Epimerization at C-2 during the Wittig reaction of 2,3,5-tri-O-benzyl-D-ribose and methylidenetriphenylphosphorane

FILLMORE FREEMAN AND KIRK D. ROBARGE

Department of Chemistry University of California, Irvine, Irvine, California 92717 (U.S.A.) (Received September 11th, 1985; accepted for publication, November 1st, 1985)

Nonstabilized and stabilized ylides undergo condensation reactions with lactols to give highly functionalized alkenes which may undergo stereoselective, electrophile-mediated cyclizations to precursors for otherwise difficulty accessible carbohydrates, *C*-nucleosides, homo-*C*-nucleosides, and natural products¹⁻¹³. We now describe the epimerization at C-2 during the Wittig reaction of 2,3,5-tri-*O*-benzyl-D-ribose (1) and methylidenetriphenylphosphorane.

RESULTS AND DISCUSSION

2,3,5-Tri-O-benzyl-D-ribose¹⁴ (1) condenses with methylidenetriphenylphosphorane in tetrahydrofuran (THF) at 22–24° to give 2,3,5-tri-O-benzyl-1,2-dideoxy-D-ribo-hex-1-enitol (2) in low yield (entry 1, Table I)¹⁰. Addition of hexamethylphosphoramide to the mixture (entry 2, Table I) did not increase the yield of 2 and led to the formation of another product from a competing, elimination reaction. In order to drive the reaction to completion and to increase the yield of 2, the experiment was performed in boiling tetrahydrofuran (entries 3–6, Table I). While this did lead to an increase in overall yield, a mixture of two products was obtained. Analysis of this mixture showed the presence of 2 and 2,3,5-tri-O-benzyl-1,2-dideoxy-D-arabino-hex-1-enitol (3) in the ratio (2:3) of 1:1.6. The product ratio was independent of the equivalents of ylide used and the heating time. The best overall yield was obtained by using six equivalents of methylidenetriphenylphosphorane and a reflux time of 4 h (entry 6, Table I).



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TABLE I

Entry	Ph ₃ P=CH ₂ ª equiv	Solvent	Reaction temp., °C	Reaction time, h	Overall yield	2 (%)	3 (%)
1	2.2	THF	22-24	18	36 ⁶	24	0
2	2.0	THF-HMPA (1:1)	22-24	18	35°	23	0
3	1.5	THF	reflux	18	43 ^d	16	27
4	2.0	THF	reflux	4	40 ^d	15	25
5	2.0	THF	reflux	12	52 ^d	20	32
6	6.0	THF	reflux	4	54°	21	33

PRODUCTS FROM THE REACTION OF 2,3,5-TRI-O-BENZYL-D-RIBOSE (1) AND METHYLIDENETRIPHENYLPHOS-PHORANE

^aYlide formed at 22–24° from BuLi. ^bYield based on recovered starting material. ^cNo starting material recovered. An unidentified product, possible 4,6-dibenzyloxy-5-hydroxy-1,3-hexadiene, was obtained in 12% yield. This product was also obtained in 42% yield by reaction of 4 with 2.2 equiv of $Ph_3P=CH_2$ in 1:1 THF:HMPA for 18 h at 22–24°. ^dRatio of alkenes 2 and 3 determined by integration (250 MHz) of OH doublets, from chromatographed product-mixture, or by integration (250 MHz) of H-4 protons of crude, iodine-mediated cyclization products. ^cAlkenes 2 and 3 separated by preparative t.l.c.



For a comparison purposes, 2,3,5-tri-O-benzyl-D-arabinose¹⁴ (4) was treated with methylidenetriphenylphosphorane in boiling THF (3 h). The sole alkene isolated was 3 (90%).

