

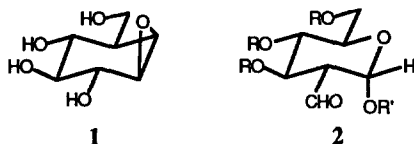
STEREOSPECIFIC INTRAMOLECULAR FORMYL TRANSFER VIA RADICAL CYCLIZATION-FRAGMENTATION: PREPARATION OF ALKYL 2-DEOXY-2 α -FORMYLGLUCOPYRANOSIDES AND SIMILAR COMPOUNDS¹

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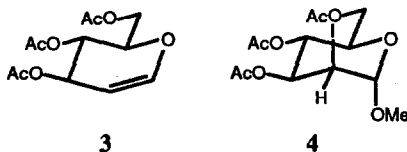
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Summary: An efficient synthesis of alkyl 2-deoxy-2 α -formylglucopyranosides is described. The key step involves a novel stereospecific intramolecular formyl transfer via a radical cyclization-fragmentation process in good yield.

For a synthesis of the β -glucosidase inhibitor, cyclophellitol 1,⁴ a potential antiviral agent, we required an efficient and general synthesis of a C2-branched hexose. In particular, we wanted to prepare the alkyl 2-deoxy-2 α -formylglucopyranoside 2 and decided to use the inexpensive D-glucose as our starting material. Of the many possible synthetic approaches, we chose to introduce a functionalized one-carbon unit via a C2-radical generated from the corresponding 2-iodoglucopyranoside. We now report an efficient method for stereospecific transfer of the formyl group via a radical cyclization-fragmentation process which permits the efficient synthesis of 2-deoxy-2 α -formylglucopyranosides.

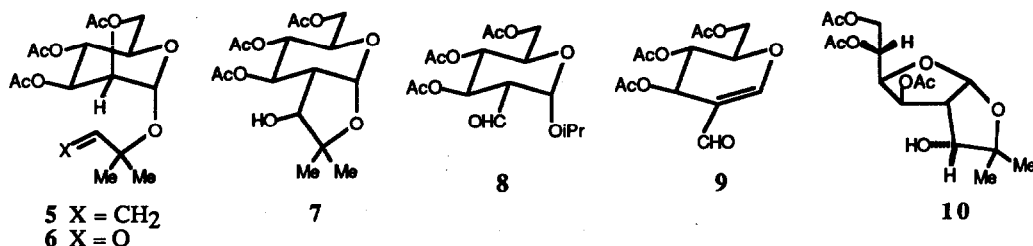


Attempts at intermolecular trapping⁵ of the radical generated from the known α -methyl 3,4,6-tri-*O*-acetyl 2-deoxy-2 β -iodoglucopyranoside 4, prepared from commercially available glucal triacetate 3 by addition of *N*-iodosuccinimide (NIS) in methanol,⁶ were generally low-yielding.⁷ This caused us to consider an intramolecular trapping



of the radical by a properly placed aldehyde (giving an alkoxy radical) followed by a thermodynamically-driven fragmentation to achieve the same net result of formyl transfer. Treatment of 3 with NIS and dimethylvinylcarbinol in

acetonitrile afforded the trans diaxial product **5** in 56% yield (90% based on recovered starting material). Ozonolysis and reduction furnished the desired iodoaldehyde **6** in 96% yield. Free-radical promoted cyclization of **6** produced a mixture of the four products **7-10** in varying ratios depending on the conditions (Table 1). With tris(trimethylsilyl)-silane in refluxing toluene at short times, the initial cyclization product **7** and the desired aldehyde **8** are produced in



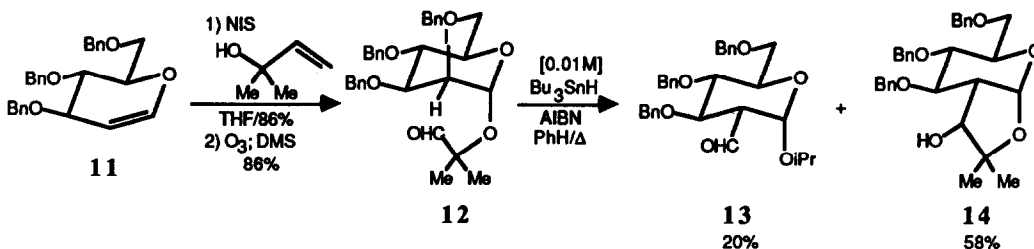
yields of 33% and 41% respectively with 11% of the enal **9** also being produced.⁸ This enal **9** can be isolated as the major product in 65% yield by using longer reaction times. Thus our proposed reaction course, namely cyclization of the C2 radical onto the aldehyde to give the oxygen radical which then would regenerate the aldehyde by producing the more stable α -isopropoxy radical, is occurring.⁹ With tributylstannane in refluxing benzene, the rearranged secondary alcohol, the annulated glucofuranose **10**, is produced in 60% yield after 30 min. After longer addition times a mixture of **7-10** results. Compound **10** is presumably formed by a rearrangement of **7** which is probably catalyzed by tributylstannane.¹⁰ The corresponding galacto isomer of **6** also undergoes intramolecular formyl transfer with

