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FRAGMENTATION AND WITTIG OLEFINATION OF GLUCOSAMINE DERIVATIVES-A SIMPLE ROUTE TO OPEN CHAIN AMINO SUGARS AND CHIRAL GLYCEROLS[1)]

ATHANASSIOS GIANNIS, PETER MÜNSTER, KONRAD SANDHOFF* and WOLFGANG STEGLICH*

Institut für Organische Chemie und Biochemie der Universität Bonn, Gerhard-Domagk-Straße 1, D-5300 Bonn, Federal Republic of Germany

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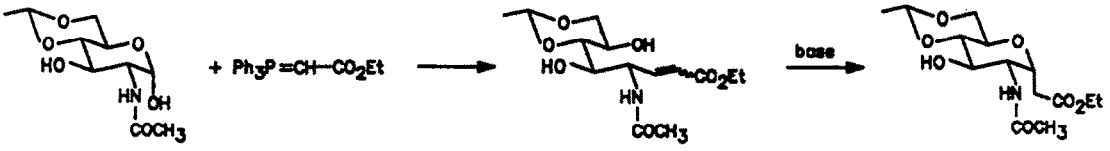
Abstract - The Wittig-reaction of 2-acylamino-2-deoxy-4,6-*O*-ethylidene glucose 1 leads either to the chiral glycerols 6, *via* a fragmentation of the sugar, or to the chain-elongated derivatives 8, depending on type of the ylide. Compounds 8 can be converted easily to the open-chain *aldehydo* sugar 10 in two steps.

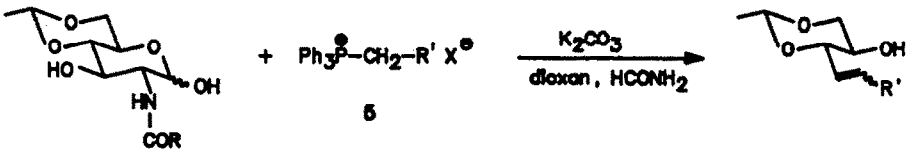
Carbohydrates are readily available chiral starting materials for the synthesis of enantiomerically and diastereomerically pure compounds[2,3)].

In an effort to synthesize optically pure amino acids, aldehydes and alcohols as well as sphingoids and C-glycosides, the Wittig reactions of partially protected amino sugars seemed to offer a convenient route. Recently, we reported the reaction of 2-acetamido-2-deoxy-4,6-*O*-ethylidene-α-*D*-glucose 1a with the resonance-stabilized carbethoxymethylene triphenylphosphorane 2 to the allylamino derivative 3, which could easily be converted to the C-glycoside 4[4)].



1a 2 3 4

In order to establish the general scope of this reaction, we also investigated the use of non-stabilized ylides 5. Surprisingly, instead of the expected chain-elongated sugars, the chiral glycerol derivatives 6a-c were formed. By use of a four fold excess of the ylides 5 the alkenes 6 were obtained in about 70% yield. These compounds are important intermediates in the synthesis of sphingoids[5)].

