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# Sequential alkoxy radical fragmentation–intermolecular allylation in carbohydrate systems

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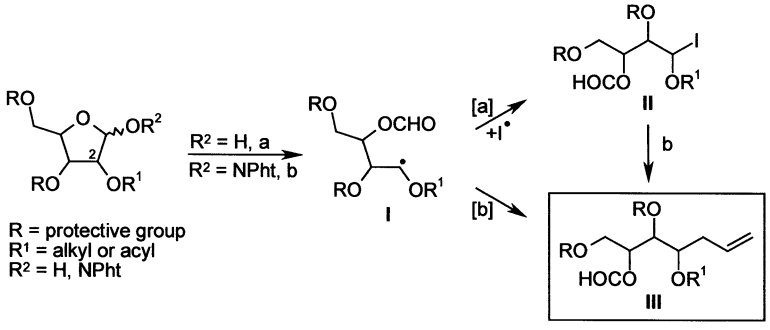
**Abstract**—The *C*-radical originated by β-fragmentation of carbohydrate anomeric alkoxy radicals, generated under reductive conditions by treatment of *N*-phthalimido glycosides with allyltri-*n*-butyltin/AIBN, may subsequently undergo an intermolecular allylation to give hept-1-enitol derivatives. These compounds can be useful chiral synthons for the synthesis of polyhydroxylated compounds. 

In previous papers from this laboratory we have described the oxidative β-fragmentation of glycopyran-1-*O*-yl and glycofuran-1-*O*-yl radicals to give C2 radicals. Weak electron-withdrawing groups (e.g. ethers) bonded to C2 favour the oxidation of the *C*-radical (**I**) to an oxycarbenium ion, and the final products are derived by nucleophilic attack onto this ion.[1] On the other hand, stronger EWG (e.g. esters) inhibit the oxidation step and α-iodoalkyl esters (**II**) were obtained by radical addition to iodine atoms present in the reaction medium (Scheme 1, path [a]).[2] Radical intermolecular allylation of these compounds following the Keck and Yates procedure gave 1,2,3-trideoxy-hept-1-enitols (**III**).[3]

With these results in mind, we reasoned that generating the alkoxy radicals under reductive conditions both reactions, fragmentation and allylation, can be realised in a single step (Scheme 1, path [b]). Furthermore, the alkoxy radical fragmentation (ARF) reaction should give access to nucleophilic or electrophilic *C*-radicals at will only by changing the protective group at C2.

Serial radical reactions where the *C*-radical formed initially by an intramolecular cyclisation, subsequently undergo intermolecular radical additions to allyltri-*n*-butyltin have been described previously.[4] The use of *C*-radicals originated by ARF reaction in intramolecular addition to olefins has also been reported.[5]

We have used the initial fragmentation of a *N*-hydroxyphthalimide derivative to generate the alkoxy radical and allyltri-*n*-butyltin as radical trap in the conditions summarised in Table 1.[6] *N*-Phthalimido glycosides were prepared by reaction of the hemiacetal alcohol with *N*-hydroxyphthalimide under Mitsunobu conditions.[7]




**Scheme 1.** *Reagents*: (a) $PhI(OAc)_2$, $I_2$; (b) allyltri-*n*-butyltin, AIBN. NPht- = *N*-phthalimido group.

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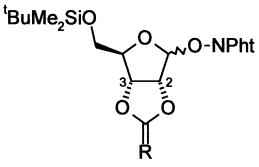
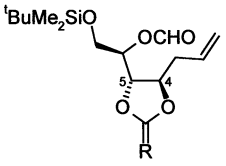
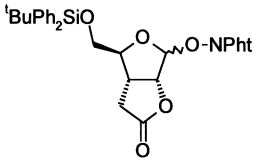
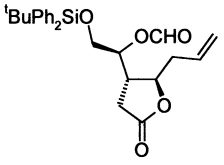
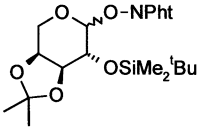
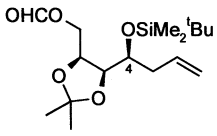
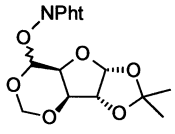
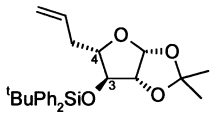
**Table 1.** Sequential alkoxy radical fragmentation–intermolecular allylation reaction[a]

| Entry | Substrate | Time h | Product | Yield % (dr) |
|---|---|---|---|---|
| 1 |  **1** R = Me, Me | 3.5 |  **3** R = Me, Me | 65[b] |
| 2 | **2** R = O | 2 | **4** R = O | 81[b] |
| 3 |  **5** | 1.5 |  **6** | 80[b] (88:12) |
| 4 |  **7** | 2.5 |  **8** | 76[b] (55:45) |
| 5[d] |  **9** | 5 |  **10** | 33[c] (94:6) |

