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Ethoxycarbonylmethylenetriphenylphosphorane in Carbohydrate Chemistry, Part II[§] : A Short and Efficient Synthesis of (+)-Goniofufurone

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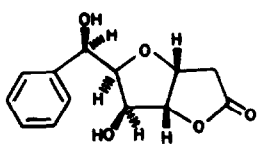
Abstract: A concise approach to the synthesis of anti-tumor compound, goniofufurone is described starting from dialdo-xylose. The key step in our synthesis is the spontaneous lactonisation and Michael-ring closure accompanying the Wittig reaction of the title ylide with the furanose-lactol having a free hydroxyl group at C-2.

Recently several bio-active compounds have been isolated from one source-ethanol extract of the stem-bark of goniothalamus giganteus (Annonaceae). Among them, two compounds - goniofufurone (**1**) and goniopypyrone (**2**) are unique in that they represent unusual natural skeletons and possess impressive cytotoxicity against human tumor cells. The constitution and relative configuration of (+)-**1** and (+)-**2** were established by spectroscopic and X-ray crystallographic analyses[1]. Absolute configuration of (+)-**1** has been established by synthesis of the natural product and its enantiomer[2]. Herein, we report a short and efficient route to **1** from the abundantly



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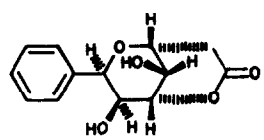

2

available chiral starting material, D-glucose. The approach is based on our recently disclosed methodology[3] to access functionalised 2-deoxy-3,6-anhydrohexono-1,4-lactones from aldehydo-sugars

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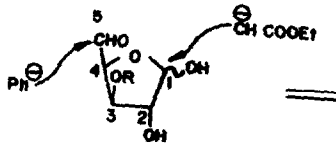
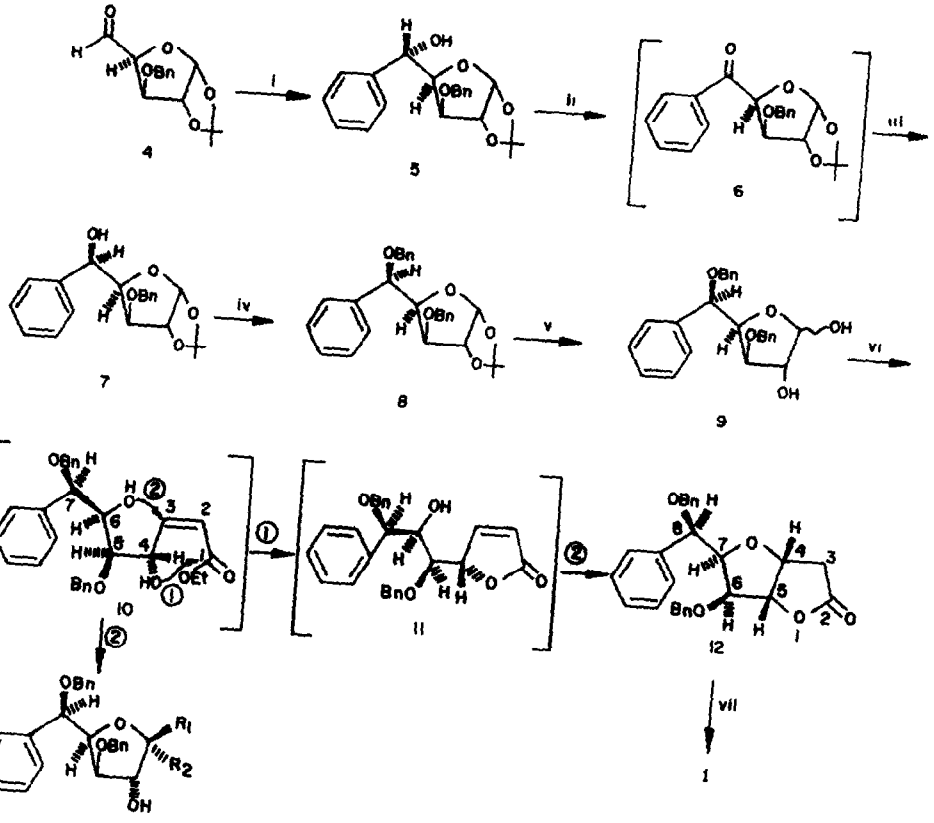
§ for Part 1, see ref.3.

