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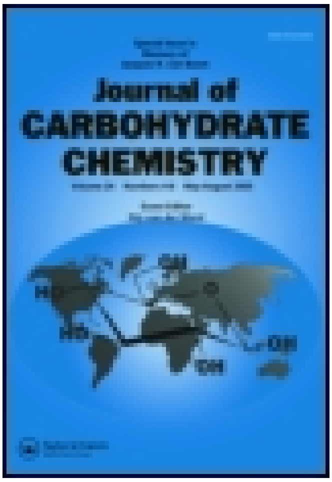

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Methods for Debrominating 4,5-Dibromopentanyl Glycosides

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METHODS FOR DEBROMINATING 4,5-DIBROMOPENTANYL GLYCOSIDES

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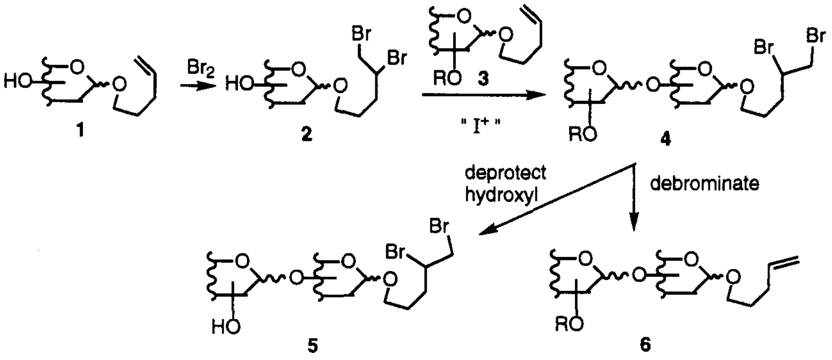
ABSTRACT

Debromination of 4,5-dibromopentanyl glycosides to (re)generate *n*-pentenyl glycosides has been accomplished using zinc, samarium(II) iodide, and sodium iodide, respectively. The choice of reagent is dependent upon the reactivity of the substrate, as well as the protecting groups thereon.

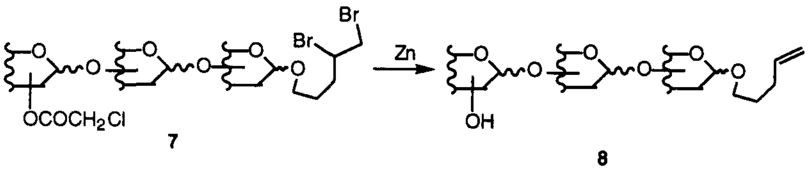
INTRODUCTION

A valuable facet of *n*-pentenyl glycosides (NPGs) for synthesis of complex oligosaccharides, is the option of "side-tracking" anomeric activation by dibromination of the double bond.[1] Thus a glycosyl donor **1** can be converted into a glycosyl acceptor, **2**, for coupling with another NPG **3**. The resulting higher saccharide, **4**, can be converted to a glycosyl acceptor **5** by deprotecting a suitable hydroxyl group, or be converted into glycosyl donor by debromination whereby NPG activity is restored in the product **6**.

Zinc in ethanol at reflux with sonication[2,3] has thus far served us well for the reductive debromination; however some recent cases have proven problematic. One of these was encountered in studies related to our recent synthesis of rat brain Thy-1 anchor,[4,5] in which a trisaccharide, depicted for simplicity as **7**, was treated under



Scheme 1

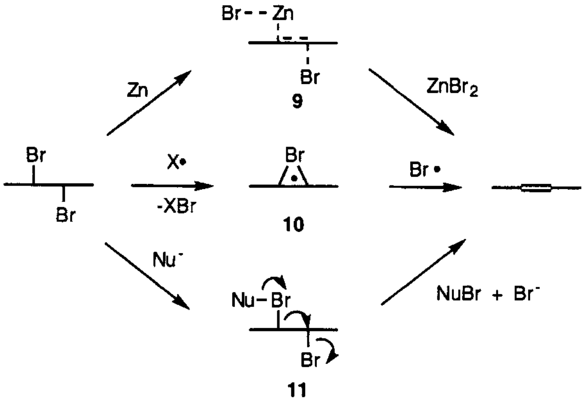


Scheme 2

the standard conditions. Although reductive elimination was accomplished, the chloroacetyl group was also cleaved,[4,6] and it was necessary to re-chloroacetylate the resulting hydroxy alkene **8**.

Another concerned a solid phase reaction in which the dibromopentanyl tether of **12a** was to be converted into the pentenyl tether **12b**. Treatment with zinc gave no reaction owing, undoubtedly, to the unfavorable solid-solid interaction that would have been required.

