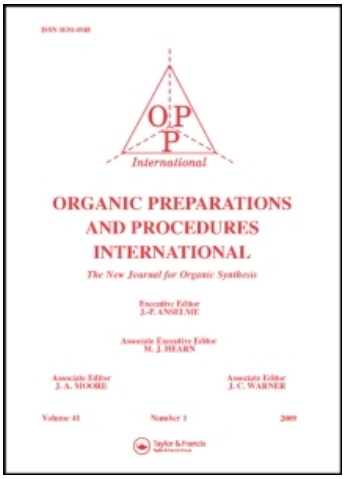


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

A FACILE STEREOCONTROLLED SYNTHESIS OF 3-DEOXY-1, 2-0-ISOPROPYLIDENE-β-L-THREO-PENTOFURANOSE FROM DIACETONE GLUCOSE

Robert D. Walkup[a]; Raymond T. Cunningham[a]
[a] Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, TX

To cite this Article Walkup, Robert D. and Cunningham, Raymond T.(1988) 'A FACILE STEREOCONTROLLED SYNTHESIS OF 3-DEOXY-1, 2-0-ISOPROPYLIDENE-β-L-THREO-PENTOFURANOSE FROM DIACETONE GLUCOSE', Organic Preparations and Procedures International, 20: 2, 129 — 134
To link to this Article: DOI: 10.1080/00304948809355800
URL: http://dx.doi.org/10.1080/00304948809355800

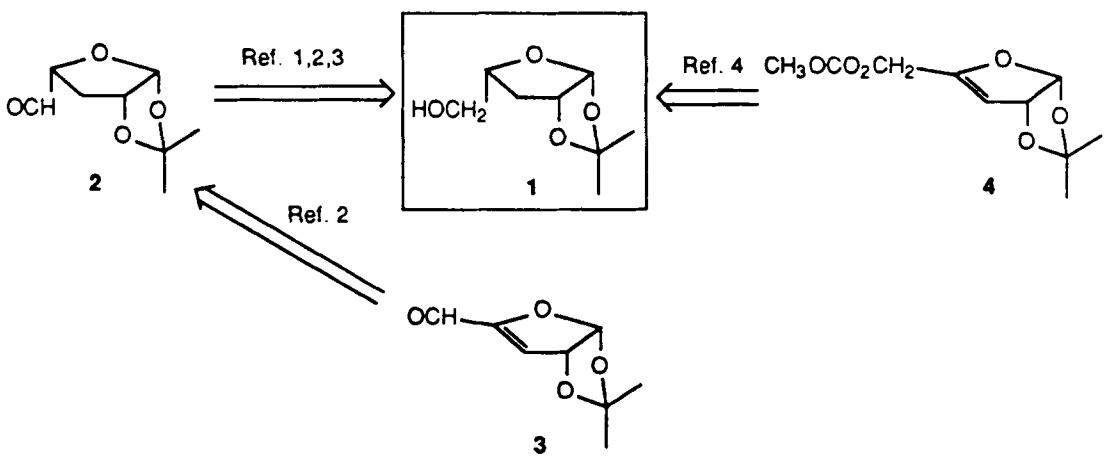
ORGANIC PREPARATIONS AND PROCEDURES INT. 20(2), 129-134 (1988)

A FACILE STEREOCONTROLLED SYNTHESIS OF 3-DEOXY-1,2-O-ISOPROPYLIDENE-β-L-THREO-PENTOFURANOSE FROM DIACETONE GLUCOSE

Robert D. Walkup* and Raymond T. Cunningham

Department of Chemistry and Biochemistry
Texas Tech University, Lubbock, TX 79409-4260