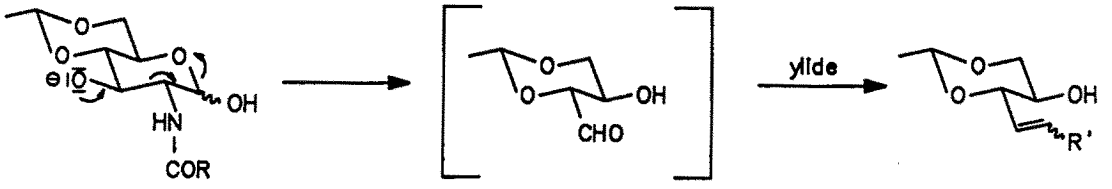


5

1	a	b
R	CH_3	OCH_2Ph

6	a	b	c
R'	H	CH_3	$C_{15}H_{31}$

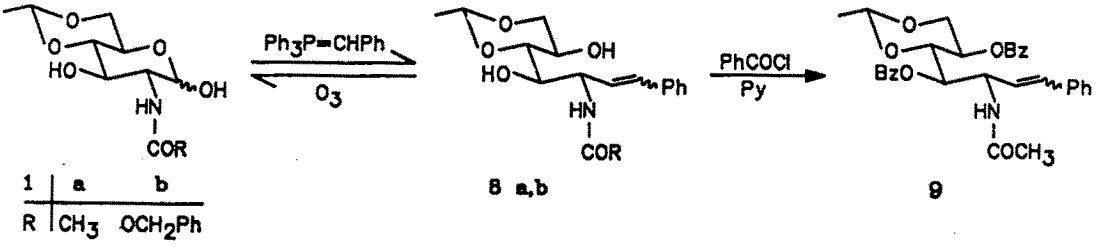
This fragmentation is consistent with a retro-aldol reaction brought about by the strongly basic ylides, followed by Wittig reaction of the aldehyde produced with excess ylide present in the reaction mixture. High field proton n.m.r. analysis indicated that no epimerization took place at the chiral centres. The E/Z-ratios range from 1:1 (6c) to 2:1 (6a,b).



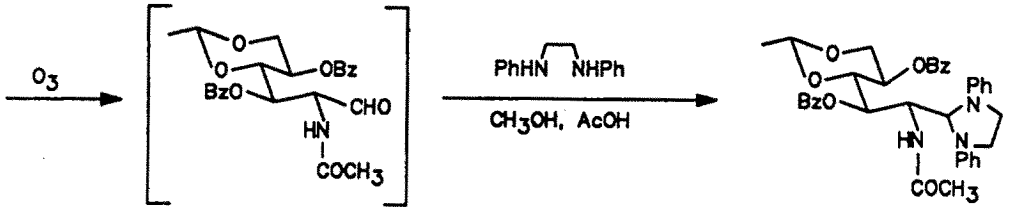
1 7 6

Of the many reaction conditions tested, the system amino sugar/phosphonium salt/potassium carbonate in dioxan containing 2% formamide[6] gave the best yields for the fragmentation products. Benzylidene triphenylphosphorane, which is intermediate between resonance-stabilized and non-stabilized ylides in basicity and Wittig reactivity, is not basic enough to cause the retro-aldol reaction but gives the expected Wittig products 8 instead. Ozonolysis of this unsaturated compound regenerates the starting amino sugar in 94% yield.

The conversion of amino sugars 1 into the alkenes 8 constitutes an easy approach to open chain amino sugar derivatives by masking the aldehyde function as a benzylidene unit. Protection of the two free hydroxy groups of compound 8a (which was not possible in the case of 3 due to C-glycoside formation via intramolecular Michael addition) and subsequent ozonolysis of the benzylidene moiety gave access to the amino sugar aldehyde 10 which is otherwise difficult to obtain[7]. This unstable compound[8] is derivatized *in situ* and isolated as the corresponding imidazolidine 11[9].



8 a,b 9



10 11

EXPERIMENTAL

M.p.s were determined with a Reichert hot-stage microscope or a Büchi melting-point apparatus and are uncorrected. IR spectra were obtained using a Perkin-Elmer 1420 infrared spectrometer. NMR spectra were measured with Varian EM 390, Bruker WH 90, AC 200 and AM 400 instruments (tetramethylsilane as internal reference). Mass spectra were obtained at 70 eV using an AEI MS 30 or MS 50 spetrometer equipped with a data system. For column chromatography Merck silica gel 40-60 μm was used. TLC was carried out on TLC aluminium sheets silica gel 60 F_{254}. Elemental analyses were performed at the Institut für Organische Chemie und Biochemie, Universität Bonn.

2-Benzyloxycarbonylamino-2-deoxy-α,β-D-glucose was synthesized under Schotten-Baumann conditions with benzylchloroformate and sodium carbonate according to ref. [10]. Yield: 90%, mp. 214°C.

2-Acetamido-2-deoxy-4,6-*O*-ethylidene-α-*D*-glucose (1a) was prepared by a modified procedure [4] analogous to lit. [11]. Yield: 88%, mp. 205-207°C.