[a] All reactions were performed in dry PhH (15 ml) at reflux temperature under nitrogen containing allyltri-*n*-butyltin (8 mmol) and AIBN (10 mmol%) for mmol of substrate. Ratios were determined by chromatographic isolation of pure compounds and the major isomer is illustrated.

[b] Partial hydrolysis of the formate ester (10%) occurs during the reaction.

[c] The reduced 3-*O*-(*tert*-butyldimethylsilyl)-1,2-*O*-isopropylidene-β-L-threofuranose (7%) is also obtained. NPht- = *N*-phthalimido group.

[d] After the reaction was completed, imidazole (2 mmol) was added and the mixture stirred at 80 °C for 15 h. Then was cooled to room temperature and more imidazole (4 mmol) and $^t$BuPh$_2$SiCl (2 mmol) were added and stirring continued for 23 h at this temperature.

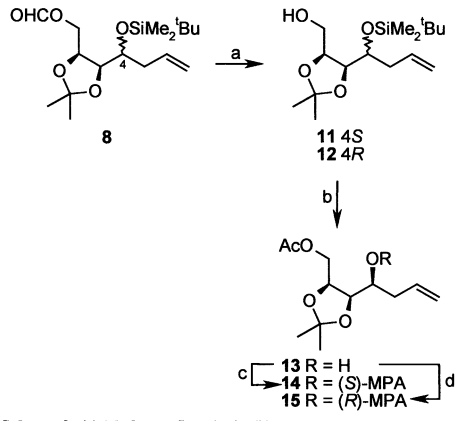
The phthalimide derivative of 2,3-*O*-isopropylidene-D-ribofuranose **1**[6] gave 1,2,3-trideoxy-4,5-*O*-isopropylidene-D-*arabino*-hept-1-enitol **3**[8] in moderate yield but with total diastereoselectivity (vide infra); only the *trans* substituted dioxolane ring could be detected in the reaction mixture (entry 1).

The carbonate **2**[6] was prepared in order to study the effect of a stronger electron-withdrawing group at C2 that should decrease the electron density at this position (entry 2). This should increase the electrophilic character of the C2-radical and a faster reaction with an electron-rich alkene such as allyltri-*n*-butyltin is expected. A significantly better yield of the addition product **4**[8] is obtained as compared to the fragmentation of the 2,3-*O*-isopropylidene **1** (entry 1). The reaction also occurs with total *trans* diastereoselectivity.

The ARF reaction of γ-lactone **5**[9] exhibited a similar behaviour as the carbonate **2**, although, apart from the expected *trans*-isomer **6**,[8] a small amount of the sterically less stable *cis*-isomer was obtained (dr approximately 9:1).

The C4 stereochemistry in compounds **3**, **4** and **6** was determined with the aid of NOESY spectra. The strong NOE correlation between H-C4 and H-C5 in **6**-*cis* suggested a *cis* relative relationship of these γ-lactone ring protons. Moreover, no NOE interactions were observed between these two protons in compounds **3**, **4** and **6**-*trans* where they are in a *trans* relationship.

This methodology was also extended to the fragmentation of a carbohydrate of the pentose series in pyranose form. The *N*-phthalimide glycoside of the D-arabinopyranose derivative **7** gave the 1,2,3-trideoxyhept-1-enitol **8**[8] as an almost equimolecular diastereoisomeric mixture (dr 55:45). It was found that the isomers could be more readily chromatographically separated after hydrolysis of the formate group and hence both primary alcohols **11** and **12**[8] were independently characterised (Scheme 2). The stereochemistry at C4 was




**Scheme 2.** *Reagents and conditions*: (a) MeOH, reflux, 24 h; (b) $Ac_2O$, Py, rt, 18 h then *n*-$Bu_4NF$, THF, rt, 18 h; (c) (*S*)-MPA acid, DCC, DMAP, $CH_2Cl_2$, rt, 26 h; (d) (*R*)-MPA acid, DCC, DMAP, $CH_2Cl_2$, rt, 16 h.

