium D-line). Chemical shifts are quoted in ppm relative to tetramethysilane (δ_H 0.00) and coupling constants (*J*) are given in Hertz. First order approximations are employed throughout. High resolution mass spectrometry was performed on Ultima Micromass Q-TOF or Waters Micromass LCT Premier mass spectrometers.

4.2. E Homoallylic trichloroacetimidate (**6**)

To a solution of **13** (150 mg, 0.215 mmol) in dry CH_3CH_2CN (3.0 mL) at −25 °C was added DBU (100 μL, 0.70 mmol) and CCl_3CN (100 μL, 0.99 mmol). The reaction mixture was stirred at this temperature for 20 min, then diluted with water and extracted with EtOAc. The organic phase was washed with brine and dried (Na_2SO_4), filtered, and concentrated in *vacuo*. The crude residue was purified by FCC to give **6** (185 mg, 92%): R_f=0.35 (20% EtOAc/hexane); ^1H NMR ($CDCl_3$) δ 8.39 (s, 1H), 7.43–7.17 (m, 20H), 5.75 (m, 1H), 5.56 (dd, *J*=6.7, 15.6 Hz, 1H), 5.49 (s, 1H), 4.97 (m, 1H), 4.89 (m, 1H), 4.62–4.40 (m, 7H), 4.22 (dd, *J*=6.8, 9.4 Hz, 1H), 4.09 (m, 1H), 3.94 (m, 1H), 3.85 (m, 1H), 3.82 (dd, *J*=3.0, 5.0 Hz, 1H), 3.67–3.62 (m, 3H), 2.33–2.05 (m, 2H), 1.95 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 170.3, 161.6, 138.7, 138.3, 138.2, 137.5, 131.1, 129.3, 128.8, 128.6, 128.5, 128.0, 127.9, 127.8, 126.5, 101.5, 79.8, 77.7, 76.8, 75.0, 74.0, 73.5, 73.4, 73.1, 72.5, 71.0, 70.6, 67.5, 66.6, 32.5, 21.2. HRMS (ESI, MNa^+) *m*/*z* calcd for $C_{44}H_{46}Cl_3NNaO_9$ 860.2136, found 862.2098.

4.3. Z Homoallylic trichloroacetimidate (**7**)

To a solution of **14** (120 mg, 0.173 mmol) in dry CH_3CH_2CN (2 mL) at −25 °C was added DBU (100 μl, 0.70 mmol), and CCl_3CN (100 μl, 0.99 mmol). The reaction was processed as described for the synthesis of the *E*-trichloroacetimidate **6**, and the crude material purified by FCC to give **7** (100 mg, 70%): R_f=0.50 (20% EtOEt/hexane); ^1H NMR ($CDCl_3$) 8.39 (s, 1H), 7.43–7.17 (m, 20H), 5.66 (m, 1H), 5.52 (m, 2H), 4.93 (m, 1H), 4.89 (dt, *J*=5.2, 9.8 Hz, 1H), 4.61–4.43 (m, 8H), 4.15 (m, 1H), 3.93 (m, 2H), 3.78 (dd, *J*=3.0, 5.4 Hz, 1H), 3.65 (m, 3H), 2.40–2.27 (m, 2H), 1.93 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 170.3, 161.8, 138.7, 138.3, 138.2, 137.4, 131.8, 129.4, 128.6, 128.5, 128.0, 127.9, 127.4, 126.5, 101.5, 77.5, 75.6, 74.7, 74.5, 73.4, 73.2, 71.2,

71.0, 67.6, 66.4, 28.9, 21.2. HRMS (ESI, MNa^+) *m*/*z* calcd for $C_{44}H_{46}Cl_3NNaO_9$ 860.2136, found 862.2118.