2-Benzyloxycarbonylamino-2-deoxy-4,6-*O*-ethylidene-α,β-*D*-glucose (1b): 2-Benzyloxycarbonylamino-2-deoxy-α,β-*D*-glucose (10 g, 32 mmol) was added to paraldehyde (100 ml) containing conc. sulfuric acid (0.2 ml). After stirring for 24 h, 100 ml of Et_2O were added. The precipitated product was filtered off and washed several times with Et_2O. Yield 10.3 g (95%), m.p. 217°C[12], [Found C, 56.77; H, 6.38; N, 4.08; $C_{16}H_{21}NO_7$ (339.34) requires C, 56.63; H, 6.24; N, 4.13%]; IR (KBr): ν_{max} 3430, 3300, 3070, 3040, 2995, 2930, 2860, 1680, 1550, 1280, 1180, 1090, 890, 690 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 1.24 (3 H, d, *J* 4.8 Hz), 3.05-3.30 (2 H, complex), 3.35-3.80 (3 H, complex), 3.87-4.07 (1 H, complex), 4.55 (0.4 H, d, *J* 8.4 Hz), 4.72 (1 H, complex), 4.97-5.40 (3.6 H, complex), 6.79 (1 H, br), 7.10 (0.6 H, d, *J* 8.4 Hz), 7.21 (0.4 H, d. *J* 9.6 Hz), 7.35 (5 H, complex); ^{13}C NMR (DMSO-d_6): δ = 20.4, 57.0, 59.8, 62.1, 65.3, 65.5, 65.9, 67.3, 67.9, 70.7, 81.1, 81.9, 91.7, 96.3, 98.7, 98.8, 127.9, 128.4, 137.1, 137.3, 156.2, 156.3.

General procedure for the fragmentation of amino sugar derivatives 1

To a solution of glucosamine derivative 1a or 1b (5 mmol) in dry dioxan (100 ml) were added the phosphonium bromide or chloride (20 mmol), potassium carbonate (2.76 g, 20 mmol) and formamide (2 ml). After refluxing for 8 h, the precipitate was filtered off, washed several times with dioxan and the solvent was evaporated under reduced pressure. The products were purified by column chromatography on silica gel (eluent: tetrachloromethane/acetone or chloroform/methanol).

(2R,4S,5R)-4-Ethenyl-5-hydroxy-2-methyl-1,3-dioxan (6a): Yield 447 mg (62%), colourless oil, $[\alpha]_D$ = -20.2° (c = 0.9, EtOAc), IR (neat): ν_{max} 3400, 2990, 2940, 2870, 1620, 1405, 1150, 1120, 1080, 1045, 935, 905, 845 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.36 (3 H, d, *J* 5 Hz), 1.80 (1 H, d, *J* 3.5 Hz), 3.43 (1 H, t, *J* 10.5 Hz), 3.46 (1 H, complex), 3.80 (1 H, t, *J* 7.5 Hz), 4.18 (1 H, dd, *J* 10.5, 5 Hz), 4.74 (1 H, q, *J* 5 Hz), 5.37 (1 H, d, *J* 11 Hz), 5.45 (1 H, d, *J* 18 Hz), 5.90 (1 H, ddd, *J* 18, 11, 7.5 Hz); ^{13}C NMR ($CDCl_3$): δ = 20.5, 65.1, 70.4, 82.8, 98.8, 119.2, 134.8; MS (150°C): m/z = 143.0707 (2.95%, $(M-H)^+$, calc. for $C_7H_{11}O_3$ 143.0708).

(2R,4S,5R)-5-Hydroxy-2-methyl-4-(1'(E/Z)-propenyl)-1,3-dioxan (6b): Yield 514.mg (65%), m.p. 48°C, [Found C, 60.66; H, 9.15; $C_8H_{14}O_3$ (158.20) requires C, 60.74; H, 8.92%]; IR (KBr): ν_{max} 3420, 2990, 2940, 2880, 1405, 1140, 1115, 1080, 1030, 975, 895 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.34 (3 H, 2d, *J* 5 Hz), 1.78 (3 H, complex), 1.80 (1 H, br), 3.34-3.57 (2 H, complex), 3.74 (0.5 H, t, *J* 10.5 Hz), 4.18 (1.5 H, complex), 4.71-4.77 (1 H, 2q, *J* 5 Hz), 5.44 (0.5 H, ddq, *J* 11, 9, 1.6 Hz), 5.51 (0.5 H, ddq, *J* 15.5, 8, 1.6 Hz), 5.87-5.97 (1 H, complex); MS (150°C): m/z = 157.0863 (0.32%, $(M-H)^+$, calc. for $C_8H_{13}O_3$ 157.0864).