determined by conversion of the major isomer **11** into the secondary alcohol **13** and then by treatment with both (*S*)-(−)- and (*R*)-(+)-α-methoxyphenylacetic acid (MPA) under standard esterification conditions to the Mosher esters **14** and **15**, respectively.[10]

The reaction of the phthalimido derivative of the α-D-*xylo*-pentodialdo **9**[6] gave a volatile alcohol which was treated in situ with imidazole and *tert*-butyldimethylsilyl chloride to give 3-*O*-[*tert*-butyl(dimethyl)silyl]-5,6,7-trideoxy-1,2-*O*-isopropylidene-β-L-*arabino*-hept-6-enofuranose[8] (**10**) in order not to lose material during the work-up and purification steps. The coupling constant $J_{3,4}=0$ Hz and the NOE interaction between H-C3 and H-C5 are consistent with the assigned (4*S*)-stereochemistry for the major isomer. On the other hand, a $J_{3,4}=2.5$ Hz and a NOE interaction of H-C1 with both protons at C-5 suggest a (4*R*)-stereochemistry for the minor diastereoisomer.

No evidence of side-products derived from the *O*- and *C*2-radical intermediates were observed in reactions described in entries 1–4. Notwithstanding a small amount (7%) of 3-*O*-(*tert*-butyldimethylsilyl)-1,2-*O*-isopropylidene-β-L-threofuranose,[6] probably arising from intermolecular hydrogen abstraction of the *C*4-radical intermediate, was obtained in the reaction of *N*-phthalimido derivative **9** (Entry 5).

This methodology may be useful for the synthesis of chiral synthons. For example, as can be observed from Table 1 (entries 1, 2 and 4, 5) a number of 1,2,3-trideoxyhept-1-enitol derivatives possessing different patterns of protection and stereochemistries have been synthesised from readily accessible carbohydrates. Using the rich sugar chemistry available, the carbohydrate skeleton can also be conveniently modified to afford the required synthetic intermediate (e.g. entry 3).

## Acknowledgements

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8. All new compounds gave correct elemental analysis. Compound **3**: oil; $[\alpha]_D$ +12.0 ($CHCl_3$, $c=0.31$); $^1H$ NMR ($CDCl_3$, 500 MHz) 0.04 (6H, s), 0.86 (9H, s), 1.36 (3H, s), 1.38 (3H, s), 2.30 (1H, ddd, $J=14.6$, 7.2, 7.2 Hz), 2.44 (1H, m), 3.74 (1H, dd, $J=11.3$, 5.9 Hz), 3.86 (1H, dd, $J=7.1$, 6.6 Hz), 3.88 (1H, dd, $J=11.3$, 3.9 Hz), 4.05 (1H, ddd, $J=7.4$, 7.4, 4.1 Hz), 5.03 (1H, ddd, $J=5.9$, 5.9, 4.0 Hz), 5.06–5.13 (2H, m), 5.83 (1H, dddd, $J=17.2$, 10.2, 7.0, 7.0 Hz), 8.10 (1H, s); $^{13}C$ NMR ($CDCl_3$, 50.3 MHz) −5.5 (2×), 18.1, 25.7 (3×), 26.8, 27.2, 37.6, 61.7, 74.4, 76.9, 77.9, 109.2, 117.7, 133.5, 160.2. Compound **6**-*cis*: oil; $[\alpha]_D$ −31.7 ($CHCl_3$, $c=0.40$); $^1H$ NMR ($CDCl_3$, 500 MHz) 1.06 (9H, s), 2.19–2.30 (2H, m), 2.29 (1H, dd, $J=17.5$, 12.0 Hz), 2.46 (1H, dd, $J=17.6$, 8.8 Hz), 3.26 (1H, m), 3.67 (1H, dd, $J=11.5$, 3.7 Hz), 3.84 (1H, dd, $J=12.0$, 3.2 Hz), 4.65 (1H, ddd, $J=8.3$, 8.3, 3.7 Hz), 5.07 (1H, ddd, $J=10.6$, 3.2, 3.2 Hz), 5.14 (1H, d, $J=9.2$ Hz),