4.4. 1-(2′-O-acetyl-3′,4′,6′-tri-O-benzyl-α-D-galactopyranosyl)-2-propene (**11**)

To a solution of **10** (250 mg, 0.53 mmol) in EtOAc (9 mL) at rt, was added DMAP (6.5 mg, 0.053 mmol) and Ac_2O (100 μl, 0.97 mmol). The reaction mixture was stirred for 20 min, then concentrated in *vacuo*, and the residue purified by FCC to give **11** (250 mg, 92%): R_f=0.45 (20% EtOEt/hexane); ^1H NMR ($CDCl_3$) δ 7.22–7.19 (m, 15H), 5.65 (m, 1H), 5.00–4.95 (m, 3H), 4.64–4.45 (m, 6H), 4.16 (m, 1H), 3.95 (m, 2H), 3.83 (dd, *J*=3.0, 5.2 Hz, 1H), 3.68 (m, 2H), 2.27–2.09 (m, 2H), 1.97 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 170.2, 138.5, 138.2, 138.1, 134.0, 128.4, 127.8, 127.7, 127.6, 127.5, 117.3, 74.7, 74.0, 73.3, 73.1, 73.0, 72.1, 70.8, 68.7, 66.2, 33.9, 21.0.

4.5. CM of 11 and 12: E- and Z-homoallylic alcohols (**13**) and (**14**)

Ethylene gas was bubbled through a mixture of **11** (250 mg, 0.49 mmol) and **12** (600 mg, 2.9 mmol) in dry dichloromethane (50 mL) for 1 h. Grubbs II catalyst (42 mg, 0.04 mmol) was then added and the reaction mixture heated at reflux for 2 h. The solvent was concentrated in vacuo and the crude mixture was subjected to FCC to give a mixture of *E* alkene **13**, *Z* alkene **14** (305 mg, 90% based on **11**; *E*:*Z* ca. 3:1). Repeat FCC afforded partial separation of E and Z alkenes, **13** and **14**.

For **13**: R_f=0.22 (40% EtOAc/hexane); ^1H NMR ($CDCl_3$) δ 7.25–7.15 (m, 20H), 5.62 (m, 1H), 5.43 (m, 1H), 5.39 (dd, *J*=8.4, 15.7 Hz, 1H), 4.89 (m, 1H), 4.61–4.41 (m, 6H), 4.23 (m, 2H), 4.04 (t, *J*=10.6 Hz, 1H), 3.90 (m, 1H), 3.85 (t, *J*=8.6 Hz, 1H), 3.79 (dd, *J*=3.0, 5.8 Hz, 1H), 3.64–3.52 (m, 3H), 3.43 (m, 1H), 3.03 (d, *J*=4.4 Hz, 1H), 2.34 (m, 1H), 2.13 (m, 1H), 2.02 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 171.3, 138.5, 138.1, 138.0, 137.9, 131.6, 130.1, 128.9, 128.4, 128.3, 127.9, 127.8, 127.7, 127.6, 126.2, 101.0, 83.9, 76.8, 74.5, 73.1, 73.0, 70.7, 70.4, 64.8, 33.4, 21.1. HRMS (ESI, MNa^+) *m*/*z* calcd for $C_{42}H_{46}NaO_9$ 717.3040, found 717.3039.

For **14**: R_f=0.26 (40% EtOAc/hexane); ^1H NMR ($CDCl_3$) δ 7.38–7.20 (m, 20H), 5.57 (dt, *J*=11.0, 4.7 Hz, 1H), 5.47 (m, 2H), 5.00 (m, 1H), 4.66–4.40 (m, 7H), 4.25 (m, 2H), 4.17 (m, 1H), 4.02 (d, *J*=10.5 Hz, 1H), 3.95 (t, *J*=11 Hz, 1H), 3.84 (dd, *J*=17.9, 5.25 Hz, 1H), 3.70 (dd, *J*=5.1, 3.0 Hz, 1H), 3.56 (m, 3H), 3.38 (dt, *J*=9.5, 5.4 Hz, 1H), 2.50 (m, 1H), 1.98 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 170.5, 138.3, 138.2, 138.9, 137.9, 131.4, 129.7, 129.2, 128.6, 128.5, 128.1, 128.0, 127.9, 126.4, 101.0, 78.6, 74.3, 73.6, 73.3, 72.4, 72.0, 71.0, 65.1, 29.2, 21.2. HRMS (ESI, MNa^+) *m*/*z* calcd for $C_{42}H_{46}NaO_9$ 717.3040, found 717.3037.

