

FREE-RADICAL REACTIONS OF SOME PHENYLTHIO-2,3-DIDEOXYHEX-2-ENOPYRANOSIDES

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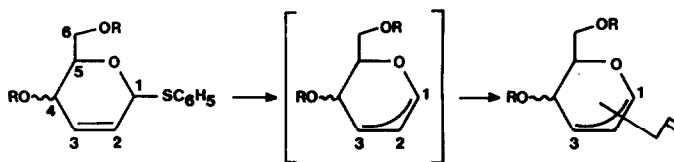
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Abstract - The free-radical reaction of some phenylthio-2,3-dideoxyhex-2-enopyranosides with allyltri-*n*-butyl stannane has been studied.

Free-radical reactions and their applications in organic synthesis have attracted considerable attention in recent years;¹ in spite of this growing interest, several problems, regarding the selectivity and the reactivity, remain to be solved.² Particularly, the chemistry of allylic free-radical species has been almost neglected, scarcely analyzed³ or limited to intramolecular processes.⁴

In this communication we report our preliminary studies on the reaction of allyl free-radicals derived from phenylthio-2,3-dideoxyhex-2-enopyranosides.⁵ Valverde and coworkers have recently described a method for the alkylation and acylation of these compounds at the anomeric center.⁶ Continuing these efforts in this area⁷ and following Keck's pioneer work in the synthesis of C-allyl glycosides using saturated phenylthio glycosides,⁸ we were attracted by substrates of type A (see Scheme), as obvious precursors⁹ for a C₁-C₃ delocalized allyl free-radical in a



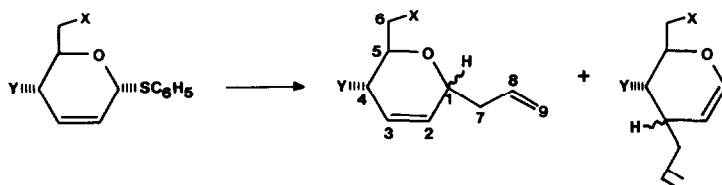
A

Scheme

carbohydrate-like system; we have studied its regio- and stereoselectivity in the reaction with allyltri-*n*-butyl stannane, analyzing the effect of different substituents at C-6 and C-4, and the absolute configuration at C-4.

With this in mind, we have synthesized compounds 1-4,⁶ 5 and 6.¹⁰ Initial experiments,

conducted thermally, using AIBN as initiator, were disappointing; so, photolysis⁸ was next tried. Under these conditions,¹¹ compound **1** gave after careful flash-chromatography, pure compounds **9** α {oil, $[\alpha]_D^{25} +64^\circ$ (c 1.0, CHCl_3)}, **9** β {oil $[\alpha]_D^{25} +130^\circ$ (c 1.24, CHCl_3)} and **10** $\alpha+\beta$, as a mixture that we could not separate, in the ratios¹² and yields shown in *Table I*. Compounds **9** have been previously synthesized by Lewis-acid promoted allyltrimethyl silane reaction with tri-*O*-acetyl-D-glucal.¹³ The stereochemistry at C-1 or C-3 in the reaction products was established by careful ¹H-NMR analysis and comparison with the spectroscopic data recorded in literature.¹⁴ The minor C-1 isomer, **9** β , the most dextrorotatory,^{14b} showed a strong NOE effect at H-1 (δ 3.89, m) upon irradiation of H-5 (δ 3.66, ddd, $J_{5,6a} = 3$ Hz, $J_{5,6b} = 5.3$ Hz, $J_{4,5} = 9.2$ Hz),¹³ and a coupling constant between H-4 and H-5 equal to 9.2 Hz, which is in accordance with a ⁴H₅ preferred conformation; in contrast, in compound **9** α this coupling constant is 5.9 Hz, due to the confor-



	9 (%) ($\alpha:\beta$) X=Y=OAc	10 (%) ($\alpha:\beta$) X=Y=OAc	Yield (%) (9 + 10)
1 X = Y = OAc	60 (1.2 : 1)	40 (1 : 2)	40
2 X = Y = OH	55 (1.5 : 1)	45 (1 : 1.3)	35 ^a
3 X = Y = OSi(CH ₃) ₂ Bu ^t	59 (1 : 1)	41 (1 : 1)	43 ^b
4 X = OSi(CH ₃) ₂ Bu ^t Y = OH	58 (1.7 : 1)	43 (1 : 1)	47 ^b