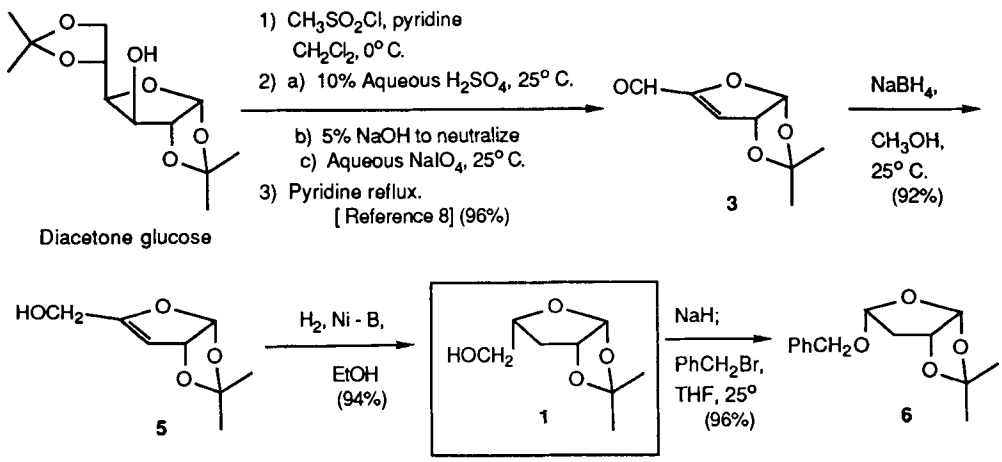
During the course of studies on the polyacetate tumor promotors, we needed 3-deoxy-1,2-O-isopropylidene-β-L-threo-pentofuranose (1) as an intermediate. This carbohydrate derivative was first prepared by Prokop and Murray from diacetone glucose via the aldehyde 2, which was formed via a low yield partial hydrolysis of 1,2:5,6-di-O-isopropylidene-3-deoxy-D-galactofuranose; the net yield of 1 from diacetone glucose was 27%.[1] Brown and Jones reported a similar synthesis from diacetone glucose via the aldehydes 3 and 2 which proceeded in only 11% overall yield.[2] Later, Zinner and Reck synthesized 1 from 1,2:5,6-di-O-isopropylidene-3-deoxy-D-galactofuranose,



again via the aldehyde 2, in 31% overall yield.[3] More recently, Lerner has reported a synthesis of 1 from 1,2-O-isopropylidene-5-O-(methoxycarbonyl)-α-D-xylo-furanose, via the pent-3-enofuranose 4, in 61% overall yield.[4] Only Zinner and Reck reported an absolute rotation for 1, $[\alpha]_D^{21}$ = -25.5° (c = 1.22, pyridine).[3] Srivastava and Lerner, in the course of a nucleoside synthesis, reported $[\alpha]_D^{27}$ = -14.2° (c = 0.8, ethanol) for 1.[5] This discrepancy is probably due to solvent and/or concentration effects. However, the aldehyde 2, an intermediate in both of the syntheses which report $[\alpha]_D$ values for 1[3,5], is known to undergo epimerization to the more stable exo aldehyde,[2] and this suggests that syntheses of 1 which proceed via 2 may form mixtures of 1 contaminated by its C_4 epimer. None of the syntheses of 1 reported so far have included full spectroscopic data on this deoxysugar, nor have they offered clearcut evidence for the endo orientation of the hydroxymethyl group.

The summary given above implies that, maugre many efforts, a truly high-yielding synthesis of 1 from a readily available starting material remains to be achieved.[6,7] We now report an extremely facile synthesis of 1 from diacetone glucose which is based upon a recently reported highly efficient synthesis of 3 and which avoids the intermediacy of an epimerizable 5-oxo species. We also discuss some spectroscopic measurements which support the assignment of 1 as the L (endo hydroxymethyl group) form.

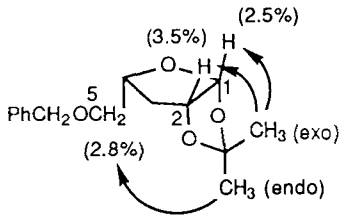
Sun and Fraser-Reid's 3-step method gave the the unstable enal 3 in 96-98% yield from diacetone glucose.[8] Sodium borohydride reduction of 3 produced the novel allylic alcohol 5 in 92-95% yield. Catalytic hydrogenation of 5 using nickel boride as the catalyst[9] yielded 1 in 94-96% yield. Thus 3-deoxy-1,2-O-isopropylidene-β-L-threo-pentofuranose was synthesized in 5 steps from diacetone glucose in 83% overall yield. For synthetic studies, we also prepared the 5-O-benzyl derivative (6) of 1 in



96% yield. The following table compares the absolute rotations that we measured for 1 with those reported in the literature:

Solvent	$[\alpha]_D^{25}$ (present study)	$[\alpha]_D$ (literature)
chloroform	-39.15° (c = 0.038)	- - -
ethanol	-16.57° (c = 0.034)	-14.2° (c = 0.800)[5]
pyridine	-9.73° (c = 0.034)	-25.5° (c = 1.220)[3]

