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Note

A novel approach to the stereocontrolled synthesis of *C*-vinyl β-D-galactopyranosides

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Abstract

Reaction of a lithiated dithiinyl reagent with a *O*-perbenzylated D-glycono-δ-lactone readily generates the corresponding masked *C*-vinyl galactosides in high yields and full β-selectivity. Removal of the sulfur mask renders the free vinyl aglycone with the vinyl group in either the Z or E configuration, depending on the desulfurization conditions chosen.

Keywords: *C*-Glycosides; Glycosylation; Dithiinyl reagents; Sialyl Lewis X mimics

C-Glycosylic compounds, often termed *C*-glycosides, are regarded as mimics of biologically relevant *O*-glycosides. The replacement of the exocyclic carbon–oxygen bond at the anomeric center with a carbon–carbon bond confers resistance to acid and enzymatic hydrolysis, resulting in hydrolytically stable carbohydrate mimics with many possible biological applications.[1] *C*-Vinyl, *C*-allyl, and *C*-alkynyl glycosides[2] constitute a group of synthetically useful compounds that allows a wide range of transformations based on the elaboration of the C–C unsaturated bond.

We report here a novel approach toward the preparation of a new class of sialyl Lewis X mimics.[3] These mimics are characterized by two modified sugar units linked through variously substituted three-carbon spacers (Fig. 1).

O-Perbenzylated-D-galactono-δ-lactone **1** (Scheme 1) was coupled with C-3 lithiated 5,6-dihydrodithiinyl reagent **2** to give the hemiacetal derivative **3**. Reagent **2**, already devised in our laboratory,[4] represents an allyl anion equivalent that accomplishes three-carbon elongations of suitable electrophiles, introducing both a fully protected double bond and a primary hydroxyl group. Dithiinyl reagents like **2** can be conveniently prepared containing a number of different side chains.[5]

The hemiacetal **3** was then treated[6] with Et_3SiH and $BF_3 \cdot Et_2O$ at −40 °C and thus converted into the expected *C*-glycoside **4**. It is noteworthy that the *O*-allyl group was essential to the conversion. When 4-methoxybenzyl protection was used, under the same conditions, spirocyclization at the anomeric carbon took place leading to 1,6-dioxaspiro[4,5]dec-3-enes.[7]

Compound **4**, which actually is the key intermediate we were working on for the synthesis of our target sialyl Lewis X mimics, was further elaborated for the purpose of getting to a *C*-vinyl glycoside with the fully deprotected aglycone moiety. It was, therefore, deallylated by *tert*-butyllithium in hexane–toluene at room temperature, and desulfurized[8] by Raney Ni in THF, to obtain the final *C*-vinyl β-D-glycoside **6**, the *S* configuration of which was ascertained by ^{1}H NMR analysis [500 MHz, $CDCl_3$: $\delta = 4.19$ (t, 1 H, ^4J 8.8 Hz, H-2)].

We consider of interest to have devised a path to prepare *C*-vinyl D-galactosides with full β-D-selectivity and in high overall yield: it is also remarkable that the aglycone moiety may present various substituents at the double bond (alkyl and formyl, besides hydroxymethyl group),[5] whereas the double bond itself may be deprotected into either Z configuration (as described by this

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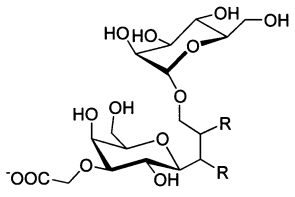
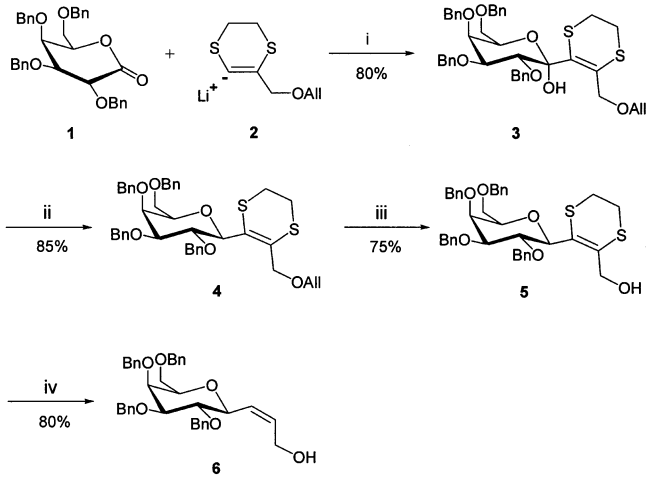


Fig. 1. General structure of new *C*-glycosyl sialyl Lewis X analogues.