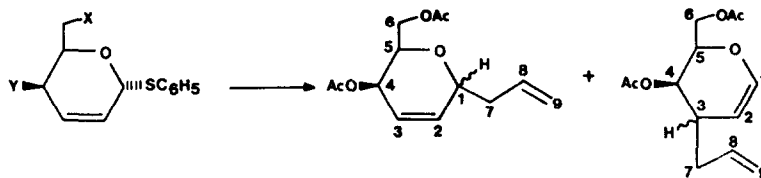
Table I. ^aOverall yield after photolysis and acetylation. ^bOverall yield after photolysis, desilylation and acetylation.

mational mobility.^{14a} The major C-3 isomer, **10** β , showed, as expected, a strong NOE effect between H-3 and H-5, and a vicinal coupling constant between H-3 and H-4 equal to 9.5 Hz. Compounds **2-4**, after photolysis, in the same conditions,¹¹ and acetylation (compound **2**) or desilylation and acetylation (compounds **3** and **4**)¹⁵ gave again the products **9** and **10**¹⁶ in the ratios and yields recorded in *Table I*.

In the *galacto* series we have observed similar results. Compound **6**, after photolysis,¹¹ desilylation and full acetylation,¹⁵ was transformed into compounds **11**^{17,18} and **12**,¹⁹ obtained also from compound **5** after photolysis, in the ratios and yields shown in *Table II*. The assignment of α configuration to the major C-1 isomer was founded on the basis of similarity of its ¹H-NMR spectrum with the corresponding to **9** α , and comparison with the spectroscopic data reported by Danishefsky^{20a} for analogous compounds. The exclusive, or major, C-3 isomer **12** showed a

vicinal coupling constant $J_{3,4} = 1.7$ Hz, which indicates a diequatorial arrangement of protons H-3 and H-4.^{20b}

In view of the values obtained for the C-1 (α : β)/C-3 (α : β) isomers, studies were conducted in order to evaluate the stability of the final products. Under the reaction conditions, neither **9** α,β nor **10** $\alpha+\beta$ isomerize and were recovered unchanged. This fact being established, and from the data in *Tables I and II*, we can conclude that: a) the C-1 substituted C-allyl glycosides are obtained in a slightly greater amount than the C-3 substituted isomers, this being due to the stabilizing effect of an α -oxygen substituted on a free radical;²¹ b) in the C-1 substituted products the major isomer is always α oriented; this facial selectivity is probably due, apart of steric factors, to the radical anomeric effect;²² and c) in the *gluco* series the major C-3 isomer is β oriented, while in the *galacto* group, the major C-3 isomer is almost exclusively α oriented; this fact could be predicted in terms of the steric effects derived from substituents in β position: axial substituents cause a shift in the direction of axial attack and equatorial substituents direct the reaction towards equatorial attack.²



		11 (%) (α : β)	12 (%) (α : β)	Yield (%) (11+12)
5	X = Y = OAc	60 (1.3 : 1)	40 (4.2:1)	42
6	X = OSi(CH ₃) ₂ Bu ^t			
	Y = OH	60 (1.4 : 1)	40 ^b	37 ^a

Table II. ^aOverall yield after photolysis, desilylation and acetylation.
^bOnly the α isomer was detected.

In summary, we have analyzed for the first time the reactivity of an allylic free-radical in a carbohydrate-like system. Moderate yields of C-3 branched chain sugars²³ and C-glycosides, with modest stereoselectivity, have been obtained in the free-radical reaction of some phenylthio-2,3-dideoxyhex-2-enopyranosides with allyltri-*n*-butyl stannane.