4.6. 1-(2′-O-tert-butyldimethylsilyl-3′,4′,6′-tri-O-benzyl-α-D-galactopyranosyl)-2-propene (**15**)

TBSCl (1.4 g, 9.2 mmol) and NaH (212 mg, 8.9 mmol) were added to a solution of alcohol **10** (1.4 g, 2.95 mmol) in dry THF (10 mL). The reaction mixture was stirred at rt for 1 h. The reaction was diluted with water and extracted with EtOAc. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo The residue was purified by FCC to give **15** (1.74 g, 98%): R_f=0.47 (10% EtOAc/hexane); ^1H NMR ($CDCl_3$) δ 7.32–7.30 (m, 15H), 5.78 (m, 1H), 5.00 (m, 2H), 4.68–4.41 (m, 6H), 3.97 (m, 1H), 3.90 (m, 2H), 3.86 (ddd, *J*=9.8, 9.0, 4.1 Hz, 1H), 3.77 (t, *J*=10.5 Hz, 1H), 3.62 (dd, *J*=10.6, 4.7 Hz, 1H), 3.50 (dd, *J*=7.0, 2.7 Hz, 1H), 2.27 (m, 2H), 0.83 (s, 9H), 0.00 (s, 3H), −0.06 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 138.8, 138.7, 135.7, 128.5, 128.5, 128.1, 127.9, 127.8, 127.7, 127.6, 116.7, 78.5, 74.2, 73.4, 73.2, 73.2, 72.7, 70.3, 67.7, 32.0, 26.0, 18.2, −4.5, −4.7. HRMS (ESI, MH^+) *m*/*z* calcd for $C_{36}H_{49}O_5Si$ 589.3349, found 589.3346.

4.7. 1-(2′-O-tert-butyldimethylsilyl-3′,4′,6′-tri-O-benzyl-α-D-galactopyranosyl)-2-ethanol (**16**)

A stream of O_3/O_2 was passed through a solution of **15** (1.0 g, 1.7 mmol) in CH_2Cl_2 (150 mL) at −78 °C for 10 min. The reaction mixture was then purged with nitrogen, PPh_3 (500 mg, 1.9 mmol) added and stirring continued at rt for 2 h. At this point the mixture was concentrated in *vacuo*. FCC of the residue afforded the derived aldehyde (0.85 g, 85%): R_f=0.50 (20% EtOAc/hexane); ^1H NMR ($CDCl_3$) δ 9.75 (s, 1H), 7.32–7.30 (m, 15H), 4.73–4.5 (m, 7H), 4.03 (m, 1H), 4.00 (m, 1H), 3.96 (m, 1H), 3.86 (t, *J*=10.3 Hz, 1H), 3.68 (dd, *J*=10.6, 4.5 Hz, 1H), 3.54 (dd, *J*=6.7, 2.5 Hz, 1H), 2.62 (m, 2H), 0.83 (s, 9H), 0.00 (s, 3H), −0.05 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 201.3, 138.5, 128.6, 128.5, 128.0, 127.9, 127.8, 127.7, 78.2, 73.7, 73.4, 73.3, 70.1, 68.2, 67.3, 42.9, 26.0, 18.2, −4.5, −4.7. HRMS (ESI, MH^+) *m*/*z* calcd for $C_{35}H_{46}O_6Si$ 591.3142, found 591.3146.