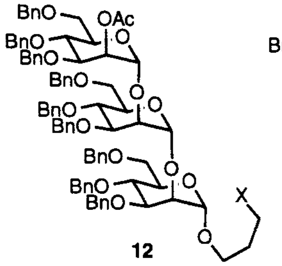
We have therefore examined alternative debromination procedures. In his treatise on 1,2-dehalogenations, Baciocchi[7] recognizes the following three categories. (i) Metal promoted debromination which is deemed to occur *via* the transition state depicted in **9**. (ii) One-electron dehalogenation which involves the three center radical **10**, the decomposition of which is dependent upon the reagent used. (iii) A two-electron dehalogenation which goes through an E2-like mechanism depicted in **11**. Since our attention has been focused thus far on the first category only, we have investigated alternative routes and some useful developments are reported in this paper.



Scheme 3

RESULTS AND DISCUSSION

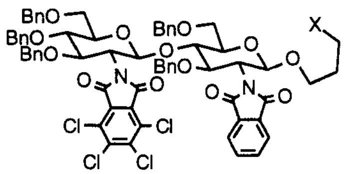
Although Baciocchi's chapter predates the explosion of interest in samarium(II) iodide,[8] this reagent belongs to the one-electron category, and since the salt is soluble in THF, it was applied to the solid phase substrate **12a**.[9] Indeed a rapid reaction occurred to restore the pentenyl tether in **12b**[10] (Table 1, entry ii).



12

a X = CHBr-CHBr–Ⓟ

b X = CH=CH–Ⓟ

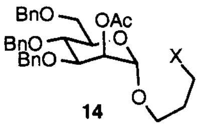


13

a X = CHBr-CH₂Br

b X = CH=CH₂

Ⓟ = polystyrene resin



14

a X = CH=CH₂

b X = CHBr-CH₂Br

We next turned our attention to the dibromopentanyl disaccharide **13a**. Surprisingly, there was no reaction either with the metal or one-electron reagents shown in Table 1, entries iv, v, and vi. We therefore resorted to the third of Baciocchi's categories and subjected the material to the action of sodium iodide in methyl ethyl ketone at reflux.[11] Entry vii shows that this procedure gave an excellent yield of the desired alkene **13b**.

Table 1

Entry	Substrate	Product	Conditions	Time	Yield
i	**12a**	NR	Zn, Bu_4NI in sonicating EtOH	3 days	-
ii	**12a**	**12b**	0.1M SmI_2 in THF	30min	*
iii	**12a**	**12b**	NaI in MEK 78°	6hrs	*
iv	**13a**	NR	Zn, Bu_4NI in sonicating EtOH	16hrs	-
v	**13a**	NR	Zn in DMF 60 °	10hrs	-
vi	**13a**	NR	0.1M SmI_2 in THF	40min	-
vii	**13a**	**13b**	NaI in MEK 78 °	6hrs	90%
viii	**14b**	**14a**	Zn, Bu_4NI in sonicating EtOH	2 days	92%
ix	**14b**	**14a**	0.1M SmI_2 in THF	1hr	72%
x	**14b**	**14a**	NaI in MEK 78 °	4hrs	85%

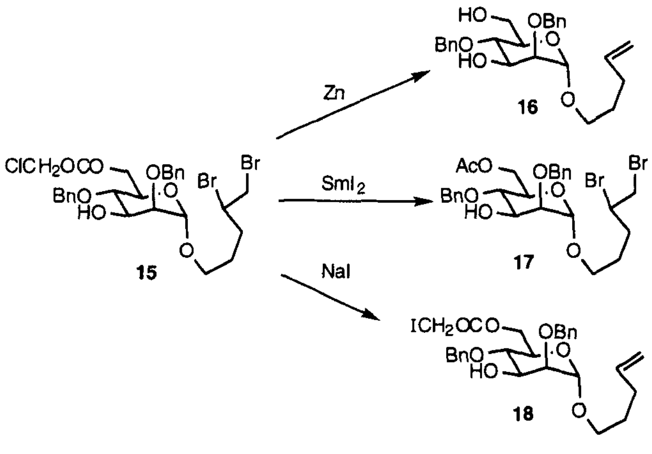
* The yields for these reactions could not be determined due to poor loading of the carbohydrate ligand on the resin which made gravimetric determination unreliable. That the reactions were successful was evident by the appearance of an IR absorbance at 965.6cm^{-1} consistent with a δ out-of-plane C-H vibration for a *trans* double bond.

In the light of the last result, we investigated the use of sodium iodide in methyl ethyl ketone on the solid substrate **12a**. As is obvious from entry iii, these conditions were also successful for debromination of the solid-phase material.