Scheme 1. Reagents and conditions: (i) THF, −78 °C, 2 h; (ii) Et_3SiH, $BF_3{\cdot}Et_2O$, 1:1 CH_2Cl_2–CH_3CN, 40 °C, 1.5 h; (iii) *t*-BuLi, 5:1 hexane–toluene, r.t., 4 h; (iv) Raney Ni, THF, r.t., 15 min.

paper) or E configuration [by $LiAlH_4/Ti(i\text{-}PrO)_4$], as already reported.[9]

In our opinion the present C-glycosylation reaction can be regarded as one paralleling the *C*-vinyl glycoside preparation via reduction of *C*-alkynyl glycosides. However, such a procedure is characterized by the near absence of selectivity of the coupling reaction, leading to mixtures of α and β epimeric glycosides.[6,10]

1. Experimental

1.1. General

^1H and ^{13}C NMR spectra: Varian Inova 500, Bruker DRX-400, Varian Gemini 200 spectrometers, in C_6D_6 unless otherwise specified; assignments were aided by ^1H–^1H COSY correlation spectroscopy and DEPT. Molecular sieves (4 Å, 8–12 mesh, Aldrich) were activated at 160 °C under vacuum for ~16 h. Optical rotations (in $CHCl_3$): JASCO P-1010 (1.0 dm cell). Combustion analyses: Perkin–Elmer Series II 2400, CHNS analyzer. TLC analyses: E. Merck Silica Gel 60 F254 plates (0.2 mm layer thickness). Column chromatography: E. Merck Kieselgel 60 (70–230 mesh). Dry solvents were distilled immediately before use.

1.2. (2*R*,3*R*,4*S*,5*S*,6*R*)-2-{3′-[(Allyloxy)methyl]-5′,6′-dihydro-1′,4′-dithiin-2′-yl}-3,4,5-tri(benzyloxy)-6-[(benzyloxy)methyl]tetrahydro-2*H*-2-pyranol (3)