$NaBH_4$ (125 mg, 3.5 mmol) was slowly added to a solution of the material from the previous step in methanol (20 mL) at 0 °C. The reaction mixture was stirred for 30 min, then diluted with saturated aqueous NH_4Cl and evaporated under reduced pressure. The residual syrup was taken up in EtOAc and washed with saturated aqueous $NaHCO_3$ and brine. The organic extract was dried (Na_2SO_4), filtered and concentrated in vacuo. FCC of the residue provided **16** as a colorless oil (730 mg, 86%): R_f=0.25 (20% EtOAc/hexane); ^1H NMR ($CDCl_3$) δ 7.32–7.30 (m, 15H), 4.71–4.50 (m, 6H), 4.09 (m, 2H), 3.98 (t, *J*=10.05 Hz, 1H), 3.89 (m, *2*H), 3.75 (m, 2H), 3.55 (dd, *J*=6.6, 2.8 Hz, 1H), 3.51 (dd, *J*=10.7, 3.5 Hz, 1H), 1.90 (m, 1H), 1.61 (m, 1H), 0.83 (s, 9H), 0.00 (s, 3H), −0.05 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 138.7, 138.5, 138.3, 128.7, 128.6, 128.5, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 78.4, 74.0, 73.4, 73.0, 72.4, 70.8, 67.8, 61.7, 30.0, 26.2, 26.0, 25.9, 25.8, 18.2, −4.6, −4.7. HRMS (ESI, MNa^+) *m*/*z* calcd for $C_{35}H_{48}NaO_6Si$ 615.3118, found 615.3112.

4.8. 1-(2′-O-tert-butyldimethylsilyl-3′,4′,6′-tri-O-benzyl-α-D-galactopyranosyl)-2-iodoethane (**17**)

I_2 (673 mg, 2.65) was added to a mixyure of alcohol **16** (630 mg, 1.06 mmol), Ph_3P (837 mg, 3.48 mmol) and imidazole (289 mg, 4.24 mmol) in toluene (20 mL). The reaction mixture was stirred at rt for 30 min, then quenched with 10% aqueous $Na_2S_2O_3$ and extracted with EtOAc. The organic phase was washed with brine, dried (Na_2SO_4) and concentrated in vacuo. FCC of the residue gave **17** as a colorless oil (691 mg, 93%): R_f=0.6 (10% EOAc/hexane); ^1H NMR ($CDCl_3$) δ 7.30–7.23 (m, 15H), 4.70–4.45 (m, 6H), 3.99 (ddd, *J*=10.6, 6.9, 3.5 Hz, 1H), 3.93–3.89 (m, *2*H), 3.67 (dd, *J*=10.4, 4.1 Hz, 1H), 3.49 (dd, *J*=6.9, 2.6 Hz, 1H), 3.27 (m, 1H), 3.18 (m, 1H), 2.05 (m, 1H), 1.92 (m, 1H), 0.82 (s, 9H), 0.00 (s, 3H), −0.06 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 138.7, 138.6, 128.7, 128.6, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 127.7, 78.8, 74.1, 73.6, 73.2, 72.9, 70.4, 68.1, 31.8, 26.2, 26.0, 25.9, 25.8, 18.2, 3.6, −4.6, −4.7. HRMS (ESI, MNa^+) *m*/*z* calcd for $C_{35}H_{47}INaO_5Si$ 725.2135, found 725.2131.

4.9. 1-(2′-O-tert-butyldimethylsilyl-3′,4′,6′-tri-O-benzyl-α-D-galactopyranosyl)-2-triphenylphosphoniumethyl iodide (**18**)

A mixture of **17** (691 mg, 0.984 mmol) and PPh_3 (2.24 g, 8.5 mmol) was fused at 80 °C for 3 h. The mixture was then cooled to rt and purified by FCC to give **18** (845 mg, 88%): R_f=0.16 (10% acetone/CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 7.75 (m, 15H), 7.65 (m, 15H), 4.61–4.47 (m, 6H), 4.13 (m, 2H), 4.04 (m, 1H), 3.86 (m, 1H), 3.75 (m, 1H), 3.69 (1H), 3.65 (d, *J*=7.6 Hz, 1H), 3.62 (dd, *J*=5.7, 2.8 Hz, 1H), 3.43 (m, 1H), 2.07–1.83 (m, 2H), 0.60 (s, 9H), −0.20 (s, 3H), −0.28 (s,