For further experiments, we decided to use the known pentenyl mannoside, **14a**.[2] Dibromination under our previously published conditions[2] gave **14b**. The latter was readily converted into the unsaturated counterpart **14a** under each set of conditions (Table 1, entries viii-x). The product, **14a**, was obtained in 92% yield after two days of sonication in ethanol with zinc, and tetra-*n*-butylammonium iodide. With 0.1 mol samarium(II) iodide in THF at room temperature, the reaction was complete after one hour, 72% yield of product being obtained. Sodium iodide in methyl ethyl ketone at reflux 4 h gave **14a** in 85% yield.

In light of the results in Table 1 we subjected the test derivative **15** to each method of dehalogenation to see whether any selectivity would be observed. It is seen that zinc led to the hydroxy alkene **16** as had been observed for **7**--->**8** (Scheme 2). With samarium(II) iodide, the product was **17** wherein the vicinal dibromide had survived while reduction of chloroacetyl to acetyl took place (Scheme 4).

Sodium iodide in methyl ethyl ketone proved to be the best reagent for debromination of substrate **15**. Complete displacement of the chloride occurred simultaneously, to give **18** as determined by mass spectroscopy. However this



Scheme 4

result was not a major problem and indeed could prove advantageous since cleavage of the iodoacetyl group is more facile.

EXPERIMENTAL

General methods. All reactions were conducted under an inert argon atmosphere. THF was distilled from sodium benzophenone ketyl. Dichloromethane was distilled from calcium hydride. Solutions of compounds in organic solvents were dried over sodium sulfate prior to rotary evaporation. TLC plates were Kieselgel 60 F254 (Merck Art. 5554). Carbohydrate compounds were visualized on the TLC plate by charring with H_2SO_4/EtOH/H_2O (1:10:10). Flash column chromatography was done with silica gel 60 (230-400 mesh, Merck). Optical rotations were determined at the sodium D line with a Perkin-Elmer 241 polarimeter. Mass spectra were recorded on a JOEL JMS-SX102A mass spectrometer operating at 3K resolution or a Hewlett-Packard 5988A mass spectrometer operating at 70 eV using ammonia as the carrier gas. Fast atom bombardment (FAB) mass spectra were conducted using a dithiothreitol/dithioerythritol matrix with xenon as the fast atom. ^1H, and ^{13}C NMR spectra were recorded on a Varian XL-300 or GE QE-300 spectrometer. Coupling constants are reported in Hertz and chemical shifts are in ppm on the delta scale . ^1H (300 MHz) and ^{13}C (75 MHz) chemical shifts are reported relative to internal tetramethylsilane (0.00 ppm). Elemental analysis were conducted by Atlantic Microlab, Inc., P.O. Box 2288, Norcross, GA 30091.

Debrominations with zinc. Soluble substrates were taken up in EtOH and a minimal amount of EtOAc to effect solubility. To the solution was added metallic Zn (5eq) and Bu_4NI (1eq). The mixture was sonicated until completion (as evident by ^1H NMR of a concentrated portion of the reaction mixture) then filtered through Celite and concentrated to dryness. The residue was taken up in EtOAc, washed with 10% (aq) sodium thiosulfate, and concentrated to dryness.

Debrominations with sodium iodide. Substrates were taken up in methyl ethyl ketone (60mL/mmol), and sodium iodide (20 eq) was added. The mixture was boiled under reflux until completion (as evident by ^1H NMR of a concentrated portion of the reaction mixture) then filtered through Celite and concentrated to dryness. The residue was taken up in EtOAc, washed with 10% (aq) sodium thiosulfate, and concentrated to dryness.

Debrominations with samarium(II) iodide. Substrates were taken up in minimal THF and samarium(II) iodide (10 eq of 0.1M solution in THF) was added dropwise by syringe. The mixture was stirred until completion (as evident by ^1H NMR of a concentrated portion of the reaction mixture) then filtered through Celite and concentrated to dryness. The residue was taken up in EtOAc, washed with 10% (aq) sodium thiosulfate, and concentrated to dryness.

Debromination of 15 with zinc. The dibromide **15**[2] (50 mg, 0.0766 mmol) was subjected to debromination with zinc. The deacetylated pentenyl glycoside **16** was recovered (33.1 mg, 0.076 mmol, 99%). For physical data see ref. 2.

4,5-Dibromopentanyl (3,4,6-Tri-*O*-benzyl-2-deoxy-2-tetrachlorophthalimido-β-D-glucopyranosyl)-(1→4)-3,6-di-*O*-benzyl-β-D-glucopyranoside (13a).