This publication is affectionately and respectfully dedicated to Dr S N Balasubrahmanyam on the occasion of his retirement from service as Professor in Organic Chemistry at the Indian Institute of Science, Bangalore, India.

Scheme 1



Scheme 2



13 R_1 = H , R_2 = CH_2COOEt

14 R_2 = H , R_1 = CH COOEt

i) PhMgBr / THF ii) PDC/DCM iii) $NaBH_4$ / MeOH iv) BnBr / NaH / DMF

v) TFA / H_2O (3 2 v/v) vi) Ph_3P=CH COOEt/MeOH vii) Pd- /H_2 / MeOH

Retrosynthetic analysis (Scheme 1) indicated that two diastereoselective nucleophilic reactions, one at each end of dialdo-xylose, - (3)-phenyl carbanion addition from the Re face of C-5 carbonyl and α-C-glycosidation with the stabilised ylide at the lactol-end - are the key steps. Following this strategy, 3-O-benzyl-1,2-O-isopropylidene-α-D-xylopentodialdo-1,4-furanose[4] (4), readily available from D-glucose was treated with PhMgBr in THF (Scheme 2) following the reported procedure[5] to obtain the unwanted chelation-controlled product, 3-O-benzyl-1,2-O-isopropylidene-5-C-phenyl-α-L-idopentofuranose (5) and the desired C-5 epimer (7) in 12:1 ratio. This diastereomeric ratio could be improved in favour of the desired gluco-epimer by subjecting the mixture to an oxidation (CrO_3/Py)-reduction ($NaBH_4$) sequence to obtain (7) and (5) in 10:1 ratio. Separation by column chromatography (solvent A) afforded pure 7 The chemical shift of H-3 in the ^{1}H NMR spectrum was diagnostic in assigning the configuration at C-5. H-3 resonated significantly upfield (Δ δ0.36 ppm) in (5) of L-ido configuration compared to (7) of D-gluco configuration because of shielding effect of the anisotropic phenyl moiety in the former[6]. To prevent the benzylic hydroxyl in 7 from taking part in ensuing reactions, it was blocked as benzyl ether by treating 7 with NaH/Benzyl bromide to obtain 8. The 1,2-acetonide moiety was then hydrolysed to get the lactol (9) with hydroxyl free at C-2. The stage was now set for the Wittig reaction. We envisaged that the acyclic Wittig product, the cis-enoate (10) that would be formed can easily be converted to the bicyclic tetrahydrofurofuranone ring system characteristic of 1, since in (10) the hydroxyls required (4-OH and 6-OH) for ring closures are active (free) and those unwanted (5-OH and 7-OH) are inactive (blocked as benzyl ethers). In fact, to our pleasant surprise, when the Wittig reaction was carried out at -20°C in MeOH (conditions found ideal for getting cis-selectivity[7]) with ethoxycarbonylmethylenetriphenylphosphorane, the sole product isolated was goniofufurone bis-benzylether (12)! The very facile and neat manner in which this bis-cyclisation (lactonisation and Michael ring-closure) took place spontaneously deserves some comments. Usually Michael-type ring-closures in the case of α,β-unsaturated enoates require base-treatment. Exceptions are those systems where a pre-existing five membered ring (like the 2,3-O-isopropylidene moiety in ribofuranoses) strongly favours the formation of a second fused five membered ring[8]. We believe that in our case, the first five-membered ring to be formed was the γ-lactone as in 11 which acted as a driving force for the Michael ring-closure. If the order of ring closures were otherwise, we would have isolated at least a small amount of β-C-furanoside (14) which for steric reasons cannot lactonise, assuming that the α -C-furanoside (13) undergoes lactonisation. A similar sequence, i.e. lactonisation taking precedence over Michael, was observed in our earlier work[3]. O-Benzyl protecting groups from 12 were removed by catalytic hydrogenolysis to obtain goniofufurone (1), whose ^{1}H-NMR, ^{13}C-NMR and optical rotation data agree well with the reported values[1].