1.6 M BuLi in hexane (1.0 mL, 1.6 mmol) was added dropwise over 5 min to a stirred solution of 5-[(allyloxy)methyl]-2,3-dihydro-1,4-dithiin (**2**) (0.3 g, 1.5 mmol) over 4 Å molecular sieves in anhyd THF (1.5 mL), at −78 °C and under an N_2 atmosphere. After 20 min, 2,3,4,6-tetra-*O*-benzyl-D-galactono-δ-lactone (0.5 g, 1.0 mmol), dissolved in the same solvent (1.5 mL), was added dropwise via cannula. The reaction mixture was kept at −78 °C for 1.5 h, then quenched with 10% aq NH_4Cl (5 mL) and extracted with AcOEt (3 × 15 mL). The combined organic layers were dried (Na_2SO_4), and the solvents were evaporated under reduced pressure. Chromatography on silica gel (7:3 petroleum ether–EtOAc) of the crude residue finally afforded the pure hemiacetal **3** (0.6 g, 80%) as an oil: $[\alpha]_D^{25}$ +12.1° (*c* 1.3, $CHCl_3$); ^1H NMR (500 MHz): δ 2.26–2.38 (m, 2 H, SCH_2), 2.41–2.48 (m, 1 H, SCH_aH), 2.59–2.67 (m, 1 H, SCH_bH), 3.61 (dd, 1 H, ^3J 8.8 Hz, ^4J 5.2 Hz, H_a-7), 3.67 (ddt, 1 H, ^3J 13.2 Hz, ^4J 5.4 Hz, ^5J 1.5 Hz, $OCH_aHCH{=}CH_2$), 3.71 (ddt, 1 H, ^3J 13.2 Hz, ^4J 5.4 Hz, ^5J 1.5 Hz, $OCH_bHCH{=}CH_2$), 3.77 (d, 1 H, ^3J 11.6 Hz, CH_aHOAll), 3.84 (t, 1 H, $^3J = {}^4J$ 8.8 Hz, H_b-7), 3.97 (dd, 1 H, ^4J 9.5 Hz, ^4J 2.9 Hz, H-4), 3.99 (dd, 1 H, ^4J 2.9, ^4J 1.5 Hz, H-5), 4.20 (d, 1 H, ^3J 11.7 Hz, H_a–Bn_i), 4.26 (d, 1 H, ^3J 11.7 Hz, H_b–Bn_i), 4.38–4.42 (m, 1 H, H-6), 4.42 (d, 1 H, ^3J 11.7 Hz, H_a–Bn_{ii}), 4.52 (d, 1 H, ^3J 11.7 Hz, H_b–Bn_{ii}), 4.62 (d, 1 H, ^3J 11.2 Hz, H_a–Bn_{iii}), 4.63 (d, 1 H, ^4J 9.5 Hz, H-3), 4.74 (d, 1 H, ^3J 10.5 Hz, H_a–Bn_{iv}), 4.90 (d, 1 H, ^3J 10.5 Hz, H_b–Bn_{iv}), 4.91 (ddd, 1 H, ^3J 3.4 Hz, ^4J 10.3 Hz, ^5J 1.5 Hz, $CH{=}CH_aH$), 5.04 (d, 1 H, ^3J 11.2 Hz, H_b–Bn_{iii}), 5.12 (ddd, 1 H, ^3J 3.4 Hz, ^4J 17.5 Hz, ^5J 1.5 Hz, $CH{=}CH_bH$), 5.26 (d, 1 H, ^3J 11.6 Hz, CH_bHOAll), 5.63–5.75 (m, 1 H, $CH{=}CH_2$), 7.02–7.45 (m, 20 H, H_{Ar}); ^{13}C NMR (125 MHz): δ 26.8, 28.0 (2 × SCH_2), 68.8, 70.9, 71.9, 72.7, 73.4, 75.1, 76.0 (C-7, $OCH_2CH{=}CH_2$, CH_2OAll, 4 × OCH_2Ph), 70.7, 75.6, 80.4, 80.9 (C-3, C-4, C-5 and C-6), 100.1 (C-2), 116.5 ($CH{=}CH_2$), 127.4–128.9 (20 × CH_{Ar}, $SC{=}CS$), 134.0 ($CH{=}CH_2$), 138.4–139.3 (4 × Ph–C_4). Anal. Calcd for $C_{42}H_{46}O_7S_2$: C, 69.39; H, 6.38. Found: C, 69.11; H, 6.32.

1.3. (2*R*,3*R*,4*S*,5*S*,6*R*)-2-{3′-[(Allyloxy)methyl]-5′,6′-dihydro-1′,4′-dithiin-2′-yl}-3,4,5-tri(benzyloxy)-6-[(benzyloxy)methyl]tetrahydro-2*H*-2-pyran (4)

Et_3SiH (0.4 mL, 2.5 mmol) was added to a magnetically stirred solution of hemiacetal **3** (0.4 g, 0.5 mmol) in 1:1 CH_2Cl_2–CH_3CN (2 mL) at −40 °C. After 1 h, a