To pent-4-enyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-tetrachlorophthalimido-β-D-glucopyranoside[12] (0.76 g, 0.98 mmol) and 4,5-dibromopentanyl 3,6-di-*O*-benzyl-2-deoxy-2-phthalimido–β-D-glucopyranoside[12] (0.46 g, 0.64 mmol) in 7 mL CH_2Cl_2 was added *N*-iodosuccinimide (0.33 g, 1.46 mmol) and triethylsilyl triflate (66 µL, 0.29 mmol). After stirring 11 minutes at room temperature the glycosyl donor had been consumed and the reaction was quenched with 4 mL 10% aq $Na_2S_2O_3$ and 4 mL of sat aq $NaHCO_3$ solution. The mixture was stirred for an additional 5 min before separating the layers and extracting the aqueous portion 3 times with $CHCl_3$. The concentrated $CHCl_3$ solution was purified *via* flash chromatography eluting with a gradient of 20→25% ethyl acetate / petroleum ether affording a white foam (0.59 g, 65%); $[\alpha]_D^{21}$ +45.8° (*c* 1.37, $CHCl_3$); R_f=.47 in 25:75 ethyl acetate/petroleum ether ^1H NMR (300 MHz, $CDCl_3$) δ 1.40-1.65 (m, 3H, $OCH_2C\underline{H}_2C\underline{H}_2CHBrCH_2Br$), 1.84-1.92 (m, 1H, $OCH_2CH_2C\underline{H}_2CHBrCH_2Br$), 3.20-4.87 (m, 27H), 4.96 (d, J=8.42 Hz, 1H, H-1A), 5.39 (d, J=8.18 Hz, 1H, H-1B), 6.64-7.31 (m, 25H, Ph), 7.67 (s, 4H, Phth); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 26.66, 26.73, 32.53, 32.58, 36.04, 52.24, 52.30, 55.29, 57.15, 67.65, 67.90, 68.09, 72.86, 73.06, 73.15, 73.69, 74.49, 74.67, 74.70, 74.97, 75.88, 77.26, 79.26, 79.62, 96.66 (C-1B), 97.89 & 97.96 (C-1A), 122.95, 123.04, 123.12, 126.35, 126.60, 126.65, 127.12, 127.27, 127.37, 127.44, 127.64, 127.99, 128.06, 128.19, 128.26, 128.96, 129.06, 131.39, 133.51, 133.63, 137.72, 137.83, 138.25, 138.34, 139.16, 162.52, 163.31; MS (FAB) *m/e* 1423.3 $(m+Li)^+$.

Pent-4-enyl (3,4,6-Tri-*O*-benzyl-2-deoxy-2-tetrachlorophthalimido-β-D-glucopyranosyl)-(1→4)-3,6-di-*O*-benzyl-β-D-glucopyranoside (13b). The dibromide **13a** (0.34 g, 0.24 mmol) was subjected to debromination with sodium iodide as described in the general procedure. The alkene was purified *via* flash chromatography eluting with 20:80 ethyl acetate/ petroleum ether affording **13b** as a white foam (0.27 g, 90%); $[\alpha]_D^{21}$ +53.8° (*c* 1.08, $CHCl_3$); R_f=.53 in 25:75 ethyl acetate/petroleum ether ^1H NMR (300 MHz, $CDCl_3$) δ 1.37-1.46 (m, 2H, $OCH_2C\underline{H}_2CH_2CH{=}CH_2$), 1.73-1.81 (m, 2H, $OCH_2CH_2C\underline{H}_2CH{=}CH_2$), 3.23-4.87 (m, 27H), 4.94 (d, J=8.43 Hz, 1H, H-1A), 5.39 (d, J=8.13 Hz, 1H, H-1B), 5.46-5.55 (m, 1H, $OCH_2CH_2CH_2C\underline{H}{=}CH_2$), 6.54-7.35 (m, 25H, Ph), 7.66 (s, 4H, Phth); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.27, 29.63, 55.44, 57.23, 67.73, 68.17, 68.34, 72.88, 73.14, 73.71, 74.54, 74.74, 74.77, 74.90, 75.05, 76.02, 77.36, 79.34, 79.71, 96.74 (C-1B), 97.99 (C-1A), 114.47 ($OCH_2CH_2CH_2CH{=}\underline{C}H_2$), 122.90, 123.03, 123.12, 126.45, 126.63, 126.66, 126.85, 127.09, 127.31, 127.46, 127.70, 127.83, 128.0, 128.13, 128.41, 129.02, 129.14, 131.47, 133.43, 133.54, 133.61, 137.59, 137.81, 137.93, 138.37, 138.42, 162.61, 163.39, 167.68; MS (FAB) *m/e* 1256.3 $(m)^-$.