Table 1: Free-Radical Promoted Cyclization of **6**

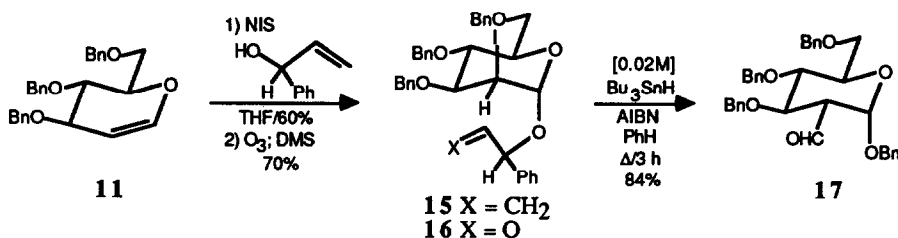
Reagent	Conc. (M)	Addition Time	Reaction Time	Isolated Yields of			
				7	8	9	10
(Me ₃ Si) ₃ SiH	0.032	1.5 h	4 h	33	41	11	---
"	0.06	5 h	4 h	17	trace	65	---
Bu ₃ SnH	0.005	0.5 h	1 h	---	trace	---	60
"	0.032	1 h	4 h	---	30	---	23
"	0.02	6 h	1 h	20	21	10	38

tributylstannane to give 43% of the galacto isomer of **8** along with 31% of a 1:3 mixture of the galacto isomers of **7** and **10**. Believing that the novel ring contraction could only occur with the peracetate (since an acyl transfer is needed to convert **7** into **10**),¹⁰ we investigated the cyclization-fragmentation process starting with the known glucofuranose ether **11**.¹¹ Conversion of **11** by the same two-step procedure afforded **12** in 74% yield. Cyclization as above afforded mainly the secondary alcohol **14** (58%) with only up to 20% of the desired aldehyde **13** being produced.¹²

It was obvious from the above results that the radical α to the oxygen atom and two methyl groups was not stable enough to drive the reaction to completion. Simply by changing this to a more stabilized benzyl radical, we were able to achieve high yields. Thus, treatment of **11** with NIS and α -phenyl allyl alcohol¹³ in acetonitrile



furnished in 60% yield (90% based on unrecovered starting material) the iodo alkene **15** which was converted to the aldehyde **16** as before in 70% yield. Treatment of **16** with tributylstannane in refluxing benzene for 3h produced the desired 2-deoxy-2- α -formylglucopyranoside **17** in 84% yield. Thus the driving force of producing a benzyl radical causes the final fragmentation to occur much more efficiently and leads to a high yield of the desired formyl transfer.



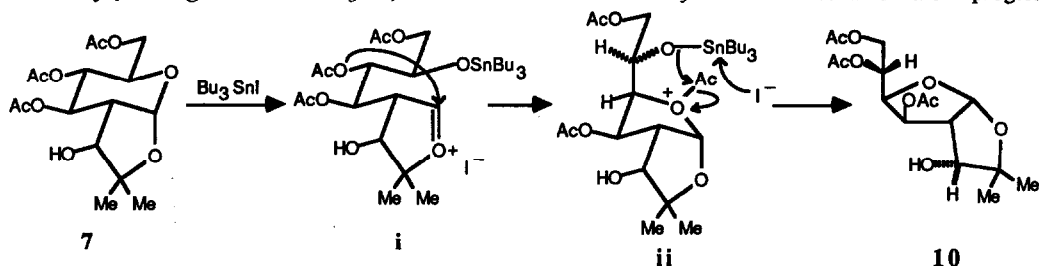
Research on similar group transfers on related systems is currently underway¹⁴ as is work on the conversion of compounds such as **17** into cyclophellitol **1**, the results of which will be reported in due course.