(2R,4S,5R)-4-(1'(E/Z)-heptadecenyl)-5-hydroxy-2-methyl-1,3-dioxan (6c): Yield 1.13 g (64%), m.p. 46.5°C, [Found C, 74.68; H, 12.03; $C_{22}H_{42}O_3$ (354.58) requires C, 74.52; H, 11.94%]; IR (KBr): ν = 3440, 2910, 2820, 1460, 1405, 1395, 1245, 1140, 1110, 1085, 1075, 1030, 890, 850, 720 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.92 (3 H, t, *J* 8 Hz), 1.15-1.61 (30 H, complex), 2.12 (2 H, complex), 3.45 (2 H, complex), 3.71 (0.5 H, t, *J* 8 Hz), 4.15 (1.5 H, complex), 4.70 (0.5 H, q, *J* 5 Hz), 4.71 (0.5 H, q, *J* 5 Hz), 5.37 (0.5 H, ddt, *J* 11, 9, 1.5 Hz), 5.45 (0.5 H, ddt, *J* 15.5, 8, 1.5 Hz), 5.83 (1 H, complex).

General procedure for the Wittig olefination of amino sugar derivatives 1 with benzyltriphenylphosphonium chloride

The amino sugar 1a or 1b (5 mmol), benzyltriphenylphosphonium chloride (5.84 g, 15 mmol) and potassium carbonate (2.08 g, 15 mmol) were refluxed in dry dioxan (80 ml) containing formamide (2 ml). After 8 h the solution was allowed to cool to room temperature and the precipitate was filtered off and washed several times with dioxan. The solvent was evaporated under reduced pressure and the products were purified by column chromatography (eluent: chloroform/methanol).

(E/Z)-3-Acetamido-5,7-*O*-ethylidene-1-phenyl-1,2,3-trideoxy-*D*-*gluco*-hept-1-enitol (8a): Yield 1.28 g (80%), m.p. 143°C, [Found C, 63.71; H, 7.36; N, 4.30; $C_{17}H_{23}NO_5$ (321.37) requires C, 63.54; H, 7.21; N, 4.36%]; IR (KBr): ν_{max} = 3300, 3040, 2980, 2940, 2860, 1640, 1530, 1195, 1095 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.34 (3 H, 2d, *J* 5 Hz), 1.93 (1.2 H, s), 2.05 (1.8 H, s), 3.08-3.70 (3 H, complex), 3.80 (1 H, complex), 3.90-4.17 (2 H, complex), 4.65 (1 H, 2q, *J* 5 Hz), 4.96 (0.6 H, complex), 5.29 (0.4 H, complex), 5.68 (0.4 H, dd, *J* 11.5, 9.5 Hz), 6.20 (0.6 H, dd, *J* 16, 6.5 Hz), 6.37 (0.4 H, d, *J* 8 Hz), 6.50-6.71 (1.6 H, complex), 7.15-7.39 (6 H, complex).

(E/Z)-3-Benzyloxycarbonylamino-5,7-*O*-ethylidene-1-phenyl-1,2,3-trideoxy-*D*-*gluco*-hept-1-enitol (8b): Yield 1.385 g (67%), colourless oil, [Found C, 66.68; H, 6.73; N, 3.31; $C_{25}H_{27}NO_6$ (413.47) requires C, 66.81; H, 6.58; N, 3.39 %]; IR (neat): ν_{max} = 3520, 3320, 1690, 1560, 1415, 1280, 1080 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.30 (3 H, d, *J* 4.5), 2.15 (1 H, br), 2.55 (1H, br), 3.23-4.14 (5 H, complex), 4.52-4.77 (2 H, complex), 5.50 (0.5 H, d, *J* 8), 5.71 (0.5 H, d, *J* 8), 6.17 (1 H, complex), 6.59 (1 H, complex), 7.28 (10 H, complex).

Ozonolysis of (E/Z)-3-benzyloxycarbonylamino-5,7-*O*-ethylidene-1-phenyl-1,2,3-trideoxy-*D*-*gluco*-hept-1-enitol (8b)

(E/Z)-3-Benzyloxycarbonylamino-5,7-*O*-ethylidene-1-phenyl-1,2,3-trideoxy-*D*-*gluco*-hept-1-enitol 8b (206.7 mg, 0.5 mmol) was dissolved in dichloromethane-methanol (2 : 1, 15 ml) and cooled to -78°C. At this temperature a stream of oxygen and ozone was passed through the solution until a bluish colour indicated an excess of ozone. After removal of excess ozone by an argon stream, dimethylsulfide (0.1 ml) was added and the solution was allowed to warm up to room temperature and stirred for another 1.5 h. The solvent was evaporated under reduced pressure and the remaining white precipitate was washed several times with Et_2O. Yield: 150 mg (88%), m.p. 216-217°C; spectroscopic data are identical with those for 1b.

