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Synthesis of 2-iodo-2-deoxy septanosides from a D-xylose-based oxepine: intramolecular cyclization in the absence of a glycosyl acceptor

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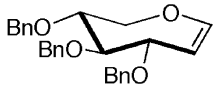
Abstract—Oxidative glycosylations of the D-xylose-based oxepine 1,6-anhydro-3,4,5-tri-*O*-benzyl-2-deoxy-D-xylosept-1-enitol (**1**) using *N*-iodosuccinimide (NIS) are reported. The reaction produced 2-deoxy-2-iodo-α-D-idoseptanosides and 2-deoxy-2-iodo-β-D-guloseptanosides **2**–**9** in good yields. When limited equivalents of a glycosyl acceptor were used, or in the absence of a glycosyl acceptor, an intramolecular cyclization predominated to form 1,6-anhydro-3,4-di-*O*-benzyl-2-deoxy-2-iodo-α-D-idopyranose (**10**).

Keywords: Septanose carbohydrates; Oxepine; Glycosylation

1. Introduction

The use of septanose glycosides in a biological setting relies on the ability to effectively synthesize these species. Septanoses are expanded variants of pyranoses that are characterized by a seven, rather than a six-membered ring structure. Considerable progress has been made toward the synthesis of septanoses; most of the strategies used to date have relied on the cyclization of a natural pyranose through the C-6 rather than C-5 hydroxyl group.[1] Both monoseptanosides and pyranosyl septanosides have yielded to this treatment.[2,3]



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We have become interested in evaluating an alternative approach to the synthesis of septanoses. It is motivated by the general utility of glycals in the synthesis of pyranoses.[4] Cyclic enol ethers, such as glycals or oxepines, are activated by electrophilic oxidants followed by attack of a nucleophile to form the glycosidic bond (Scheme 1).[4–9] We have recently shown that oxepines such as 1,6-anhydro-3,4,5-tri-*O*-benzyl-2-deoxy-D-xylosept-1-enitol (**1**), derived from protected pyranoses,[10] can serve as glycosyl donors in the synthesis of septanosides using dimethyldioxirane (DMDO) as the oxidant.[11] Here we demonstrate the reactivity of the same oxepine **1** with *N*-iodosuccinimide (NIS) as an electrophilic oxidant to form 2-deoxy-2-iodo septanosides **2**–**9**. Diminished stereoselectivity of glycoside formation relative to the DMDO mediated glycosylations was observed when using NIS as electrophile. Further, in reactions where the number of equivalents of glycosyl acceptor was reduced or eliminated completely, the appearance of a specific side product was observed. This product, 1,6-anhydro-3,4-di-*O*-benzyl-2-deoxy-2-iodo-α-D-idopyranose (**10**), resulted from intramolecular attack by the C-5 oxygen on the β-iodonium species (**11**).

2. Results and discussion

2.1. NIS mediated glycosylation of 1,6-anhydro-3,4,5-tri-*O*-benzyl-2-deoxy-D-xylosept-1-enitol (1)

The preparation of 2-iodoglycosides from glycal donors using oxidative iodine sources such as iodo-di-*sym*-collidine

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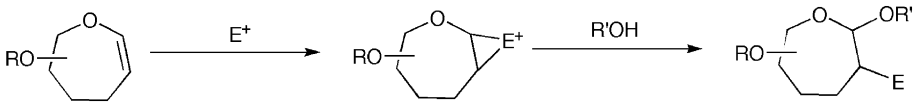


Scheme 1. General method for activation of cyclic enol ethers.

perchlorate (IDCP) and NIS is well documented.[5,6] Here we have extended the demonstration of the functional equivalence of carbohydrate-based oxepines with glycals by subjecting oxepine **1** to the NIS glycosylation reaction. Variable anomeric selectivity in the formation of 2-deoxy-2-iodopyranosides has been noted using glycals based on protecting groups, iodine source, or reaction conditions. We were interested in determining if the selectivity observed in the DMDO epoxidation of oxepine **1** would persist in the NIS glycosylations. Reactions were conducted by addition of NIS to a solution of oxepine **1** and the specific nucleophile in dichloromethane (DCM) at room temperature. Table 1 collects the results from reactions where methanol, 2-propanol, 1,2:3,4-di-*O*-isopropylidene D-galactose (diacetone galactose), and acetic acid[12] were used as nucleophiles. The products of these reactions are shown in Figure 1.

The reaction showed good yields but with limited stereoselectivity in the formation of the α-2-deoxy-2-iodo-D-idoseptanosides (**2**, **4**, **6**, **8**) over the β-2-deoxy-2-iodo-D-guloseptanosides (**3**, **5**, **7**, **9**). The yields and selectivities observed were in contrast to the highly selective formation of α-pyranosides using tri-*O*-benzyl glucal,[5a] but similar to those reported for a series of acetate protected glycals.[6a] Product distributions were not significantly different when the solvent was changed to toluene (entry 2) or THF (entry 5), or when the iodine source was IDCP instead of NIS (entry 6). The NIS mediated iodoalkoxylation described here can be active in two mechanistic manifolds based on whether iodonium ion formation is reversible or irreversible.[6a] Variable α/β product ratios as a function of nucleophile were correlated with reversible iodonium ion formation for glycals.[6a] Similarly, the variable α/β product ratios in Table 1 suggested that iodonium ion formation was reversible under the reaction conditions evaluated.