3H). ^{13}C NMR ($CDCl_3$) δ 139.0, 138.5, 135.2, 134.0, 133.9, 130.8, 130.7, 128.6, 128.5, 128.1, 128.0, 127.9, 127.7, 127.6, 118.4 (J_{C-P}=85.8 Hz), 73.9, 73.6, 73.5, 73.0, 72.4, 70.3, 68.1, 25.9, 23.2, 19.5 (J_{C-P}=52.4 Hz), 18.0, −4.6, −4.9. HRMS (ESI, M−I) *m*/*z* calcd for $C_{53}H_{62}O_5PSi$ 837.4104, found 837.4102.

4.10. (2R,4S,5R)-5-((4-Methoxybenzyl)oxy)-2-phenyl-4-vinyl-1,3-dioxane (**19**)

To a solution of **12** (1.0 g, 4.9 mmol) in dry DMF (20 mL) at 0 °C was added NaH (213 mg, 5.3 mmol). The mixture was stirred at this temperature for 15 min, at, which time PMBCl (1.0 mL, 7.2 mmol) was added slowly, and stirring continued at rt for 2 h. The mixture was then quenched with methanol (0.5 mL), diluted with water and extracted with EtOAc. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. FCC of the residue provided **19** (1.4 g, 86%): R_f=0.55 (20% EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 7.48 (d, *J*=1.8 Hz, 2H), 7.32 (m, 3H), 7.23 (d, *J*=9.2 Hz, 2H), 6.86 (d, *J*=8.6 Hz, 2H) 6.03 (ddd, *J*=17.3, 10.8, 5.8 Hz, 1H), 5.35 (dd, *J*=95.8, 16.8 Hz 2H), 4.45 (m, 2H), 4.25 (dd, *J*=10.9, 5.1 Hz, 1H), 4.12 (dd, *J*=9.2, 5.9 Hz, 1H), 3.79 (s, 3H), 3.62 (t, *J*=10.4, 1H) 3.42 (dt, *J*=9.5, 5.1 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 159.7, 137.9, 135.2, 130.1, 129.8, 129.6, 129.1, 128.4, 126.4, 101.0, 81.5, 72.8, 72.7, 69.9, 55.5. HRMS (ESI, MNa^+) *m*/*z* calcd for $C_{20}H_{22}NaO_5$ 349.1416, found 349.1413.

4.11. (2R,4R,5R)-5-((4-Methoxybenzyl)oxy)-2-phenyl-1,3-dioxane-4-carbaldehyde (**20**)

Alkene **19** (1.00 g, 3.06 mmol) was subjected to the standard ozonolysis procedure described in the preparation of **16**. FCC of the crude reaction product afforded **20** (500 mg, 50%): R_f=0.17 (20% EtOAc/hexane); ^{1}H NMR ($CDCl_3$) 9.72 (d, *J*=1.0 Hz, 1H), 7.46 (m, 2H), 7.35 (m, 3H), 7.25 (m, 2H), 6.88 (d, *J*=8.7 Hz, 2H), 5.51 (s, 1H), 4.55 (ABq, $\Delta\delta$=0.04 ppm, *J*=11.3 Hz, 2H), 4.29 (dd, *J*=5.1, 10.8 Hz, 1H), 4.18 (d, *J*=9.7 Hz, 1H), 3.78 (s, 3H), 3.74 (m, 1H), 3.65 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 197.3, 159.9, 137.0, 130.1, 129.5, 128.6, 126.4, 114.2, 101.1, 83.0, 72.7, 69.6, 67.9, 55.5. HRMS (ESI, MNa^+) *m*/*z* calcd for $C_{19}H_{20}NaO_5$ 351.1208, found 351.1209.