5.15 (1H, dd, $J=17.6$, 0.9 Hz), 5.79 (1H, dddd, $J=17.1$, 10.2, 6.5, 6.5 Hz), 7.38–7.47 (6H, m), 7.60–7.63 (4H, m), 7.90 (1H, s); $^{13}$C NMR ($CDCl_3$, 125.7 MHz) 19.1, 26.7 (3×), 30.3, 34.5, 38.9, 63.8, 72.6, 80.2, 119.1, 127.8 (2×), 127.9 (2×), 130.0 (2×), 132.1, 132.4, 132.5, 135.4 (2×), 135.5 (2×), 159.8, 174.8. Compound **6**-*trans*: oil; $[\alpha]_D$ −9.9 ($CHCl_3$, $c=0.60$); $^1$H NMR ($CDCl_3$, 500 MHz) 1.06 (9H, s), 2.29 (1H, dd, $J=17.8$, 7.2 Hz), 2.36 (1H, ddd, $J=13.8$, 6.4, 6.4 Hz), 2.54 (1H, m), 2.63 (1H, dd, $J=18.0$, 9.7 Hz), 2.80 (1H, m), 3.72 (1H, dd, $J=11.5$, 4.6 Hz), 3.75 (1H, dd, $J=11.6$, 4.7 Hz), 4.48 (1H, ddd, $J=6.0$, 6.0, 6.0 Hz), 5.04 (1H, ddd, $J=6.9$, 4.6, 4.6 Hz), 5.16 (1H, dd, $J=8.7$, 1.3 Hz), 5.17 (1H, dd, $J=17.1$, 1.3 Hz), 5.78 (1H, dddd, $J=17.1$, 10.6, 6.9, 6.9 Hz), 7.39–7.46 (6H, m), 7.61–7.64 (4H, m), 8.00 (1H, s); $^{13}$C NMR ($CDCl_3$, 125.7 MHz) 19.1, 26.7 (3×), 31.4, 38.9, 39.3, 63.0, 74.7, 80.9, 119.5, 127.9 (4×), 130.1 (2×), 131.7, 132.4 (2×), 135.4 (2×), 135.5 (2×), 160.0, 175.0. Compound **10**-α: oil; $[\alpha]_D$ −26.0 ($CHCl_3$, $c=1.23$); $^1$H NMR ($CDCl_3$, 500 MHz) 1.08 (9H, s), 1.26 (3H, s), 1.45 (3H, s), 1.98 (1H, ddd, $J=14.2$, 7.0, 7.0 Hz), 2.25 (1H, ddd, $J=14.3$, 8.0, 6.3 Hz), 3.96 (1H, dd, $J=7.8$, 7.0 Hz), 4.15 (1H, s), 4.52 (1H, d, $J=3.8$ Hz), 4.83–4.87 (2H, m), 5.42 (1H, dddd, $J=17.1$, 10.4, 7.1, 7.1 Hz), 5.95 (1H, d, $J=3.8$ Hz), 7.37–7.45 (6H, m), 7.62–7.66 (4H, m); $^{13}$C NMR ($CDCl_3$, 125.7 MHz) 19.1, 26.0, 26.7, 26.9 (3×), 38.0, 78.9, 87.0, 88.3, 105.9, 112.1, 117.1, 127.7 (2×), 127.8 (2×), 129.9 (2×), 133.0, 133.1, 134.2, 137.8 (4×). Compound **10**-β: oil; $[\alpha]_D$ −11 ($CHCl_3$, $c=0.38$); $^1$H NMR ($CDCl_3$, 500 MHz) 1.09 (9H, s), 1.12 (3H, s), 1.39 (3H, s), 2.33 (1H, ddd, $J=14.6$, 6.2, 6.2 Hz), 2.54 (1H, ddd, $J=14.7$, 7.4, 7.4 Hz), 4.10 (1H, ddd, $J=8.0$, 5.7, 2.5 Hz), 4.21 (1H, d, $J=2.5$ Hz), 4.26 (1H, d, $J=3.8$ Hz), 5.04 (1H, dd, $J=10.2$, 0.8 Hz), 5.09 (1H, dd, $J=17.2$, 1.5 Hz), 5.80 (1H, dddd, $J=17.0$, 10.2, 6.7, 6.7 Hz), 5.83 (1H, d, $J=3.9$ Hz), 7.39–7.46 (6H, m), 7.63–7.69 (4H, m); $^{13}$C NMR ($CDCl_3$, 125.7 MHz) 19.5, 26.0, 26.6, 26.9 (3×), 32.8, 77.2, 80.7, 84.7, 104.4, 111.1, 116.8, 127.8 (4×), 129.9, 130.0, 132.7, 133.8, 134.8, 135.7 (2×), 135.8 (2×). Compound **11**: oil; $[\alpha]_D$ −46.2 ($CHCl_3$, $c=0.76$); $^1$H NMR ($CDCl_3$, 500 MHz) 0.12 (3H, s), 0.14 (3H, s), 0.90 (9H, s), 1.32 (3H, s), 1.44 (3H, s), 2.39–2.43 (2H, m), 2.96 (1H, dd, $J=7.0$, 7.0 Hz, OH), 3.56 (1H, ddd, $J=11.7$, 6.5, 6.4 Hz), 3.71 (1H, ddd, $J=11.7$, 6.6, 6.6 Hz), 4.05 (1H, dd, $J=5.4$, 4.7 Hz), 4.14 (1H, ddd, $J=6.2$, 6.0, 4.6 Hz), 4.17 (1H, ddd, $J=6.2$, 6.2, 5.7 Hz), 5.08–5.14 (2H, m), 5.81 (1H, dddd, $J=17.3$, 10.2, 7.2, 7.2 Hz); $^{13}$C NMR ($CDCl_3$, 50.3 MHz) −4.6, −4.5, 18.0, 25.6, 25.7 (3×), 28.0, 39.3, 61.6, 70.4, 77.0, 78.1, 107.5, 118.0, 133.5. Compound **12**: oil; $[\alpha]_D$ −28.6 ($CHCl_3$, $c=0.71$); $^1$H NMR ($CDCl_3$, 500 MHz) 0.07 (3H, s), 0.08 (3H, s), 0.89 (9H, s), 1.35 (3H, s), 1.47 (3H, s), 2.18 (1H, ddd, $J=14.6$, 7.4, 7.4 Hz), 2.30–2.38 (2H, m), 3.64 (2H, dd, $J=6.2$, 5.5 Hz), 3.84 (1H, ddd, $J=7.7$, 7.7, 3.6 Hz), 4.07 (1H, dd, $J=7.9$, 5.9 Hz), 4.15 (1H, ddd, $J=6.5$, 5.8, 5.8 Hz), 5.07 (1H, br d, $J=10.3$ Hz), 5.08 (1H, br d, $J=16.8$ Hz), 5.84 (1H, dddd, $J=17.1$, 10.3, 7.2, 7.2 Hz); $^{13}$C NMR ($CDCl_3$, 125.7 MHz) −4.7, −4.3, 18.2, 25.3, 25.8 (3×), 27.9, 38.8, 61.5, 70.7, 77.1, 79.6, 108.2, 117.3, 134.6.