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10. Compound 6 has been obtained from 2 by Mitsunobu inversion at C-4 (86%), hydrolysis (MeOH, MeONa, 98%) and silylation at C-6 (99%). Compound 5 has been obtained from 6 after desilylation and full acetylation (75%).
11. In a typical experiment, the starting material, dissolved in dry toluene (0.01 M), degassed with argon, was treated with allytri-*n*-butyl stannane (2 eq) and photolyzed in an immersion wall apparatus with a Pyrex filter and a 125 W medium-pressure Hg arc lamp for 18-24 h. The solvent was evaporated and the residue dissolved in ether, treated with 10% potassium fluoride aqueous solution and stirred overnight. The organic layer was separated, dried and evaporated. The residue was finally submitted to flash-chromatography.
12. The crude mixtures were analyzed in capillar GLC: OV-1 on SiO₂, 25 m, 0.22 mm ϕ , 100°C \rightarrow 250°C (2°C/min): 10 β (t_r 26.89 min), 10 α (27.40 min), 9 β (27.86 min), 9 α (29.52 min); 12 α (t_r 18.37 min), 11 β (18.72 min), 12 β (19.32 min), 11 α (20.24 min).
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15. Desilylation was promoted under standard conditions: tetra-*n*-butylammonium fluoride, 0°C \rightarrow room temperature, overnight, and evaporation. When necessary, acetylations were performed with acetic anhydride/pyridine, room temperature, 24 h.
16. All new compounds gave satisfactory analytical and spectroscopic data.
17. 11 α : Oil; $|\alpha|_D^{25}$ -189° (c 1.7, CHCl₃); ¹H-NMR (300 MHz, CDCl₃) δ 6.03 (dd, $J_{2,3}$ = 10.3 Hz, $J_{1,2}$ = 2.7 Hz, 1H, H-2), 5.95 (m, 1H, H-3), 5.81 (ddd, J = 6.9, 10.2 and 15.9 Hz, 1H, H-8), 5.14-5.08 (m, 2H, H-9), 5.04 (dd, $J_{4,3}$ = 4.9 Hz, $J_{4,5}$ = 2.4 Hz, 1H, H-4), 4.32-4.25 (m, 1H, H-1), 4.14 (dd, $J_{5,6a}$ = 2.0 Hz, 1H, H-6a), 4.12 (dd, $J_{5,6b}$ = 2.2 Hz, 1H, H-6b), 4.07 (m, 1H, H-5), 2.42-2.32 (m, 1H, H-7a), 2.27-2.17 (m, 1H, H-7b), 2.02-2.01 (s, s, 3H, 3H, CH₃COO-). No NOE effect was observed in H-1 upon irradiation of H-5.
18. 11 β : Oil; $|\alpha|_D^{25}$ -204° (c 0.4, CHCl₃); ¹H-NMR (300 MHz, CDCl₃) δ 6.00-5.88 (m, 2H, H-2, H-3), 5.82 (ddd, J = 7, 10 and 16 Hz, 1H, H-8), 5.18-5.01 (m, 3H, H-4, 2H-9), 4.18 (m, 2H, H-6), 4.15 (m, 1H, H-1), 3.87 (dd, $J_{5,6}$ = 6.7, $J_{4,5}$ = 2.4 Hz, 1H, H-5), 2.50-2.25 (m, 2H, H-7), 2.05, 2.03 (s, s, 3H, CH₃COO-). Irradiating at H-1 showed a clear NOE effect at H-5.
19. 12 α : Oil; $|\alpha|_D^{25}$ +130° (c 1.5, CHCl₃); ¹H-NMR (300 MHz, CDCl₃) δ 6.42 (d, $J_{1,2}$ = 6.3 Hz, 1H, H-1), 5.80 (m, 1H, H-8), 5.14-5.04 (m, 2H, H-9), 4.92 (m, $J_{4,5}$ = 1.7 Hz, $J_{4,3}$ = 1.7 Hz, $J_{1,2}$ = 1.2 Hz, 1H, H-4), 4.74 (ddd, $J_{2,4}$ = 1.4 Hz, $J_{2,3}$ = 3.7 Hz, $J_{1,2}$ = 6.3 Hz, 1H, H-2), 4.21 (m, 2H, H-6), 4.10 (m, 1H, H-5), 2.28-2.10 (m, 3H, H-3, 2H-7), 2.10, 2.09 (s, s, 3H, 3H, CH₃COO-). We could not isolate pure the 12 β isomer in the reaction of compound 5.
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