4.12. Z-p-Methoxybenzyl ether (**21**)

NaHMDS (0.57 mL of a 2M solution in THF, 1.14 mmol) was added at −78 °C to a solution of **18** (1.10 g, 1.14 mmol) in anhydrous 2:1 THF/CH_2Cl_2 (24 mL). The resulting bright orange solution was stirred for 1 h at this temperature, at, which time a solution of **20** (450 mg, 1.37 mmol) in THF (10 mL) was added dropwise. The resulting mixture was warmed to rt over 5 h, then poured into saturated aqueous NH_4Cl and extracted with EtOAc. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. FCC of the residue gave **21** (385 mg, 46%): R_f=0.23 (10% EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 7.38−7.20 (m, 22H), 6.8 (m, 2H), 5.8 (m, 1H), 5.6 (t, *J*=9.6 Hz, 1H), 5.45 (s, 1H), 4.75−4.40 (m, 10H), 4.20 (m, 1H), 4.04 (m, 1H), 3.94 (m, 3H), 3.89 (m, 1H), 3.32 (m, 1H), 3.79 (s, 3H), 3.64 (m, 1H), 3.57 (m, 1H), 3.47 (m, 1H), 3.42 (m, 1H), 2.6−2.4 (m, 2H), 0.86 (s, 9H), −0.02 (s, 3H), −0.08 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 159.6, 139.0, 138.5, 135.2, 134.0, 133.9, 130.8, 130.7, 128.6, 128.5, 128.1, 128.0, 127.9, 127.7, 127.6, 114.0, 101.1, 78.9, 77.5, 74.3, 73.5, 73.2, 72.5, 72.3, 68.1, 55.5, 26.1, 18.3, −4.5, −4.6. HRMS (ESI, MNa^+) *m*/*z* calcd for $C_{54}H_{66}NaO_9Si$ 909.4374, found 909.4373.

4.13. Z-Homoallylic alcohol 14 from Wittig reaction

To a solution of **21** (370 mg, 0.4 mmol) in THF (10 mL) at 0 °C was added dropwise a 1M solution of Bu_4NF in THF (0.8 mL, 0.8 mmol). The reaction mixture was warmed to rt, stirred at this temperature for 2 h, then diluted with water and extracted with EtOAc. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was dissolved in EtOAc (2 mL) and treated with Ac_2O (0.2 mL) and DMAP (5 mg). After stirring for 10 min at rt. the organic solvent was concentrated in vacuo, and the crude product was purified by FCC to give a homogeneous product (330 mg, 98%): R_f=0.25 (30% EtOAc/hexane). DDQ (190 mg, 0.80 mmol) was added to a mixture of this material (330 mg, 0.40 mmol), CH_2Cl_2 (4.5 mL) and saturated aqueous $NaHCO_3$ (0.5 mL). The reaction mixture was stirred at rt for 30 min, then concentrated in vacuo. FCC of the residue gave **14** (160 mg, 95% brsm). This material was identical by TLC, ^{1}H and ^{13}C NMR to a sample of **14** prepared via the CM route.