solution (3% v/v in CH_2Cl_2) of $BF_3 \cdot Et_2O$ (0.2 mL) was carefully added, and after 20 min the reaction was quenched with Et_3N (0.03 mL, 0.2 mmol). The organic layer was washed with brine and dried (Na_2SO_4), and the solvents were evaporated under reduced pressure to afford a crude residue, the chromatography of which on silica gel column (8:2 petroleum ether–EtOAc) afforded the pure product **4** (0.3 g, 85%) as an oil: $[\alpha]_D^{25}$ +12.9° (*c* 3.0, $CHCl_3$); ^{1}H NMR (500 MHz): δ 2.50–2.62 (m, 3 H, SCH_2CH_aHS), 2.76–2.83 (m, 1 H, SCH$_2$CH_bHS), 3.40 (dd, 1 H, ^4J 9.2 Hz, ^4J 2.4 Hz, H-4), 3.51 (dd, 1 H, ^4J 5.3 Hz, ^4J 8.8 Hz, H-6), 3.58 (dd, 1 H, ^3J 8.8 Hz, ^4J 5.3 Hz, H_a-7), 3.72 (t, 1 H, $^3J = {}^4J$ 8.8 Hz, H_b-7), 3.86–3.88 (m, 2 H, OCH_2CH=CH$_2$), 3.90 (br d, 1 H, ^4J 2.4 Hz, H-5), 3.98 (d, 1 H, ^3J 12.3 Hz, CH_aHOAll), 4.17 (d, 1 H, ^3J 11.7 Hz, H_a–Bn$_i$), 4.22 (d, 1 H, ^3J 11.7 Hz, H_b–Bn$_i$), 4.44 (d, 1 H, ^3J 12.1 Hz, H_a–Bn$_{ii}$), 4.49 (d, 1 H, ^3J 12.1 Hz, H_b–Bn$_{ii}$), 4.50–4.54 (m, 2 H, H-2 and H-3), 4.61 (d, 1 H, ^3J 11.7 Hz, H_a–Bn$_{iii}$), 4.78 (br d, 2 H, ^3J 11.7 Hz, H_a–Bn$_{iv}$ and CH_bHOAll), 4.87 (d, 1 H, ^3J 11.7 Hz, H_b–Bn$_{iii}$), 4.98 (ddd, 1 H, ^3J 3.4 Hz, ^4J 10.5 Hz, ^5J 1.5 Hz, CH=CH_aH), 5.03 (d, 1 H, ^3J 11.7 Hz, H_b–Bn$_{iv}$), 5.23 (ddd, 1 H, ^3J 3.7 Hz, ^4J 17.1 Hz, ^5J 1.9 Hz, CH=CH_bH), 5.76–5.85 (m, 1 H, CH=CH$_2$), 7.25–7.65 (m, 20 H, H_{Ar}); ^{13}C NMR (125 MHz): δ 21.7, 29.2 (2 × SCH_2), 67.6, 69.1, 69.2, 71.1, 72.1, 73.5, 74.2 (C-7, OCH_2CH=CH$_2$, CH$_2$OAll, 4 × OCH$_2$Ph), 73.3, 76.0, 76.2, 77.1, 83.3 (C-2, C-3, C-4, C-5 and C-6), 114.9 (CH=CH$_2$), 126.0–127.1 (20 × CH$_{Ar}$, SC=CS), 134.1 (CH=CH$_2$), 137.2–138.3 (4 × Ph–C$_4$). Anal. Calcd for $C_{39}H_{42}O_6S_2$: C, 69.82; H, 6.31. Found: C, 70.01; H, 6.28.

1.4. (2*R*,3*R*,4*S*,5*S*,6*R*)(3-{3,4,5-Tri(benzyloxy)-6-[(benzyloxy)methyl]tetrahydro-2*H*-2-pyranyl}-5,6-dihydro-1,4-dithiin-2-yl)methanol (5)

2.0 M *t*-BuLi in hexane (0.22 mL, 0.44 mmol) was added dropwise over 10 min to a stirred solution of **4** (0.3 g, 0.4 mmol) in anhyd 5:1 hexane–toluene (4 mL), at room temperature (r.t.) and under N_2 atmosphere. After 4 h (TLC monitoring), the reaction mixture was quenched with 10% aq NH_4Cl (5 mL) and extracted with AcOEt (2 × 10 mL). The combined organic layers were dried (Na_2SO_4), and the solvents were evaporated under reduced pressure. Chromatography on silica gel (8:2 petroleum ether–EtOAc) of the crude residue finally afforded the pure product **5** (0.2 g, 75%) as an oil: $[\alpha]_D^{25}$ −2.5° (*c* 3.02, $CHCl_3$); ^{1}H NMR (500 MHz): δ 2.26–2.45 (m, 3 H, SCH_2CH_aHS), 2.62–2.69 (m, 1 H, SCH$_2$CH_bHS), 3.11 (bs, 1 H, OH), 3.31 (dd, 1 H, ^4J 9.3 Hz, ^4J 2.9 Hz, H-4), 3.36–3.41 (m, 1 H, H-6), 3.56 (dd, 1 H, ^3J 9.0 Hz, ^4J 5.3 Hz, H_a-7), 3.65 (t, 1 H, ^3J 9.0 Hz, ^4J 7.8 Hz, H_b-7), 3.82 (bd, 1 H, ^4J 2.9 Hz, H-5), 4.15 (d, 1 H, ^3J 11.7 Hz, CH_aHPh), 4.20 (d, 1 H, ^3J 11.7 Hz, CH_bHPh), 4.22 (d, 1 H, ^3J 10.3 Hz, CH_aHPh), 4.37 (d, 1 H, ^4J 9.3 Hz, H-2), 4.40 (s, 2 H, C=C–CH_2OH), 4.41 (d, 1 H, ^3J 10.3 Hz, CH_bHPh), 4.48 (t, 1 H, ^4J 9.3 Hz, H-3), 4.59 (d, 1 H, ^3J 11.7 Hz, CH_aHPh), 4.72 (d, 1 H, ^3J 10.7 Hz, CH_aHPh), 4.78 (d, 1 H, ^3J 10.7 Hz, CH_bHPh), 5.00 (d, 1 H, ^3J 11.7 Hz, CH_bHPh), 6.95–7.45 (m, 20 H, H_{Ar}); ^{13}C NMR (125 MHz): δ 26.4, 29.5 (2 × SCH_2), 64.1, 68.9, 73.4, 74.4, 74.7, 77.6 (C-7, CH$_2$OH, 4 × OCH_2Ph), 72.3, 76.0, 77.4, 79.4, 84.5 (C-2, C-3, C-4, C-5 and C-6), 125.7, 130.2 (SC=CS), 127.5–129.1 (20 × CH$_{Ar}$), 138.1–139.5 (4 × Ph–C$_4$). Anal. Calcd for $C_{42}H_{46}O_6S_2$: C, 70.96; H, 6.52. Found: C, 71.22; H, 6.56.

