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Intramolecular Hydrogen Atom Abstraction in Carbohydrates and Nucleosides: Inversion of an α- to β-Mannopyranoside and Generation of Thymidine C-4' Radicals

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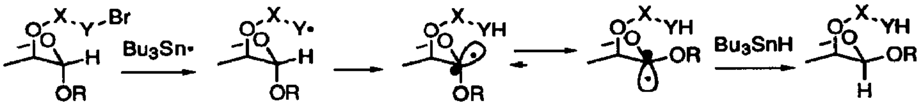
Summary: Treatment of 1-bromo-2-methyl-2-propyl ether derivatives of alcohols with $Bu_3SnH(D)$ results in 1,5-Hydrogen abstraction reactions: the system is applied to the inversion of an α- to β-mannoside and to the formation of nucleoside C4' radicals.

Intramolecular hydrogen atom abstraction through six-membered cyclic transition states (δ- or 1,5-H abstraction) by means of aminium radical cations or alkoxy radicals has a long and venerable history.[1,2,3] 1,5-H abstraction by vinyl and aryl radicals has been introduced by Curran, who has designed a series of protecting groups for alcohols carrying precursors to such radicals which enable functionalization, by hydrogen atom abstraction, of the derivatized alcohol.[4] Here, we present the application of 1,5-hydrogen atom abstraction to the long standing problem of the formation of β-*O*-mannopyranosidic linkages,[5] as found for example in the common core pentasaccharide of the *N*-linked glycoproteins,[6] and to the formation of nucleoside C-4' radicals relevant to the mode of action of numerous antitumor antibiotics.[7]

1-Alkoxy-1-glycosyl radicals are selectively quenched along the axial direction by thiols and stannanes to give equatorial glycosides.[8] Therefore, we evisaged the process for the inversion of α- to β-mannopyranosides depicted in Scheme 1 where X is a suitable tether that may be readily appended onto *O*-2 of an α-mannopyranoside and which serves to position the electrophilic radical Y• for 1,5-hydrogen atom abstraction from the anomeric site. The so-formed, equatorial, pyramidal, σ-type anomeric radical[9] would then invert to the more stable axial configuration followed by quenching to give the β-mannoside.

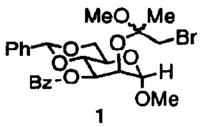


Scheme 1

Numerous systems in which Y• was a either an sp^2-hybridized carbon or a heteroatom centered radical, and X various tethers, were assayed to no avail. However, Norrish type II photochemistry of *O*-phenacyl tetrabenzyl-α-mannopyranoside led cleanly to tetrabenzyl-1,5-mannolactone, and at the same rate as the corresponding β-*O*-phenacyl derivative of glucose gave tetrabenzylgluconolactone, indicating that there was no fundamental impediment to the abstraction of the equatorial anomeric hydrogen in α-mannopyranosides.[10]

Rather, it appeared that the problem lay in the well known susceptibility[1] of 1,5-hydrogen atom abstractions to subtle conformational effects, and that the XY combinations tried did not permit attainment of the required transition state for hydrogen atom abstraction. Thus, attention was directed at less rigid combinations of XY• with no sp^2 hybridized atoms other than a π-type radical Y• in which the required, distorted, chair-like cyclic transition state[11] might be more readily attained.

Treatment of **1**,[12] as a mixture of two diastereomers, in benzene at reflux with tributyltin hydride and AIBN dropwise over 5 h gave a complex reaction mixture, which after stirring with moist silica gel yielded 30% of the desired β-mannoside **2b**, together with approximately 34% of **3b**, 22% of the 2-ketone **4**, and 8% of the α-glucoside **5b** (Table, entry 1). Clearly, this particular tether permits the required 1,5-H abstraction from the anomeric site resulting in the formation of **2a**, and thence of **2b**.[13] The α-mannoside **3b** (from deprotection of **3a**) is the product of simple reduction of the initial radical by the stannane.[13,14] Replacement of Bu_3SnH by the catalytic Me_3SnCl / $NaBH_3CN$ couple in ^tBuOH at reflux gave grossly similar results. It should be possible to improve the **2b**:**3b** ratio by the use of the poorer hydrogen donor $(Me_3Si)_3SiH$[15] but we have yet to explore this possibility. The main competing reaction is 1,4-H- abstraction from C2[16] followed by either expulsion of 2-methoxy-2-propyl radical giving **4**,[13] or quenching by the stannane giving **5a** and so **5b**[13] after deprotection. In the accompanying manuscript Professor Curran describes a parallel solution to this problem, developed in his laboratory, using a 1,6-hydrogen atom abstraction process.[17]