^{1}H NMR coupling constant analysis was used to assign the anomeric stereochemistry in products **2**–**9**. The septanosides were partitioned into two groups based on the similarities of their ^{1}H NMR spectra (Fig. 2). One anomer from each pair of septanosides was represented in a set; therefore septanosides **2**, **4**, **6**, and **8** (set A) were grouped together as were **3**, **5**, **7**, and **9** (set B). The anomeric acetates **8** and **9** served as representative examples of theses two groups; we expected a *trans*-1,2-relationship for each based on nucleophilic attack of the iodonium intermediate in the reaction. Assuming the *trans*-1,2-relationship and knowing the fixed stereochemistry at C-3 from oxepine **1**,[11] we realized α-septanoside **8** had two *trans* vicinal relationships between H-1, H-2 ($J = 9.5$ Hz) and H-2, H-3 ($J = 9.8$ Hz). Similarly, the β-septanoside (**9**) had one *trans* vicinal relationship (H-1, H-2, $J = 8.9$ Hz) and one *cis* relationship (H-2, H-3, $J = 1.1$ Hz). Homonu-

Table 1. Reactions of various nucleophiles with NIS/IDCP and **1**

Entry	Nucleophile (ROH)	Conditions	Product(s)	Yield (%)	α/β
1	CH_3OH	NIS, DCM, rt	**2**, **3**	94	55:45
2	CH_3OH	NIS, $PhCH_3$, rt	**2**, **3**	96	64:36
3	$(CH_3)_2CHOH$	NIS, DCM, rt	**4**, **5**	97	67:33
4	Diacetone galactose	NIS, DCM, rt	**6**, **7**	24	64:36
5	Diacetone galactose	NIS, THF, rt	**6**, **7**	22	50:50
6	Diacetone galactose	IDCP, DCM, rt	**6**, **7**	47	60:40
7	CH_3CO_2H	NIS, DCM, rt	**8**, **9**	64	64:36

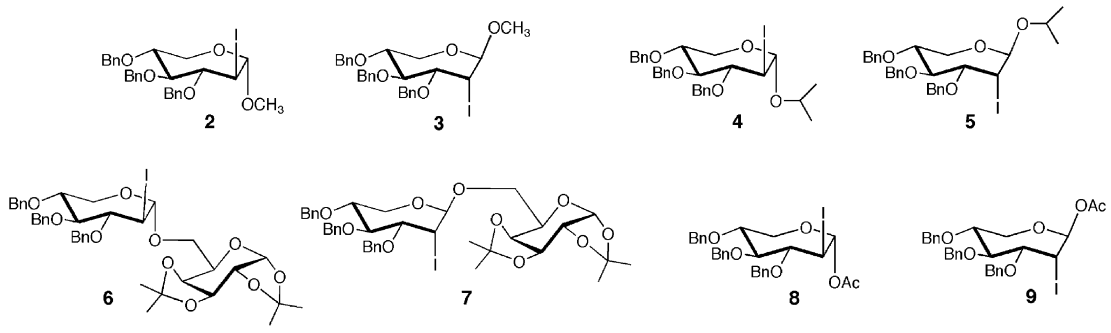
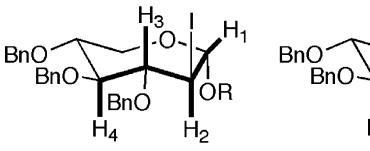


Figure 1. 2-Deoxy-2-iodo-D-septanoside products from reactions described in Table 1.

clear decoupling experiments supported this assignment. Selective irradiation of the anomeric proton of **8** eliminated the H-1, H-2 coupling and simplified the ^{1}H signal of H-2 into an apparent doublet with coupling ($^3J_{H2,H3}$) of 9.8 Hz. A similar experiment conducted on **9** provided a signal for H-2 that was a doublet with a coupling ($^3J_{H2,H3}$) of 1.1 Hz (Fig. 2).

The ^{1}H NMR spectra of the α-D-idoseptanosides (**2**, **4**–**6**, **8**, set A) were characterized by an extra coupling in the signal for the H-2 protons (in addition to H-1, H-2 and H-2, H-3 couplings). The magnitude of the coupling (2.5–3.4 Hz) suggested that it may be a $^4J_{H,H}$ between H-2 and H-4. Systems that demonstrate such large $^4J_{H,H}$ often arise from 'W-couplings' in rigid cyclic (especially bridged bicyclic) structures.[13] The preferred conformation of the α-D-idoseptanosides was expected