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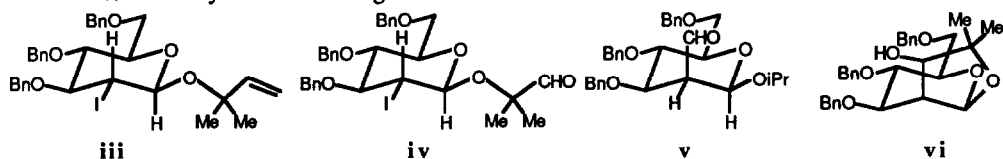
References and Notes

- 1) Presented at the 33rd GECO Conference, Corsica, France, September 1992.
- 2) UCLA McCoy Award recipient, 1991-92; UCLA Hanson-Dow Teaching Award recipient, 1992.
- 3) UCLA Mentorship Awardee, 1991-92.
4. a) Isolation: Atsumi, S.; Umezawa, K.; Iinama, H.; Naganawa, H.; Nakamura, H.; Iitaka, Y.; Takeuchi, T. *J. Antibiot.* **1990**, *43*, 49. b) Syntheses: Tatsuta, K.; Niwata, Y.; Umezawa, K.; Toshima, K.; Nakata, M. *Tetrahedron Lett.* **1990**, *31*, 1171. Moritz, V.; Vogel, P. *Tetrahedron Lett.* **1992**, *33*, 5243. Akiyama, T.; Ohnari, M.; Shima, H.; Ozaki, S. *Synlett* **1991**, 831. c) Synthetic approach: Barton, D. H. R.; Dalko, P.; Gero, S. D. *Tetrahedron Lett.* **1991**, *32*, 2471.
5. For example, see: Giese, B.; Gröming, K. *Tetrahedron Lett.* **1984**, *25*, 2743.
6. a) Chen, S. H.; Horvath, R. F.; Joglar, J.; Fisher, M. J.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 5834. b) Thiem, J.; Karl, H.; Schwentner, J. *Synthesis* **1978**, 696.

7. For example, trapping with fumaro- or maleonitrile⁵ followed by elimination and oxidation could not be made to proceed in high yield. It should be noted that a new process, namely trapping of a radical generated with triphenylgermane with carbon monoxide at 1400 psi followed by in situ reduction afforded the corresponding primary alcohol in 37% yield. Gupta, V.; Kahne, D. *Tetrahedron Lett.* **1993**, *34*, 591.
8. This is a new route to 2-formylglucals, being more general than the other known route via Vilsmeier-Haack reaction, since that does not allow acid-sensitive protecting groups. Ramesh, N. G.; Balasubramanian, K. K. *Tetrahedron Lett.* **1991**, *32*, 3875.
9. For a similar formyl transfer, see: Tsang, R.; Dickson, J. K., Jr.; Pak, H.; Walton, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1987**, *109*, 3484; Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, *108*, 8102.
10. We assume that rearrangement of **7** to **10** involves complexation of the pyran oxygen with the Lewis acidic iodo-stannane, opening to the onium ion **i**, reaction with the 4-acetate to give **ii**, which then transfers the acetate intramolecularly (with regeneration of Bu₃SnI) to afford **10**. Studies to verify this novel mechanism are in progress.



11. Chmielewski, M.; Kaluza, Z. *Carbohydr. Res.* **1987**, *167*, 143.
12. Treatment of **11** with NIS and dimethylvinylcarbinol in acetonitrile rather than THF produced a 3:1 mixture of the diaxial 2 β -iodo 1 α -alkoxy compound (leading ultimately to **12**) and the diequatorial 2 α -iodo β -alkoxy compound **iii**. Ozonolysis-reduction of **iii** and cyclization of the aldehyde **iv** gave the 2 β -formyl compound **v** in 14% yield along with 67% of the alcohol **vi** as a single diastereomer. Under different conditions, the yield of **vi** could be raised to 82% with only traces of **v** being formed.



13. Easily prepared by addition of vinylmagnesium bromide to benzaldehyde.
14. Preliminary results show that a cyano group can be similarly transferred intramolecularly by using a cyanohydrin in the reaction of the glucal with NIS followed by generation of the radical. Other procedures for the production of the 2 α - and 2 β -formylglycosides are under investigation.