The data indicates a significant solvent effect upon the rotation of 1. While our value in ethanol is in reasonable agreement with that of Srivastava and Lerner,[5] the discrepancy between our measurement and that of Zinner and Reck[3] in pyridine is likely due to density effects, as the latter workers measured their rotation on a very concentrated solution. ^{13}C NMR spectroscopy of 1 from our route indicated no isomers of 1 nor any other impurities. A difference nuclear Overhauser effect spectrum of the benzyl derivative 6 clearly indicated the endo stereochemistry, as irradiation of the endo methyl signal (at 1.45 ppm) induces a 2.8% enhancement of the C_5 proton signals while irradiation of the exo methyl signal (at 1.30 ppm) induces a 1.8% enhancement. By comparison, irradiation of the endo methyl signal induces 1.1% enhancements of both the C_1 and the C_2 methine signals while irradiation of the exo methyl signal induces 2.5% and 3.5% enhancements of the C_1 and C_2 methine signals, respectively.[10]



In summary, an improved synthesis of 1 from an inexpensive starting material has been devised, and evidence for its assignment as the endo (L) form is given for the first time. The utility of 1 as an intermediate for the synthesis of nucleoside analogues has already been demonstrated,[1,5] and 1 is a promising starting material for the syntheses of numerous chiral polyfunctional products.

EXPERIMENTAL SECTION

^1H and ^{13}C NMR spectra were obtained on an IBM AF-300 instrument. IR spectra were recorded using a Nicolet MX-S spectrometer. Rotations were determined using a Perkin-Elmer Model 141 polarimeter. NMR chemical shifts are reported in ppm relative to TMS internal standard in deuteriochloroform solvent.

3-Deoxy-1,2-O-isopropylidene-α-D-glycero-pent-3-enofuranose (5).-To a stirred solution of 0.500 g (2.9 mmol) of the enal 3[8] in 10 ml methanol in a 50 ml flask fitted with a $CaCl_2$ drying tube was slowly added 0.111 g (3.0 mmol) of powdered sodium borohydride. The reaction mixture was allowed to stir at room temperature for 16 hours, then the methanol was removed using a rotary evaporator. The resulting glassy residue was suspended in dry diethyl ether and eluted through an 8 cm x 1 cm (i.d.) column of 230-400 mesh silica gel with diethyl ether. Concentration of the filtrate under vacuum yielded 0.454 g (92%) of the pure alcohol 5 as a colorless oil. $[\alpha]_D^{25}$ = - 8.01° ($CHCl_3$, c = 0.133 g/ml). ^1H NMR: δ 6.08 (d, J = 3.5 cps, 1H); 5.30 (d of d, J = 3.5, 0.6 cps, 1H); 5.19 (d, J = 0.6 cps; 1H); 4.15 (s, 2H); 1.46 (s, 3H); 1.42 (s, 3H). ^{13}C NMR: δ 161.2; 113.0; 107.1; 99.0; 84.1; 58.4; 28.3; 28.0. IR (film): 3500, 1650 cm^{-1}.

3-Deoxy-1,2-O-isopropylidene-β-L-threo-pentofuranose (1). - A solution of 0.372 g (1.5 mmol) of nickel(II) acetate tetrahydrate in 50 ml distilled water was stirred under argon while 3 ml of a 1 M aqueous solution of sodium

borohydride was added. An additional 1.5 ml of the sodium borohydride solution was added 3 minutes later. The water was then decanted away from the resulting black precipitate, and the precipitate was carefully washed three times with 5 ml portions of ethanol. A solution of 0.593 g (3.5 mmol) of 5 in 50 ml ethanol was then added, and the mixture was agitated under 38 psi of hydrogen gas for 6 hrs. The reaction mixture was then filtered and concentrated to give 0.559 g (94%) of the pure pentofuranose 1 as a clear colorless oil. ^{1}H NMR: δ 5.83 (d, J = 4.0 cps, 1H); 4.77 (d of d, J = 5.6, 4.1 cps, 1H); 4.33 (br m, 1H); 3.83 (d of d, J = 11.5, 8.0 cps, 1H); 3.63 (d of d, J = 11.5, 4 cps, 1H); 2.19 (d of d of d, J = 14.5, 8.7, 6 cps, 1H); 2.02 (d of d, J = 14.5, 2.7 cps, 1H); 1.56 (s, 3H); 1.32(s, 3H). ^{13}C NMR: δ 112.5; 105.5; 81.7; 80.8; 65.1; 33.3; 27.1; 26.0. IR (film): 3550 cm^{-1}.