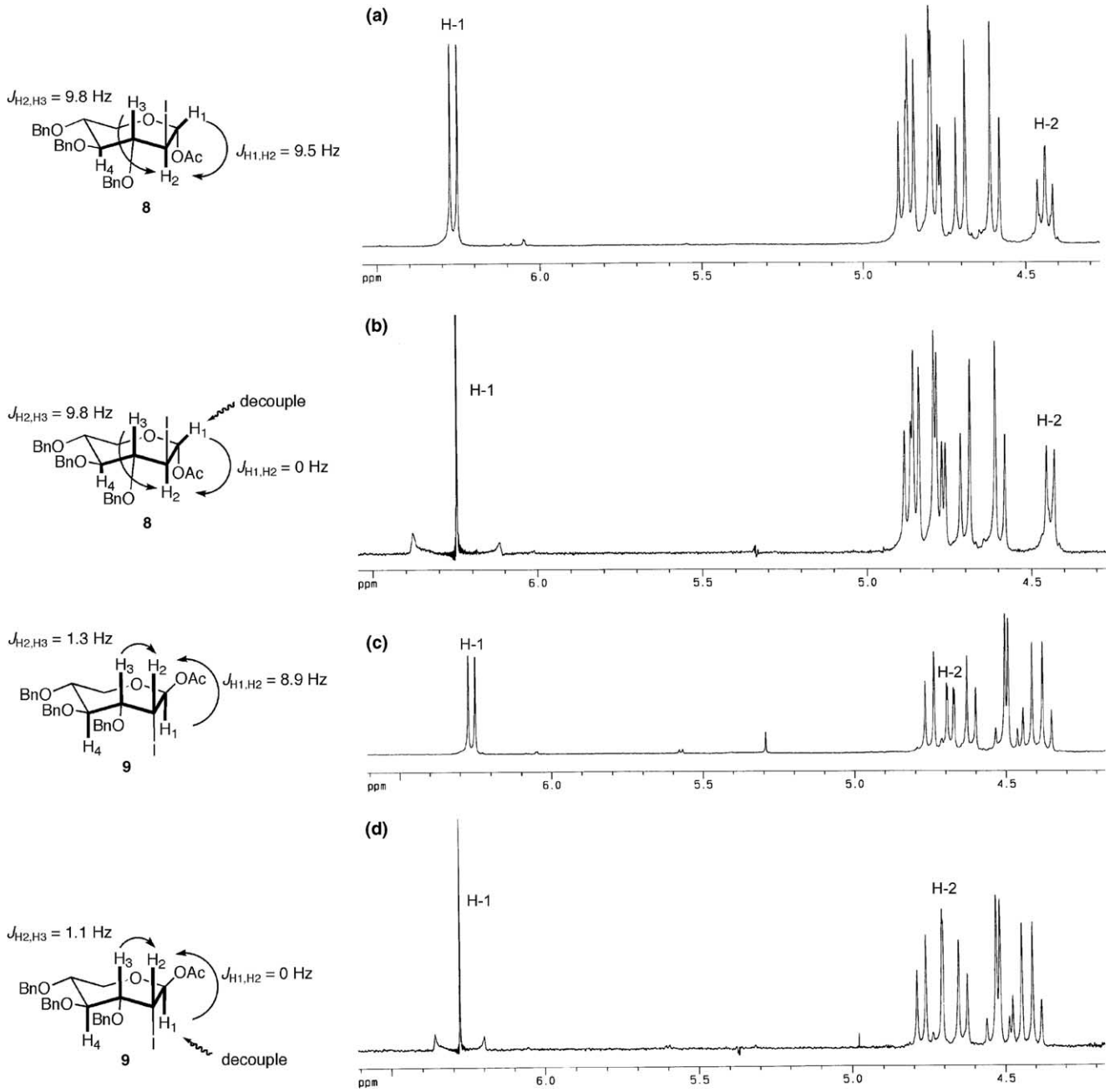


Figure 2. (a) Partial ^{1}H NMR spectrum of **8**, (b) partial ^{1}H NMR spectrum of **8** with irradiation on H-1, (c) partial ^{1}H NMR spectrum of **9** and (d) partial ^{1}H NMR spectrum of **9** with irradiation on H-1.

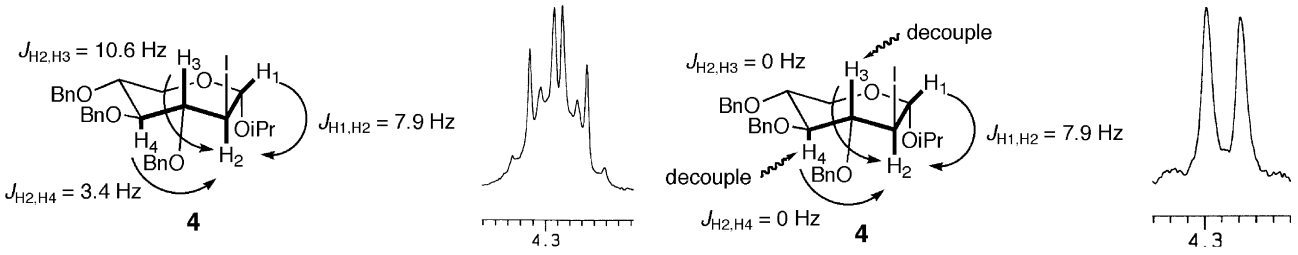
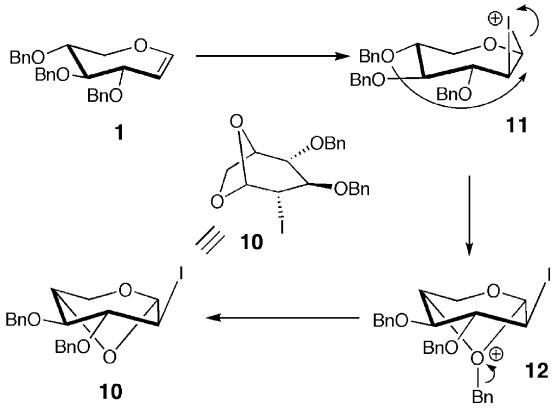


Figure 3. H NMR signal for H-2 of **4** with (right) and without (left) irradiation of H-3/H-4.

to be close to the $^{3,4}TC_{5,6}$ conformation based on the reported analysis of the enantiomeric methyl 2,3,4,5-tetra-*O*-acetyl-α-L-idoseptanoside, which was shown to adopt the $^{5,6}TC_{3,4}$ conformer.[2a] The $^{3,4}TC_{5,6}$ conformation does not put H-2 and H-4 in an orientation appropriate for W-coupling, although the W-orientation is not compulsory for long-range coupling to be observed. Using α-septanoside **4** (representative of set A), a selective homonuclear decoupling experiment (Fig. 3) showed that the multiplet for the H-2 signal (left) simplified to a doublet (right) upon irradiation of the H-3 and H-4 signals. Due to chemical shift overlap of the H-3 and H-4 signals, the long-range (H-2, H-4) coupling could not be completely confirmed, however. The conformational implications of this result are unclear but are currently under investigation.