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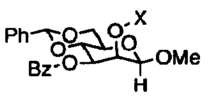
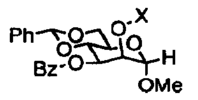
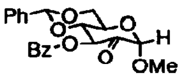


2a: X = $C(OMe)Me_2$
2b: X = H

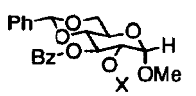


3a: X = $C(OMe)Me_2$
3b: X = H

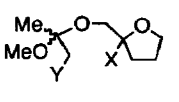


4

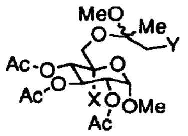
Application to the less conformationally rigid systems **6a** and **7a** was, predictably, more successful as evidenced by the relatively high levels of deuterium incorporation on treatment with Bu_3SnD (Table, entries 2 and 3). No evidence for 1,4-H abstraction was found in these systems. The C5-radical derived from **7a** was quenched with a modest axial selectivity of ~ 3:1, with the minor, inverted, product adopting the $^5S_1$ conformation. The minor product **9** arising from **7a** (Table, entry 3) is apparently the result of 1,5-H abstraction followed by acetoxy migration and eventual elimination of acetic acid.[18,19]



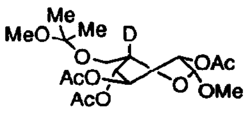
5a: X = $C(OMe)Me_2$
5b: X = H



6a: X = H, Y = Br
6b: X = D, Y = H
6c: X = H, Y = D
6d: X = allyl, Y = H

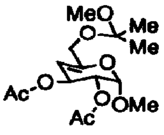


7a: X = H, Y = Br
7b: X = D, Y = H
7c: X = H, Y = D



8

The system was also suitable for generation of nucleoside C4' radicals as evidenced by the treatment of **10a** with Bu_3SnD giving **10b** and **11** in an ~ 1.6:1 ratio, together with the reduction product **10c** (Table, entry 4). Interestingly, treatment of **12**[20] with Bu_3SnH gave only **13**, resulting from the relatively slow vinyl migration, and none of the expected H-abstraction followed by cyclization (Table, entry 5). This observation could indicate that the methoxy group is important in achieving the correct conformation for 1,5-H abstraction (through an anomeric effect) or simply that abstraction is less rapid than the closure of substituted homoallylic radical to the corresponding cyclopropylmethyl radical (10^3 - 10^4 s^{-1})[21] Carbon-carbon bond formation could be achieved by substitution of $Bu_3SnH(D)$ by allyltributyltin as indicated in entry 6 of the Table.



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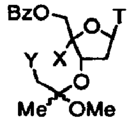
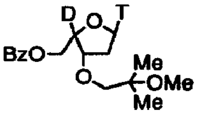
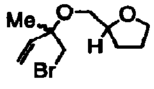


10a: X = H, Y = Br
10b X = D, Y = H
10c: X = H, Y = D

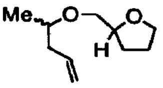


1 1

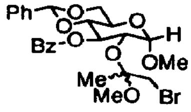


1 2

The system is very susceptible to minor changes in geometry of the tether. Thus, the α-glucoside **14** gave only reduction and 1,4-H abstraction (Table, entry 7) whilst the two bromomethylsilanes **15a** and **16a** gave only reduction (Table, entries 8 and 9).



1 3



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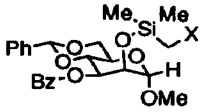
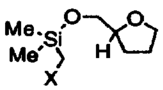


15a: X = Br
15b: X = H



16a: X = Br
16b: X = D

Table

Entry	Substrate	Reagent	Products (% Yield)
1	**1**	Bu_3SnH^a	**2b** (30), **3b** (34), **4** (22), **5b** (8)
2	**6a**	Bu_3SnD	**6b** + **6c** (~ 100, ratio 86:14)
3	**7a**	Bu_3SnD	**7b** + **7c** (61, ratio 55:45), **8** (11), **9** (14)
4	**10a**	Bu_3SnD	**10b** + **10c** (61, ratio 70:30), **11** (26)
5	**12**	Bu_3SnH	**13** (>95)
6	**6a**	$Bu_3SnCH_2CH{=}CH_2$	**6d** (29)
7	**14**	Bu_3SnH	**5b** (~30), **4** (~70)
8	**15a**	Bu_3SnH	**15b** (>95)
9	**16a**	Bu_3SnD	**16b** (>95)

a) Followed by brief treatment with SiO_2/CH_2Cl_2.

Further studies on the optimization of this convenient 1,5-H abstraction system are currently underway, as is the application to the synthesis of complex β-mannopyranosides and to the study of nucleotide C4' radicals. Progress in these directions will be reported in due course.

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