3-Deoxy-5-O-benzyl-1,2-O-isopropylidene-β-L-threo-pentofuranose (6). - A solution of 0.111 g (0.64 mmol) of the furanose 1 in 2 ml dry THF was added dropwise to a stirred suspension of 0.05 g (2 mmol) of sodium hydride (obtained by washing 0.083 g of a 60% dispersion of sodium hydride in mineral oil three times with dry hexane) in 20 ml of dry THF in a 100 ml flask fitted with a gas inlet adapter. The resulting cloudy suspension was stirred at 25° under a nitrogen atmosphere for 20 min., then 0.12 g (0.67 mmol) of benzyl bromide was added. The reaction flask was then fitted with a $CaCl_2$ drying tube and the mixture was stirred at room temperature for 12 hrs., then partitioned between 20 ml ether and 25 ml of 5% aqueous HCl. The organic phase was washed with water, then with saturated aqueous NaCl, and then it was dried over anhydrous sodium sulfate. Removal of the solvents in vacuo left a yellow oil which was chromatographed on 20 g of 230-400 mesh silica gel, using 90:10 (v/v) hexane:ethyl acetate as eluent, to yield 0.162 g (96%) of 6 as a colorless oil. $[\alpha]_D^{25}$ = -27.4° ($CHCl_3$, C = 0.045 g/ml). ^{1}H NMR: δ 7.3 (s, 5H); 5.79 (d, J = 3.9 cps, 1 H); 4.70 (d of d, J = 4, 1.3 cps, 1 H); 4.63 (d, J = 12.1 cps, 1 H); 4.56 (d, J = 12.1 cps, 1 H); 4.30

(br m, 1 H); 3.69 (d of d, J = 9.6, 6.9 cps, 1 H); 3.57 (d of d, J = 9.7, 6.8 cps, 1 H); 2.18 (d of d of d, J = 18.0, 8.0, 6.0 cps, 1 H); 2.07 (complex d of d, J = ~18.0, ~1.3 cps, 1 H); 1.45 (s, 3H); 1.30 (s, 3H). ^{13}C NMR: δ 139.14; 128.16; 128.58; 128.39; 112.93; 107.38; 81.19; 80.17; 73.82; 73.13; 34.35; 27.22; 26.16.

ACKNOWLEDGEMENTS.- This research was made possible by a grant from the Robert A. Welch Foundation (Grant #D-998). The NMR spectrometer was purchased with funds from the National Science Foundation (grant #CHE-8514104). We are indebted to Mr. David W. Purkiss for his assistance with the NMR experiments. Financial assistance to RTC from the Texas Tech University Graduate School Summer Research Award program is gratefully acknowledged.

REFERENCES

1. J. Prokop and D. H. Murray, J. Pharm. Sci. 54, 359 (1965).

2. D. M. Brown and G. H. Jones, J. Chem. Soc. C, 249 (1967).

3. H. Zinner and R. Reck, J. prakt. Chem., 315, 137 (1973).

4. L. M. Lerner, Carbohydrate Res., 132, 168 (1984).

5. V. K. Srivastava, and L. M. Lerner, J. Med. Chem., 22, 24 (1979); see also L. M. Lerner, ibid., 25, 825 (1982).

6. For a synthesis of DL-1, see J. Buddrus, H. Herzog, and H. Bauer, Ann., 1950 (1983).

7. For a synthesis of a pyranose corresponding to 1, starting from arabinose, see R. G. S. Ritchie, D. M. Vyas and W. A. Szarek, Can. J. Chem., 56, 794 (1978).

8. K. M. Sun and B. Fraser-Reid, Synthesis, 28 (1982).

9. T. W. Russell and R. C. Hoy, J. Org. Chem., 36, 2018 (1971).

10. Control experiments indicated an error of ±0.1% for these measurements, which were run as described in Derome, A. E., "Modern NMR Techniques for Chemistry Research," Pergamon Press, Inc., New York, NY 1987, Chapter 5.

(Received June 16, 1987; in revised form August 10, 1987)