2.2. Formation of 1,6-anhydro-3,4-di-*O*-benzyl-2-deoxy-2-iodo-α-D-idopyranose (10)

In the glycosylation reactions involving diacetone galactose and acetic acid as acceptors (Table 1, entries 4–7) an additional product was recovered in 64%, 7%, 49%, and 26% yield, respectively. The ^{1}H and ^{13}C NMR data indicated that the new product had lost a benzyl group relative to the starting oxepine **1**, and no signals from the glycosyl acceptors were observed. Mindful of other reports that demonstrated the reactivity of benzyl protected ethers,[14] we suspected that the product may have arisen from intramolecular nucleophilic attack by a benzyl ether oxygen. The appearance of **10** was attributed to the reduced equivalents of nucleophilic acceptor used in these reactions relative to the methanol and 2-propanol examples and to the reduced inherent nucleophilicity of the acetic acid and diacetone galactose acceptors. It was formed by attack of the C-5 oxygen on the iodonium species (**11**) to form **12** and subsequent loss of benzyl cation (Scheme 2). The structural assignment is based on analysis of the NMR spectra (^{1}H, ^{13}C, COSY, HMQC, HMBC) and its similarity to the reported spectra of 1,6-anhydro-3,4-di-*O*-benzyl-2-deoxy-2-iodo-α-D-glucopyranose.[15] Also, when oxepine **1** was placed under the standard reaction conditions in the absence of a glycosyl acceptor, **10** was the exclusive product isolated in 62% yield. Similar intramolecular reactions were not observed when DMDO was used as



Scheme 2. Formation of 1,6-anhydro-3,4-di-*O*-benzyl-2-deoxy-2-iodo-α-D-idopyranose (**10**).

oxidant in the glycosylation of oxepine **1**.[11] We attribute the observed intramolecular reaction to the increased reactivity of the intermediate iodonium species (such as **11**) relative to the 1,2-anhydroseptanoses in the DMDO reactions. Although temperature was not evaluated as a reaction parameter in the formation of **10**, changing the solvent from DCM to THF reduced the yield of **10** from 64% to 7% with recovery of significant quantities (66%) of the starting material (**1**).

The NIS-mediated glycosylations of oxepine **1** to form 2-deoxy-2-iodo-α-D-idoseptanosides and 2-deoxy-2-iodo-β-D-guloseptanosides are relatively efficient, although not selective. The results underscore the potential reactivity of the benzyl protected ethers toward intramolecular cyclization as in the formation of **10** and suggest that glycosylations using stoichiometric equivalents of acceptors may be problematic. In summary, we have demonstrated that the reactivity of carbohydrate-based oxepines is that of a ring expanded glycal; further developments toward this goal will be reported in due course.

3. Experimental

3.1. General methods

Unless stated otherwise, all reactions were conducted at room temperature (rt) under N_2 atmosphere. 1,6-Anhydro-3,4,5-tri-*O*-benzyl-2-deoxy-D-*xylo*-hept-1-enitol (**1**) was synthesized by the route of Peczuh et al.[10,11] NIS

was used without purification as purchased (Aldrich, St. Louis, MO). IDCP was prepared as reported.[6b] Reactions were monitored by TLC (glass backed, silica gel, 60 Å, F_{254}, 250 μm). Visualization was conducted either under UV light or by charring with 2.5% *p*-anisaldehyde in H_2SO_4, acetic acid, and ethanol solution. Preparative chromatography was conducted on silica gel (60 Å, 32–63 μm, Sorbent Technologies, Atlanta, GA). Melting points are uncorrected. Optical rotations were measured at 22 ± 2 °C. ^{1}H NMR spectra were collected at 400 MHz with chemical shifts referenced to $(CH_3)_4Si$ (δ_H 0.00 ppm) or the residual peak in $CHCl_3$ (δ_H 7.27 ppm). ^{13}C NMR were collected at 100 MHz and referenced to the residual peak in $CDCl_3$ (δ_C 77.2 ppm) or CD_3OD (δ_C 49.1 ppm).

3.2. Methyl 3,4,5-tri-*O*-benzyl-2-deoxy-2-iodo-α-D-idoseptanoside (2) and methyl 3,4,5-tri-*O*-benzyl-2-deoxy-2-iodo-β-D-guloseptanoside (3)

Oxepine **1** (0.050 g, 0.12 mmol) was dried via azeotropic distillation from toluene (3 × 5 mL) under reduced pressure and dissolved in anhydrous CH_3OH (1 mL). The solution was cooled to 0 °C and NIS (0.032 g, 0.144 mmol) followed by anhydrous CH_2Cl_2 (1 mL) were added. The mixture was stirred and allowed to warm to rt over 30 min. The reaction mixture was diluted with CH_2Cl_2 (25 mL) and washed with aqueous $Na_2S_2O_3$ (1 M, 3 × 15 mL). The aqueous fractions were extracted with CH_2Cl_2 (2 × 20 mL). The collected organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. Purification of the residue by column chromatography using 19:1, petroleum ether–EtOAc as eluent gave two fractions. The first fraction gave **2** (0.036 g, 52%) as a yellow solid; R_f 0.40 (17:3, hexanes–EtOAc); Mp 120–125 °C; $[\alpha]_D$ −17.9 (*c* 1.7, $CHCl_3$); IR (KBr) cm^{-1}: 3027.69, 2904.27, 1496.49, 1454.06, 1398.14, 1361.50, 1216.86, 1106.94, 1064.51, 732.82, 694.25; ^{1}H NMR ($CDCl_3$): δ 7.40–7.25 (m, 15H), 4.98 (d, *J* = 8.1 Hz, 1H), 4.89 (d, *J* = 10.7 Hz, 1H), 4.87 (d, *J* = 9.9 Hz, 1H), 4.79 (d, *J* = 9.9 Hz, 1H), 4.78 (d, *J* = 10.9 Hz, 1H), 4.73 (d, *J* = 11.4, 1H), 4.64 (d, *J* = 11.4 Hz, 1H), 4.32 (ddd, *J* = 10.6, 7.9, 3.2 Hz, 1H), 3.64 (m, 2H), 3.53 (m, 2H), 3.47 (dd, *J* = 10.9, 2.5 Hz, 1H), 3.39 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 138.8, 138.2, 137.8, 128.7, 128.5 (2), 128.4, 128.1, 128.0, 127.9 (2), 127.7, 106.5, 87.8, 79.9, 77.8, 76.4, 75.4, 74.0, 58.3, 56.0, 36.8; FAB-MS $[M-H]^+$ *m*/*z* calcd for $C_{28}H_{31}IO_5$ 573.1138, found 573.1164.