The following experiments were performed in order to gain insight into the possible mechanism of the epimerization. Reaction of 1 with either 0.2 or 1 equiv. of methylidenetriphenylphosphorane in boiling tetrahydrofuran under reflux for 4 h gave a complex mixture of products (t.l.c.). However, none of the *arabino* sugar derivative (4) was isolated from either of these reaction mixtures. Similarly, 4 was not isolated from the reaction of 1 with 2.2 equiv of potassium *tert*-butoxide in boiling tetrahydrofuran (4 h). Resubjecting alkene 2 to the Wittig reaction conditions (THF, 4 h, reflux, 2.0 equiv, Ph₃P=CH₂) led to quantitative recovery of the unchanged alkene 2. Similar results were obtained upon subjecting alkene 3 to the same experimental conditions. Though the exact mechanistic details of the epimerization are unclear, it is likely that the loss of stereochemistry occurs through the enolate of the aldehyde initially formed from 1. It is also noteworthy that this epimerization does not occur when 1 is treated with a stabilized ylide¹³.

EXPERIMENTAL

General methods. — Melting points were determined in open capillary tubes with a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were performed by Robertson Laboratory, Florham Park, NJ. Optical rotations were measured with a Perkin-Elmer 241 polarimeter in an unthermostatted, 10-cm glass cell at the sodium D line. I.r. spectra were obtained with a Perkin-Elmer 283 spectrophotometer. Spectra were obtained for dilute solutions in CCl_4 , neat films, or KBr disks.

Medium-resolution mass spectra were obtained with a Finnigan 9610 g.l.c.c.i. mass spectrometer with a Nova 3 data-system operating at an ionization potential of 70 or 100 eV. Chemical ionization mass spectra were obtained by using 2-methylpropane as the reactant gas. Peaks greater than $\approx 10\%$ relative intensity are generally reported.

¹H-N.m.r. spectra were recorded at 250 MHz (Bruker WM-250) with the solvent(s) noted. Chemical shifts (δ) are reported downfield from internal Me₄Si (~0.5% for Fourier transform) at $\delta = 0.000$ p.p.m. The following descriptions are used: ABq = Ab quartet, br = broad, d = doublet, m = multiplet, q = quartet, s = singlet, and t = triplet. Apparent coupling-constants (J) are reported in hertz (Hz). Because of the data digitization with the F.t. instrument, J values are ±0.40 Hz maximum, but normally are accurate to ±0.20 Hz. ¹³C-N.m.r. data were obtained with a Bruker WM-250 spectrometer.

Silica gel 60 (230–400 mesh) was used for flash-column chromatography. T.l.c. was performed on Merck Silica Gel 60 F-254 (0.25 mm, precoated on glass).

Solvents used for extraction and chromatography were nanograde quality or distilled. Tetrahydrofuran (THF) and ether were distilled from sodium benzophenone anion prior to use. Dichloromethane was distilled from CaH_2 prior to use. *N*,*N*-Dimethylformamide (DMF) was predried over BaO and then distilled under diminished pressure from CaH_2 in the dark and stored over 4-Å sieves. Other reagents were used as supplied or purified as noted. Butyllithium in hexane (Alfa) was titrated at 25° in THF with 2,5-dimethoxybenzyl alcohol.

All reactions were performed in oven- or flame-dried glassware under argon with magnetic stirring, unless noted otherwise. Solutions and liquids were delivered by syringe or cannula through rubber septa or by pressure-equalizing dropping funnels where appropriate.

2,3,5-Tri-O-benzyl-1,2-dideoxy-D-ribo-hex-1-enitol (2) and 2,3,5-tri-O-benzyl-1,2-dideoxy-D-arabino-hex-1-enitol (3). — To a stirred solution of 509 mg (1.42 mmol) of methyltriphenylphosphonium bromide (Aldrich) in 6 mL of dry THF at 24° under argon was added dropwise 0.59 mL (1.42 mmol) of 2.4M butyllithium in hexane over 1 min. A color change from yellow to red occurred. The mixture was stirred for 15 min at 24° and a solution of 100 mg (0.24 mmol) of 2,3,5-tri-O-benzyl-D-ribose¹⁴ in 3 mL of THF was added quickly. Solids began to form in the cream-colored suspension. The mixture was boiled under reflux for 12 h and quenched upon cooling by the addition of wet ether. The mixture was extracted several times with ether, the combined organic layers were washed with 5 mL of saturated aqueous NaCl, and dried (K_2CO_3). Removal of solvent under diminished pressure, followed by flash-column chromatography of the residue on 4 g of silica gel with 3:1:1 petroleum ether (35–60°)–ether–dichloromethane) afforded 54.0 mg (54%) of a 1:1.6 (2:3) mixture of alkenes. The ratio of alkenes was determined by integration of the O-H doublets in the ¹H-n.m.r. spectrum. The alkenes were separated by multiple-elution preparative t.l.c. Onto an analytical t.l.c. plate (0.25 mm, 20 × 20 cm) was loaded 21.0 mg of the mixture of alkenes. Elution three times with 9:1:1 petroleum ether (35–60°)–ether–dichloromethane separated the two bands. Cutting, followed by washing with ethyl acetate, filtering, and evaporation *in vacuo* gave 4.5 mg of the *ribo* alkene (2) and 10.0 mg of the *arabino* alkene (3); 69% recovery from the preparative t.l.c. plate.