4.14. C-Glycoside oxazine (**22**)

To a solution of **6** (165 mg, 0.197 mmol) in dry CH_3CH_2CN (4 mL) at −25 °C was added anhydrous K_2CO_3 (55 mg, 0.80 mmol) and IBr (243 mg, 1.18 mmol). The reaction was stirred at this temperature for 2 h, then diluted with aqueous $Na_2S_2O_3$ and extracted with EtOAc. The organic phase was washed with brine and dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude material was purified by FCC to give an inseparable mixture of **22** and an unidentified impurity (139 mg). The purity of **22** was estimated at ca. 85 mol % by ^{1}H NMR, corresponding to a yield of 62% of **22** from **7**. Repeated FCC gave a pure sample of **22**: R_f=0.18 (0.5% EtOH/CH_2Cl_2); $[\alpha]_D^{18}$ 47 (*c* 1.5, CH_2Cl_2); ^{1}H NMR (C_6D_6) δ 7.70 (dd, *J*=1.3 Hz, 2H), 7.50 (m, 2H), 7.42 (m, 2H), 7.33−7.18 (m, 14H), 5.47 (m, 1H), 5.19 (s, 1H), 5.11 (m, 1H), 4.77 (m, 2H),4.70 (apparent d, *J*=11.5 Hz, 1H), 4.61 (ABq, *J*=11.0 Hz, $\Delta\delta$=0.06 ppm, 2H), 4.54 (m, 3H), 4.40 (m, 2H), 4.27 (dd, *J*=4.5, 7.0 Hz, 1H), 4.07 (m, 2H), 3.96 (dd, *J*=3.0, 5.2 Hz, 1H), 3.87 (dd, *J*=3.0, 5.3 Hz, 1H), 3.45 (dd, *J*=6.9, 10.3 Hz, 1H), 3.28 (t, *J*=10.2 Hz, 1H), 2.57 (m, 1H), 2.35 (m, 1H), 1.73 (s, 3H). ^{13}C NMR (C_6D_6) δ 169.7, 152.5, 139.5, 139.0, 137.8, 129.7, 129.0, 128.9, 128.8, 128.5, 128.0, 127.1, 103.2, 76.6, 75.7, 75.1, 74.3, 74.2, 73.2, 72.6, 72.0, 68.6, 68.2, 66.6, 59.0, 38.0, 30.5, 20.8. HRMS (ESI, MK^+) *m*/*z* calcd for $C_{44}H_{45}Cl_3IKNO_9$ 1002.0842, found 1004.0811.

4.15. C-Glycoside oxazine (**23**)

To a solution of **7** (85 mg, 0.1 mmol) in dry CH_3CH_2CN (2.0 ml) at −78 °C was added anhydrous K_2CO_3 (56 mg, 0.4 mmol) and IBr (150 mg, 0.7 mmol). Processing of the reaction as described for the iodocyclization of *E*-trichloroacetimidate **6**, and FCC of the crude product gave **23** (68 mg, 70%): R_f=0.43 (20% EtOAc/hexane); $[\alpha]_D^{18}$ 11 (*c* 0.8, CH_2Cl_2); ^{1}H NMR (C_6D_6) δ 7.40−7.18 (m, 20H), 5.51 (m, 1H), 5.33 (s, 1H), 5.10 (t, *J*=6.2 Hz, 1H), 4.73 (m, 2H), 4.60 (ABq, *J*=11.0 Hz, $\Delta\delta$=0.05 ppm, 2H), 4.52 (m, 3H), 4.35 (m, 2H), 4.08 (m, 1H), 4.02 (dd, *J*=5.3, 10.3 Hz, 1H) 3.96 (m, 2H), 3.90 (m, 1H), 3.78 (dt, *J*=5.5, 10.0 Hz, 1H), 3.42 (dd, *J*=1.8, 8.8 Hz, 1H), 3.36 (t, *J*=10.3 Hz, 1H), 2.76−2.61 (m, 2H), 1.73 (s, 3H), ^{13}C NMR (C_6D_6) δ 169.8, 153.0, 139.7, 139.1, 139.0, 137.7, 130.0, 129.6, 129.0, 128.9, 127.9, 127.1, 126.9, 102.4, 77.7, 75.7, 74.7, 74.2, 74.0, 73.2, 72.7, 72.0, 69.9, 68.3, 67.9, 61.6, 37.6, 30.6, 20.8. HRMS (ESI, MNa^+) *m*/*z* calcd for $C_{44}H_{45}Cl_3INNaO_9$ 986.1102, found 988.1075.

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Supplementary data

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