The second fraction from the chromatographic separation above gave **3** as a yellow oil (0.029 g, 42%). R_f 0.30 (17:3, hexanes–EtOAc); $[\alpha]_D$ +45.24 (*c* 1.0, $CHCl_3$); IR (KBr) cm^{-1}: 3029.62, 2925.48, 1496.49, 1454.06, 1348.00, 1207.22, 1112.73, 1064.51, 736.67, 698.11; ^{1}H NMR ($CDCl_3$): δ 7.38–7.17 (m, 15H), 4.95 (d, *J* = 8.1 Hz, 1H), 4.75 (d, *J* = 11.7 Hz, 1H), 4.63 (d, *J* = 11.7 Hz, 1H), 4.59 (dd, *J* = 8.1, 1.2 Hz, 1H), 4.52 (s, 2H), 4.40 (d, *J* = 12.0 Hz, 1H), 4.35 (d, *J* = 12.0 Hz, 1H), 4.05 (d, *J* = 5.1 Hz, 1H), 3.96 (dd, *J* = 13.3, 2.5 Hz, 1H), 3.68 (dd, *J* = 13.3, 4.3 Hz, 1H), 3.61 (m, 1H), 3.52 (m, 1H), 3.39 (s, 3H); ^{13}C NMR (CD_3OD): δ 139.7, 139.2, 129.7, 129.6, 129.5, 129.4(2), 129.3(2), 129.0(2), 107.8, 85.8, 80.6, 78.2, 74.9, 73.5, 72.7, 61.4, 56.4, 30.3; FAB-MS $[M-H]^+$ *m*/*z* calcd for $C_{28}H_{31}IO_5$ 573.1138, found 573.1141.

3.3. Methyl 3,4,5-tri-*O*-benzyl-2-deoxy-2-iodo-α-D-idoseptanoside (2) and methyl 3,4,5-tri-*O*-benzyl-2-deoxy-2-iodo-β-D-guloseptanoside (3) [method B]

Oxepine **1** (0.040 g, 0.098 mmol) was dried via azeotropic distillation from toluene (3 × 5 mL) under reduced pressure and dissolved in dry toluene (1 mL) and anhydrous CH_3OH (0.5 mL). To this solution was added NIS (0.026 g, 0.117 mmol) and the mixture was stirred at rt for 30 min. The reaction mixture was diluted with CH_2Cl_2 (25 mL) and washed with aqueous $Na_2S_2O_3$ (1 M, 3 × 15 mL). The aqueous fractions were extracted with additional CH_2Cl_2 (2 × 20 mL). The combined organic fractions were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was purified by column chromatography using 19:1, petroleum ether–EtOAc as eluent to give **2** (0.034 g, 61%) as a yellow solid and **3** (0.020 g, 35%) as a yellow oil.

3.4. Isopropyl 3,4,5-tri-*O*-benzyl-2-deoxy-2-iodo-α-D-idoseptanoside (4) and isopropyl 3,4,5-tri-*O*-benzyl-2-deoxy-2-iodo-β-D-guloseptanoside (5)

Oxepine **1** (0.036 g, 0.087 mmol) was dried via azeotropic distillation from toluene (3 × 5 mL) under reduced pressure and dissolved in anhydrous 2-propanol (2 mL). The solution was cooled to 0 °C and a solution of NIS (0.024 g, 0.104 mmol) in 2-propanol (1 mL) and CH_2Cl_2 (0.5 mL) was added dropwise. The mixture was stirred and allowed to warm to rt over 30 min. The reaction mixture was diluted with CH_2Cl_2 (25 mL) and washed with aqueous $Na_2S_2O_3$ (1 M, 3 × 15 mL). The aqueous fractions were extracted with CH_2Cl_2 (2 × 20 mL). The collected organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. Purification of the residue by column chromatography using 19:1, petroleum ether–EtOAc as eluent gave two fractions. The first fraction gave **4** (0.034 g, 65%) as a white solid. R_f 0.45 (17:3, hexanes–EtOAc); Mp 136–141 °C; $[\alpha]_D$ −11.1 (*c* 1.3, $CHCl_3$); IR (KBr) cm^{-1}: 3029.62, 2965.98, 2904.27, 1496.49, 1454.06, 1365.35, 1349.93, 1060.66, 730.89, 694.25; ^{1}H NMR ($CDCl_3$): δ 7.39–7.27 (m, 15H), 5.15 (d, *J* = 8.1 Hz, 1H), 4.89 (d, *J* = 10.8 Hz, 1 H), 4.87 (d, *J* = 9.9 Hz, 1H), 4.77 (d, *J* = 10.3 Hz, 2H), 4.72 (d, *J* = 11.4 Hz, 1H), 4.64 (d, *J* = 11.4 Hz, 1H), 4.29 (ddd, *J* = 10.6, 7.9, 3.4 Hz, 1H),

3.87 (sept, $J = 6.2$ Hz, 1H), 3.73–3.62 (m, 2H), 3.55–3.50 (m, 2H), 3.44 (d, $J = 8.1$ Hz, 1H), 1.21 (d, $J = 6.1$ Hz, 3H), 1.20 (d, $J = 6.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 138.9, 138.5, 138.4, 138.0, 128.6 (2), 128.5, 128.4, 128.0 (2), 127.9, 127.8, 127.7, 103.7, 88.0, 80.0, 77.9, 76.4, 75.4, 73.9, 70.5, 58.1, 38.2, 23.6, 21.4; FAB-MS $[M-H]^+$ *m/z* calcd for $C_{30}H_{35}IO_5$ 601.1451, found 601.1448.