9. Glucose was converted into 5-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-3-[(ethoxycarbonyl)methylene]-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranose ((a) Xie, M.; Berges, D. A.; Robins, M. J. *J. Org. Chem.* **1996**, *61*, 5178–5179; (b) Robins, M. J.; Doboszewski, B.; Timoshchuk, V. A.; Peterson, M. A. *J. Org. Chem.* **2000**, *65*, 2939–2945; (c) Lourens, G. J.; Koekemoer, J. M. *Tetrahedron Lett.* **1975**, *16*, 3719–3722), which was subsequently hydrogenated (Pd/C, EtOH, rt, 4 h), hydrolysed (TFA/$H_2O$, 3:7, rt, 72 h), silylated (TBDPSCl, imidazole, DMF, 0°C, 30 min, 40% three steps), and treated with *N*-hydroxyphthalimide under Mitsunobu conditions (89%) to give compound **5**.
10. The *S* configuration at C-4 was assigned on the basis of $\Delta\delta=(\delta^R-\delta^S)\times10^3$ calculated by the $^1$H NMR and COSY spectra of **14** and **15** [$\Delta\delta>0$ for protons C1 through C3 (+364 to +120) and $\Delta\delta<0$ for protons C-5 to C-7 (−72 to −421)]. See: (a) Latypov, Sh. K.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1996**, *61*, 8569–8577. For the determination of the absolute configuration of a related homoallylic alcohol, see: (b) Mohapatra, D. K.; Datta, A. *J. Org. Chem.* **1998**, *63*, 642–646; (c) Ling, R.; Yoshida, M.; Mariano, P. S. *J. Org. Chem.* **1996**, *61*, 4439–4449.