Anal. Calcd for $C_{68}H_{62}N_2O_{13}C_{14}\bullet 2H_2O$ (1293.09): C,63.16; H, 5.14. Found: C, 63.40; H, 5.04.

Attempted debromination of 15 with samarium(II) iodide. The dibromide **15**[2] (50 mg, 0.0766 mmol) was subjected to debromination with samarium(II) iodide according to the general procedure. The acetylated dibromide **17** was recovered as a colorless syrup (30 mg, 0.048 mmol, 58%); ^1H NMR ($CDCl_3$) δ 1.60-1.90 (m, 3H, $OCH_2C\underline{H}_2C\underline{H}_2CHBrCH_2Br$), 2.08 (s, 3H, $OCOCH_3$), 2.15-2.43 (m, 1H, $OCH_2CH_2C\underline{H}_2CHBrCH_2Br$), 3.38-3.50 (m, 1H, $OC\underline{H}_2CH_2CH_2CHBrCH_2Br$), 3.53-3.89 (m, 6H), 3.93-4.04 (m, 1H), 4.10-4.40 (m, 3H), 4.52-4.62 (m, 2H, $C\underline{H}_2Ph$), 4.68-4.75 (m, 1H, $C\underline{H}_2Ph$), 4.87-4.95 (m, 2H, H-1, $C\underline{H}_2Ph$), 7.10-7.36 (m, 10H, Ph); ^{13}C NMR ($CDCl_3$) δ 20.94 ($CO\underline{C}H_3$), 26.66, 26.70, 32.91, 35.99, 52.24, 52.31, 63.60, 66.58, 69.32, 70.83, 71.87, 72.92, 74.91, 76.29, 76.61, 78.37, 96.70 (C-1), 110.13, 127.90, 128.06, 128.13, 128.28, 128.42, 128.48, 128.62, 137.59, 138.06, 170.87 ($O\underline{C}OCH_3$); CIMS: *m/z* 629 $(MH)^+$, 647 $(M+NH_4)^+$.

Debromination of 15 with sodium iodide. The dibromide **15**[2] (53 mg, 0.0812 mmol) was subjected to debromination with sodium iodide as described in the general procedure. The iodoacetate **18** was recovered as a colorless syrup (40.3 mg, 0.081 mmol, 99%); ^{1}H NMR ($CDCl_3$) δ 1.60-1.75 (m, 2H, $OCH_2C\underline{H}_2CH_2CH{=}CH_2$), 2.04-2.18 (m, 2H, $OCH_2CH_2C\underline{H}_2CH{=}CH_2$), 3.36-3.43 (m, 1H, $OC\underline{H}_2CH_2CH_2CH{=}CH_2$), 3.62-3.83 (m, 5H), 3.88-4.06 (m, 2H), 4.29-4.48 (m, 2H), 4.56-4.79 (m, 3H, $C\underline{H}_2Ph$), 4.87-5.06 (m, 4H, $C\underline{H}_2Ph$, $OCH_2CH_2CH_2CH{=}C\underline{H}_2$, H-1), 5.71-5.86 (m, 1H, $OCH_2CH_2CH_2C\underline{H}{=}CH_2$), 7.24-7.40 (m, 10H, Ph); ^{13}C NMR ($CDCl_3$) δ 28.56 ($OCH_2\underline{C}H_2CH_2CH{=}CH_2$), 30.27 ($OCH_2CH_2\underline{C}H_2CH{=}CH_2$), 64.99, 67.22, 69.08, 71.96, 72.89, 75.06, 76.24, 78.48, 96.76 (C-1), 115.05 ($OCH_2CH_2CH_2CH{=}\underline{C}H_2$), 127.92, 128.13, 128.19, 128.27, 128.52, 128.62, 128.71, 129.97, 137.92 ($OCH_2CH_2CH_2\underline{C}H{=}CH_2$), 168.51 ($\underline{C}OCH_2I$); CIMS: *m/z* 488 $(M+NH_4-I)^+$, 614 $(M+NH_4)^+$.

ACKNOWLEDGMENT

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9. Description of the synthesis of the solid phase substrate **12a** is beyond the scope of this paper but will be reported in due course.
10. The solid phase substrate **12a** was subjected to the same standard debromination procedures used for the soluble substrates to afford the alkene **12b**. Reaction times were estimated based upon the time until observation of the definitive IR absorbance at 965.6cm^{-1}.
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12. Prepared in our laboratory by procedures to be published soon.