The second fraction from the above chromatographic separation gave **5** as a yellow oil (0.017 g, 32%). R_f 0.36 (17:3, hexanes–EtOAc); $[\alpha]_D$ +6.0 (*c* 1.0, $CHCl_3$); IR (KBr) cm^{-1}: 3029.62, 2969.84, 2927.41, 1496.49, 1454.06, 1378.85, 1330.64, 1072.23, 736.67, 698.11; ^{1}H NMR ($CDCl_3$): δ 7.41–7.17 (m, 15H), 5.13 (d, $J = 8.0$ Hz, 1H), 4.75 (d, $J = 11.8$ Hz, 1H), 4.66 (d, $J = 11.8$ Hz, 1H), 4.58 (dd, $J = 8.0$, 1.2 Hz, 1H), 4.52 (s, 2H), 4.37 (d, $J = 11.9$ Hz, 1H), 4.33 (d, $J = 11.9$ Hz, 1H), 4.06 (d, $J = 5.1$ Hz, 1H), 3.98 (dd, $J = 13.3$, 2.3 Hz, 1H), 3.89 (sept, $J = 6.2$, 1H), 3.62 (dd, $J = 13.8$, 3.7 Hz, 1H), 3.59–3.57 (m, 1H), 3.49 (m, 1H), 1.19 (d, $J = 6.2$, 3H), 1.16 (d, $J = 6.1$, 3H); ^{13}C NMR ($CDCl_3$): δ 138.4, 138.1, 137.8, 128.7 (2), 128.6, 128.4, 128.2, 128.1, 128.0 (3), 103.3, 84.2, 79.1, 77.7, 74.0, 72.5, 71.7, 70.1, 60.3, 31.5, 23.7, 21.6; FAB-MS $[M+H]^+$ *m/z* calcd for $C_{30}H_{36}IO_5$ 603.1608, found 603.1577.

3.5. 1,2;3,4-Di-*O*-isopropylidene-6-*O*-(3,4,5-tri-*O*-benzyl-2-deoxy-2-iodo-α-D-idoseptanosyl)-α-D-galactopyranose (6) and 1,2;3,4-di-*O*-isopropylidene-6-*O*-(3,4,5-tri-*O*-benzyl-2-deoxy-2-iodo-β-D-guloseptanosyl)-α-D-galactopyranose (7)

Oxepine **1** (0.050 g, 0.12 mmol) and 1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranose (0.047 g, 0.180 mmol) together were dried via azeotropic distillation from toluene (3 × 5 mL) under reduced pressure and dissolved in anhydrous CH_2Cl_2 (1.5 mL). The solution was cooled to 0 °C and NIS (0.032 g, 0.144 mmol) was added. The mixture was stirred and allowed to warm to rt over 30 min. The reaction mixture was diluted with CH_2Cl_2 (25 mL) and washed with aqueous $Na_2S_2O_3$ (1 M, 3 × 15 mL). The aqueous fractions were extracted with CH_2Cl_2 (2 × 20 mL). The collected organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. Purification of the residue by column chromatography using 3:1 hexanes–EtOAc as eluent gave three fractions (**6**, **7**, **10**). The first fraction gave **10** (see below). The second fraction gave **6** (0.009 g, 15%) as a yellowish oil. R_f 0.18 (17:3, hexanes–EtOAc); $[\alpha]_D$ −15.6 (*c* 1.80, $CHCl_3$); IR (KBr) cm^{-1}: 3030.59, 2920.66, 1455.03, 1381.75, 1256.40, 1211.08, 1069.33, 1004.73, 734.75, 697.14; ^{1}H NMR ($CDCl_3$): δ 7.39–7.23 (m, 15H), 5.55 (d, $J = 5.0$ Hz, 1H), 5.10 (d, $J = 8.1$ Hz, 1H), 4.87 (d, $J = 10.8$ Hz, 1H), 4.85 (d, $J = 9.0$ Hz, 1H), 4.76 (d, $J = 10.4$ Hz, 2H), 4.70 (d, $J = 11.4$ Hz, 1H), 4.62 (d, $J = 11.4$ Hz, 1H), 4.61 (m, 1H), 4.39 (dd, $J = 8.0$, 1.7 Hz, 1H), 4.33 (ddd, $J = 10.5$, 8.1, 2.5 Hz, 1H), 4.30 (dd, $J = 5.0$, 2.3 Hz, 1H), 3.99 (ddd, $J = 6.6$, 6.6, 1.5 Hz, 1H), 3.76 (dd, $J = 10.4$, 6.1 Hz, 1H), 3.69–3.65 (m, 3H), 3.52–3.46 (m, 3H), 1.55 (s, 3H), 1.45 (s, 3H), 1.34 (s, 3H), 1.34 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 138.8, 138.3, 137.9, 128.6, 128.5, 128.4, 128.1, 127.9, 127.7, 109.4, 108.8, 105.9, 96.5, 87.9, 79.9, 77.8, 76.4, 75.4, 73.9, 71.0 (2), 70.8, 67.6, 66.6, 58.4, 36.8, 26.4, 26.2, 25.2, 24.6; FAB-MS $[M-H]^+$ *m/z* calcd for $C_{39}H_{46}IO_{10}$ 801.2136, found 801.2170.