2,3,5-Tri-O-benzyl-1,2-dideoxy-D-ribo-hex-1-enitol (2) had $R_{\rm F}$ 0.30 (3:1:1 petroleum ether-ether-dichloromethane); $\nu_{\rm max}^{\rm film}$ 3600-3400 (br OH), 3080, 3040 (alkene, arom), 2929, 2880, (CH₃) 1500, 1460 (arom ring), 1220, 1100, 1000, 935 (vinyl), 750, and 700 cm⁻¹; ¹H-n.m.r. (CDCl₃) 7.38-7.23 (m, 15 H, Ph), 5.96 (ddd, 1 H, $J_{1,2(trans)}$ 17.0, $J_{1,2(cis)}$ 11.0, $J_{2,3}$ 8.0 Hz, H-2, X part of ABX), 5.37 (m, 2 H, H-1), 4.69 (ABq, 2 H, $\Delta\nu_{\rm AB}$ 10.10, $J_{\rm AB}$ 12 Hz, OCH₂Ph), 4.62 (ABq, 2 H, $\Delta\nu_{\rm AB}$ 16.3, $J_{\rm AB}$ 12 Hz, OCH₂Ph), 4.52 (ABq, 2 H, $\Delta\nu_{\rm AB}$ 6.4, $J_{\rm AB}$ 9.5 Hz, OCH₂Ph), 4.16 (dd, 1 H, $J_{2,3}$ 8.0, $J_{3,4}$ 4.0 Hz, H-3), 3.85 (m, 1 H, H-5), 3.72 (dd, 1 H, $J_{3,4}$ 4.0, $J_{4,5}$ 8.0 Hz, H-4), 3.63 (m, 2 H, H-6), 2.70 (d, 1 H, $J_{\rm OH,5}$ 5.0 Hz, OH); ¹³C-n.m.r. (CDCl₃): δ 138.65, 138.20 (s, $C_{\rm quat}$ OCH₂Ph), 135.35 (d, C-2), 128.52–127.59 (m, OCH₂Ph), 119.72 (t, C-1), 82.16 (d, C-3), 81.24 (d, C-4), 74.18 (t, OCH₂Ph), 73.50 (t, C-6), 71.31 (t, OCH₂Ph), 70.89 (d, C-5), and 70.59 (t, OCH₂Ph); *m/z* (c.i.): 419 (MH⁺), 181, 107, and 91.

Anal. Calc. for C₂₇H₃₀O₄: C, 77.48; H, 7.22. Found: C, 77.35; H, 7.41.