(E/Z)-3-Acetamido-4,6-di-*O*-benzoyl-5,7-*O*-ethylidene-1-phenyl-1,2,3-trideoxy-*D*-*gluco*-hept-1-enitol (9): (E/Z)-3-Acetamido-5,7-*O*-ethylidene-1-phenyl-1,2,3-trideoxy-*D*-*gluco*-hept-1-enitol 8a (250 mg, 0.78 mmol) and benzoyl chloride (0.36 ml, 3.12 mmol) were dissolved in pyridine (15 ml) and stirred at room temperature. After 12 h the solution was poured onto a mixture of sodium bicarbonate, water and ice. The product was extracted with dichloromethane and purified by column chromatography on silica gel (eluent: tetrachloromethane/acetone 5:1). Yield 380.mg (92%), m.p. 94°C, [Found C, 69.56; H, 5.22; N, 2.67; $C_{31}H_{31}NO_7$ (529.59) requires C, 70.31; H, 5.90; N, 2.64%]; IR (KBr): ν = 3400, 2910, 2840, 1720, 1710, 1650, 1440, 1260, 1105, 705 cm^{-1}; ^1H NMR ($CDCl_3$) for (E)-9 : δ = 1.50 (3 H, d, *J* 5 Hz), 1.80 (3 H, s), 3.51 (1 H, t, *J* 10.5 Hz), 4.07 (1 H, dd, *J* 10, 2 Hz), 4.33 (1 H, dd, *J* 10.5, 5.5 Hz), 4.73 (1 H, q, *J* 5 Hz), 5.13 (1 H, td, *J* 10.5, 5.5 Hz), 5.28 (1 H, complex), 5.40 (1 H, dd, *J* 9, 2 Hz), 6.04 (1 H, d, *J* 9 Hz), 6.11 (1 H, dd, *J* 16, 7.5 Hz), 6.73 (1 H, d, *J* 16 Hz), 7.26-7.46 (9 H, complex), 7.54-7.60 (2 H, complex), 7.91-7.95 (2 H, complex), 8.25-8.74 (2 H, complex).

1,3-Diphenyl-2-(1'-acetamido-1'-deoxy-2',4'-di-*O*-benzoyl-3',5'-*O*-ethylidene-*D*-*gluco*-pentyl) imidazolidine (11): (E/Z)-4,6-*O*-Benzoyl-3-benzyloxycarbonylamino-5,7-*O*-ethylidene-1-phenyl-1,2,3-trideoxy-*D*-*gluco*-hept-1-enitol 9 (106 mg, 0.2 mmol) was ozonized as already described for compound 8b. After the addition of dimethylsulfide (0.18 ml), the solution was stirred at room temperature for 1.5 h. Subsequently, a mixture of 1.2-dianilinoethane[9] (1 g, 4.7 mmol) in methanol (10 ml) and acetic acid (50 %, 0.25 ml) was added. The solution was warmed up to 40°C and stirred for 0.5 h. The solvent was evaporated under reduced pressure and the product was purified by column chromatography on silica gel (eluent: tetrachloromethane/acetone 4:1). Yield 58.5.mg (45%), colourless oil, IR (neat): ν = 3405, 3060, 2995, 2960, 2860, 1725, 1675, 1600, 1500, 1375, 1315, 1270, 1110 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.37 (3 H, d, *J* 5 Hz), 1.82 (3 H, s), 3.47-3.70 (5 H, complex), 3.92 (1 H, complex), 4.68 (1 H, q, *J* 5 Hz), 5.00 (1 H, complex), 5.63 (1 H, dd, *J* 4.5, 2 Hz), 5.91 (1 H, d, *J* 4.5 Hz), 6.64-8.10 (20 H, complex); MS (180°C): m/z = 649.2781 (0.03%, M^+, calc. for $C_{38}H_{39}N_3O_7$ 649.2788).

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