The third fraction of the above chromatographic separation provided **7** as a yellow oil (0.005 g, 9%). R_f 0.13 (17:3, hexanes–EtOAc); $[\alpha]_D$ −16.7 (*c* 1.0, $CHCl_3$); IR (KBr) cm^{-1}: 3029.62, 2923.56, 1455.03, 1380.78, 1254.47, 1211.08, 1070.30, 1000.87, 736.67, 698.11; ^{1}H NMR ($CDCl_3$): δ 7.36–7.26 (m, 15H), 5.52 (d, $J = 5.0$ Hz, 1H), 5.12 (d, $J = 8.0$ Hz, 1H), 4.74 (d, $J = 11.8$ Hz, 1H), 4.65–4.58 (m, 3H), 4.51 (s, 2H), 4.39–4.34 (m, 3H), 4.30 (dd, $J = 5.0$, 2.4 Hz 1H), 4.04–3.96 (m, 3H), 3.85 (dd, $J = 11.0$, 7.3 Hz, 1H), 3.71 (dd, $J = 11.1$, 6.1 Hz, 1H), 3.68 (dd, $J = 9.8$, 4.3 Hz, 1H), 3.58 (m, 1H), 3.49 (m, 1H), 1.55 (s, 3H), 1.43 (s, 3H), 1.33 (s, 3H), 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 138.4, 138.1, 137.8, 128.7(2), 128.6, 128.4, 128.2, 128.1, 128.0 (3), 109.4, 108.8, 105.4, 96.6, 84.1, 79.1, 77.9, 74.0, 72.6, 71.7, 71.1, 70.8 (2), 66.8, 66.1, 60.6, 30.5, 26.3, 26.2, 25.2, 24.8; FAB-MS $[M-H]^+$ *m/z* calcd for $C_{39}H_{46}IO_{10}$ 801.2136, found 801.2138.

3.6. 1,6-Anhydro-3,4-di-*O*-benzyl-2-deoxy-2-iodo-α-D-idopyranose (10)

The first fraction during chromatography of **6** and **7** gave **10** (0.021 g, 64%) as a yellow oil. Compound **10** was also isolated in 26% yield during the preparation of **8** and **9** below. R_f 0.36 (17:3, hexanes–EtOAc); $[\alpha]_D$ −79.3 (*c* 1.5, $CHCl_3$); IR (KBr) cm^{-1}: 3029.62, 2919.70, 1454.06, 1363.43, 1120.44, 1027.87, 738.60, 696.18; ^{1}H NMR ($CDCl_3$): δ 7.41–7.23 (m, 15H), 5.55 (s, 1H), 4.90 (d, $J = 10.5$ Hz, 1H), 4.87 (d, $J = 10.5$, 1H), 4.72 (d, $J = 11.7$ Hz, 1H), 4.62 (d, $J = 11.7$ Hz, 1H), 4.55 (dd, $J = 4.5$, 4.5 Hz, 1H), 4.18 (d, $J = 7.73$ Hz, 1H), 3.96–3.87 (m, 2H), 3.78–3.72 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 138.1, 137.9, 128.8, 128.6 (2), 128.4, 128.2, 128.1, 128.0, 103.6, 83.5, 80.8, 76.2, 73.8, 73.3, 65.9, 32.1; FAB-MS $[M-H]^+$ *m/z* calcd for $C_{20}H_{20}IO_4$ 451.0406, found 451.0399.

3.7. 1,2;3,4-Di-*O*-isopropylidene-6-*O*-(3,4,5-tri-*O*-benzyl-2-deoxy-2-iodo-α-D-idoseptanosyl)-α-D-galactopyranose (6) and 1,2;3,4-di-*O*-isopropylidene-6-*O*-(3,4,5-tri-*O*-benzyl-2-deoxy-2-iodo-β-D-guloseptanosyl)-α-D-galactopyranose (7) [method B]

Oxepine **1** (0.040 g, 0.096 mmol) and 1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranose (0.038 g, 0.144 mmol)

together were dried via azeotropic distillation from toluene (3 × 5 mL) under reduced pressure and dissolved in anhydrous THF (1.5 mL). The solution was cooled to 0 °C and NIS (0.032 g, 0.144 mmol) was added. The mixture was stirred and allowed to warm to rt over 2 h. The reaction mixture was diluted with CH_2Cl_2 (25 mL) and washed with aqueous $Na_2S_2O_3$ (1 M, 3 × 15 mL). The aqueous fractions were extracted with CH_2Cl_2 (2 × 20 mL). The collected organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. Purification of the residue by column chromatography using 3:1, hexanes–EtOAc as eluent gave four fractions (**1**, **6**, **7**, **10**). The first fraction gave **1** (0.026 g, 66%). The second fraction gave **10** (0.003 g 7%) and the third and fourth gave **6** (0.008 g, 11%) and **7** (0.008 g, 11%), respectively.