1.5. (Z)-1-{(2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-Tri(benzyloxy)-6-[(benzyloxy)methyl]tetrahydro-2*H*-2-pyranyl}-1-propen-3-ol (6)

A solution of product **5** (0.2 g, 0.3 mmol) in THF (3 mL) was added in one portion to a stirred suspension of Raney Ni (W2) (2.7 g, wet) in the same solvent (2 mL) at r.t. The suspension was stirred for 15 min (TLC monitoring), and the solid was then filtered off and washed with EtOAc. The filtrate was neutralized with saturated aq Na_2CO_3 and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine until neutral and dried (Na_2SO_4), and the solvents were evaporated under reduced pressure to afford a crude residue. Chromatography of the latter on silica gel column (8:2 petroleum ether–EtOAc) gave the pure sulfur-free product **6** (0.1 g, 80%) as an oil: $[\alpha]_D^{25}$ +25.1° (*c* 0.41, $CHCl_3$); ^{1}H NMR (500 MHz): δ 3.35 (dd, 1 H, ^4J 9.4 Hz, ^4J 2.9 Hz, H-4), 3.42–3.47 (m, 1 H, H-6), 3.61 (dd, 1 H, ^3J 8.9 Hz, ^4J 5.4 Hz, H_a-7), 3.69 (dd, 1H, ^3J 8.9 Hz, ^4J 7.7 Hz, H_b-7), 3.86 (m, 2 H, H-3 and H-5), 4.05 (dd, 1 H, ^3J 13.3 Hz, ^4J 4.3 Hz, CH_aHOH), 4.09 (dd, 1 H, ^3J 13.3 Hz, ^4J 4.3 Hz, CH_bHOH), 4.18–4.26 (m, 3 H, 2 × H–Bn$_i$ and H-2), 4.37–4.44 (m, 3 H, H_a–Bn$_{ii}$ and 2 × H–Bn$_{iii}$), 4.58 (d, 1 H, ^3J 11.3 Hz, H_a–Bn$_{iv}$), 4.77 (d, 1 H, ^3J 10.7 Hz, H_b–Bn$_{ii}$), 4.98 (d, 1 H, ^3J 11.3 Hz, H_b–Bn$_{iv}$), 5.57–5.69 (m, 2 H, HC=CH), 6.98–7.40 (m, 20 H, H_{Ar}); ^{13}C NMR (125 MHz): δ 59.6, 69.2, 72.3, 73.5, 75.1, 75.6 (4 × OCH$_2$Ph, C-7 and CH$_2$OH), 74.7, 76.2, 76.9, 79.2, 84.7 (C-2, C-3, C-4, C-5 and C-6), 127.7–128.5 (20 × CH$_{Ar}$), 129.5, 133.5 (HC=CH), 138.6, 138.9, 139.0, 139.4 (4 × Ph–C$_4$). Anal. Calcd for $C_{37}H_{40}O_6$: C, 76.53; H, 6.94. Found: C, 76.38; H, 6.91.

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