2,3,5-Tri-O-benzyl-1,2-dideoxy-D-arabino-hex-1-enitol (3) had $R_{\rm F}$ 0.30 (3:1:1 petroleum ether-ether-dichloromethane); $\nu_{\rm max}^{\rm film}$ 3540-3460 (br OH), 3100, 3080, 3040 (alkene, arom), 2920, 2880, (CH₃), 1500, 1460 (arom ring), 1400, 1350, 1225, 1080, 930, (vinyl), 740, and 700 cm⁻¹; ¹H-n.m.r. (CDCl₃) 7.35-7.24 (m, 15 H, Ph), 5.97 (ddd, 1 H, $J_{1,2(trans)}$ 16.5, $J_{1,2(cis)}$ 11.3, $J_{2,3}$ 7.5 Hz, H-2, X part of ABX), 5.33 (m, 2 H, H-1), 4.60 (ABq, 2 H, $\Delta\nu_{AB}$ 18.4, J_{AB} 11.5 Hz, OCH₂Ph), 4.52 (s, 2 H, OCH₂Ph), 4.51 (ABq, 2 H, $\Delta\nu_{AB}$ 69.5, J_{AB} 12.0 Hz, OCH₂Ph), 4.09 (dd, 1 H, $J_{2,3}$ 7.5, $J_{3,4}$ 4.0 Hz, H-3), 4.03 (m, 1 H, H-5), 3.64 (dd, 1 H, $J_{3,4}$ 4.0, $J_{4,5}$ 7.0 Hz, H-4), 3.61 (d, 2 H, $J_{5,6}$ 4.0 Hz, H-6), and 2.84 (d, 1 H, $J_{5,OH}$ 5.0 Hz, O-H); ¹³C-n.m.r. (CDCl₃): δ 138.47, 138.38, 138.17 (s, (C_{quat}, OCH₂Ph), 135.40 (d, C-2), 128.61-127.91 (m, OCH₂Ph), 119.31 (t, C-1), 80.89 (d, C-3), 80.48 (d, C-4), 74.35 (t, OCH₂Ph); 73.62 (t, C-6), 71.22 (t, OCH₂Ph), 70.95 (d, C-5), and 70.65 (t, OCH₂Ph); m/z (c.i.): 419 (MH⁺), 219, 181, 129, 107, and 91.

Anal. Calc. for C₂₇H₃₀O₄: C, 77.48; H, 7.22. Found: C, 77.42; H, 7.37.

Compound 2 was also prepared in 23% yield (35% based on recovered starting material) by following the procedure of Russo and coworkers¹⁰.

Compound **3** was also prepared by the reaction of methylidenetriphenylphosphorane (2.0 equiv. from the phosphonium bromide and BuLi, 15 min, THF, 25°) and 2,3,5-tri-O-benzyl-D-arabinose¹⁴ (18 h, 25°, THF, or boiling THF, 3 h) in 90% yield.

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REFERENCES

- 1 F. FREEMAN AND K. D. ROBARGE, Carbohydr. Res., 137 (1985) 89-97.
- 2 F. FREEMAN AND K. D. ROBARGE, Tetrahedron Lett., (1985) 1943-1946.
- 3 J. R. POUGNY, M. A. M. NASSR, AND P. SINAŸ, J. Chem. Soc., Chem. Commun., (1981) 375-376.
- 4 J.-M. LANCELIN, J.-R. POUGNY, AND P. SINAY, Carbohydr. Res., 136 (1985) 369-374.
- 5 J. MANN AND P. D. KANE, J. Chem. Soc., Perkin Trans. 1, (1984) 657-660.
- 6 A. G. M. BARRETT AND H. B. BROUGHTON, J. Org. Chem., 49 (1984) 3673-3674.
- 7 K. SUZUKI AND T. MUKAIYAMA, Chem. Lett., (1982) 683-686.
- 8 J. M. J. TRONCHET, Colloq. Inst. Natl. Santé Rech. Med., 81 (1978) (Publ. 1979); 117-144; Chem. Abstr., 92 (1980) 76803j.
- 9 A. B. REITZ, S. O. NORTEY, AND B. E. MARYANOFF, Tetrahedron Lett., 26 (1985) 3915-3918.
- 10 F. NICOTRA, R. PEREGO, F. RONCHETTI, G. RUSSO, AND L. TOMA, Gazz. Chim. Ital., 114 (1984) 193-195.
- 11 H. OHRUI, G. H. JONES, J. G. MOFFATT, M. L. MADDOX, A. T. CHRISTENSEN. AND S. K. BYRAM, J. Am. Chem. Soc., 97 (1975) 4602–4613.
- 12 M. C. CLINGERMAN AND J. A. SECRIST, III, J. Org. Chem., 48 (1983) 3141-3145.
- 13 J. G. BUCHANAN, A. R. EDGAR, M. J. POWER, AND P. D. THEAKER, Carbohydr. Res., 38 (1974) C22.
- 14 R. BARKER AND H. G. FLETCHER, JR., J. Org. Chem., 26 (1961) 4605-4609.