3.8. 1,2;3,4-Di-*O*-isopropylidene-6-*O*-(3,4,5-tri-*O*-benzyl-2-deoxy-2-iodo-α-D-idoseptanosyl)-α-D-galactopyranose (6) and 1,2;3,4-di-*O*-isopropylidene-6-*O*-(3,4,5-tri-*O*-benzyl-2-deoxy-2-iodo-β-D-guloseptanosyl)-α-D-galactopyranose (7) [method C]

Oxepine **1** (0.030 g, 0.072 mmol) and 1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranose (0.028 g, 0.108 mmol) together were dried via azeotropic distillation from toluene (3 × 5 mL) under reduced pressure and dissolved in anhydrous CH_2Cl_2 (1.5 mL). Molecular sieves (4 Å) were added and the solution was stirred at rt for 30 min. IDCP (0.023 g, 0.216 mmol) was added and the mixture was stirred for 2 h. The mixture was diluted with CH_2Cl_2 (25 mL) and washed with aqueous $Na_2S_2O_3$ (1 M, 3 × 15 mL). The aqueous fraction was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic fractions were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was purified by column chromatography using 3:1, hexanes–EtOAc as eluent to give **10** (0.016 g, 49%), **6** (0.016 g, 28%), and **7** (0.011 g, 19%).

3.9. 3,4,5-Tri-*O*-benzyl-2-deoxy-2-iodo-α-D-idoseptanosyl acetate (8) and 3,4,5-Tri-*O*-benzyl-2-deoxy-2-iodo-β-D-guloseptanosyl acetate (9)

Oxepine **1** (0.042 g, 0.102 mmol) was dried via azeotropic distillation from toluene (3 × 5 mL) under reduced pressure and dissolved in anhydrous CH_2Cl_2 (1 mL). Glacial AcOH (0.5 mL) was added and the solution was cooled to 0 °C. NIS (0.021 g, 0.095 mmol) and additional CH_2Cl_2 (1 mL) were added. The mixture was stirred and allowed to warm to rt over 30 min. The reaction mixture was diluted with CH_2Cl_2 (25 mL) and washed with satd $NaHCO_3$ (3 × 15 mL) and aqueous $Na_2S_2O_3$ (1 M, 3 × 15 mL). The aqueous fractions were extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. Purification of the residue by column chromatography using 3:2, hexanes–EtOAc as eluent gave three fractions (**8**, **9**, **10**). The first fraction gave **10** (0.012 g, 26%). The second fraction provided **8** (0.025 g, 41%) as a yellow solid. R_f 0.23 (17:3, hexanes–EtOAc); Mp 104–108 °C; $[\alpha]_D$ −8.02 (*c* 0.5, $CHCl_3$); IR (KBr) cm^{-1}: 3029.62, 2904.27, 2869.56, 1752.98, 1454.06, 1371.14, 1228.43, 1076.08, 1012.45, 954.59, 732.82, 696.18; ^1H NMR ($CDCl_3$): δ 7.30–7.24 (m, 15H), 6.26 (d, J = 9.0 Hz, 1H), 4.88 (d, J = 10.8 Hz, 1H), 4.86 (d, J = 9.8 Hz, 1H), 4.78 (d, J = 10.0 Hz, 1H), 4.78 (d, J = 10.9 Hz, 1H), 4.70 (d, J = 11.4 Hz, 1H), 4.60 (d, J = 11.4 Hz, 1H), 4.44 (ddd, J = 9.5, 9.5, 2.8 Hz, 1H), 3.72–3.55 (m, 5H), 2.11 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 169.7, 138.6, 138.0, 137.6, 128.7, 128.6, 128.5, 128.1 (2), 128.0, 127.9, 127.8, 97.8, 87.0, 79.5, 78.3, 76.3, 75.6, 73.9, 61.2, 34.0, 21.1; FAB-MS $[M-H]^+$ *m/z* calcd for $C_{29}H_{30}IO_6$ 601.1087, found 601.1107.

The third fraction from the chromatographic separation above gave **9** as a yellow oil (0.014 g, 23%). R_f 0.18 (17:3, hexanes–EtOAc); $[\alpha]_D$ +8.4 (*c* 0.2, $CHCl_3$); IR (KBr) cm^{-1}: 3029.62, 2923.56, 2857.99, 1752.98, 1496.49, 1454.06, 1371.14, 1224.58, 1072.23, 1008.59, 956.52, 738.60, 698.11; ^1H NMR ($CDCl_3$): δ 7.36–7.28 (m, 15H), 6.26 (d, J = 8.9 Hz, 1H), 4.75 (d, J = 11.6 Hz, 1H), 4.68, (dd, J = 8.9, 1.3 Hz, 1H), 4.62 (d, J = 11.6 Hz, 1H), 4.52 (d, J = 12.2 Hz, 1H), 4.48 (d, J = 12.2 Hz, 1H), 4.43 (d, J = 11.9 Hz, 1H), 4.37 (d, J = 11.9, 1H), 4.11 (d, J = 5.2 Hz, 1H), 4.02 (dd, J = 13.2, 3.1 Hz, 1H), 3.86 (dd, J = 13.1, 5.9 Hz, 1H), 3.66 (dd, J = 5.1, 2.4 Hz, 1H), 3.59 (m, 1H), 2.07 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 169.4, 138.2, 137.7, 137.6, 128.8, 128.7, 128.6, 128.5, 128.3, 128.1, 128.0, 98.0, 83.5, 79.2, 78.0, 74.0, 72.7, 71.7, 63.0, 28.3, 21.2; FAB-MS $[M-H]^+$ *m/z* calcd for $C_{29}H_{30}IO_6$ 601.1087, found 601.1085.

3.10. 1,6-Anhydro-3,4-di-*O*-benzyl-2-deoxy-2-iodo-α-D-idopyranose (10)

Oxepine **1** (0.030 g, 0.072 mmol) was dried via azeotropic distillation from toluene (3 × 5 mL) under reduced pressure and dissolved in anhydrous CH_2Cl_2 (1.5 mL). The solution was cooled to 0 °C and NIS (0.018 g, 0.080 mmol) was added. The mixture was stirred and allowed to warm to rt over 30 min, and worked up as described above. Column chromatography of the reaction mixture gave **10** (0.020 g) in 62% yield.

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