In conclusion, we have achieved an enantioselective synthesis of goniofufurone via an unusual spontaneous bis-cyclisation process, making use of the chirality in the abundantly and cheaply available D-glucose.

Acknowledgement: We thank Dr A V Rama Rao, Director for the excellent facilities made available and also for evincing keen interest and encouragement.

Experimental

General : Melting points were measured on a Fischer-Johns apparatus and are uncorrected NMR spectra were recorded with Varian Gemini-200 spectrometer (200 MHz for proton and 50 MHz for ^{13}C nuclei) in $CDCl_3$ solutions using TMS as internal standard for ^{1}H-spectra and central line of $CDCl_3$ triplet (77.0 ppm) for ^{13}C spectra. Chemical shifts are reported in δ values and J in Hz and NMR data for the aromatic region are omitted. Optical rotations were measured at 25°C using a Jasco DIP-370 digital polarimeter from 1% solution in chloroform unless otherwise mentioned. Chromatography was done using Acme Silica gel finer than 200 mesh. Reagents and solvents were purified and dried using standard methods. Elemental analyses were carried out by IDPL, Hyderabad. Solvent-combinations used in chromatography : 10% Ethyl acetate in hexane-solvent A, 10% ethyl acetate in toluene-solvent B and 50% ethyl acetate in toluene-solvent C.

3-O-Benzyl-1,2-O-isopropylidene-5-C-phenyl-α-D-glucopentofuranose (7):

To 0.09 g (3.776 mmol) of magnesium in 50 ml of dry THF bromobenzene (0.59 g, 0.4 ml, 3.77 mmol) was added dropwise under nitrogen atmosphere. After 30 minutes of stirring at room temperature. 3-O-Benzyl-1,2-O-isopropylidene-α-D-xylopentodialdo-1,4-furanose[4] (4) (0.7 g, 2.517 mmol) in 10 ml of dry THF was added slowly while cooling the flask in an ice bath. Stirring was continued until the starting material disappeared (TLC). The reaction mixture was poured into ice cold 0.5M HCl solution and extracted with CH_2Cl_2. Combined organic extracts were dried over Na_2SO_4 and concentrated to yield 0.8 g (89.3%) of 3-O-benzyl-1,2-O-isopropylidene-5-C-phenyl-α-L-idopentofuranose (5) and its C-5 epimer (7) in the ratio of 12:1. Rf (5) = 0.27 (solvent-B).

^{1}H NMR:(5) 6.0 (d, $J_{1,2}$=3.74, 1H, H-1), 5.05 (d, $J_{4,5}$=7.6, 1H, H-5), 4.58 (d, $J_{2,3}$=0, 1H, H-2), 4.28 (dd, $J_{3,4}$=3.2, 1H, H-4), 3.6 (d, 1H, H-3), 4.56 and 4.32 (2xd, J=11.0, 2H, benzylic CH_2), 1.5 and 1.32 (2xs, 3H each, isoprop. methyls).

The above diastereomeric mixture was refluxed with PDC (0.8 g, 2.25 mmol) in dry CH_2Cl_2 (50 ml) for 2 h to yield the phenyl ketone (6). Solvent was removed, 200 ml of ether added and filtered through silica gel column. After removal of ether, 20 ml MeOH was added to the residue and stirred with $NaBH_4$ (0.18 g, 4.6 mmol) for 3 h at room temperature. Methanol was removed under vacuo and the residue, 0.65 g (81%) was separated by column chromatography (solvent-A) to obtain 3-O-benzyl-1,2-O-isopropylidene-5-C-phenyl-α-D-glucopentofuranose (7) as a syrup and its C-5 epimer (5) in the ratio of 10:1. $[\alpha]_D$ (7) -93°, Rf (7) = 0.49 (solvent-B).

^{1}H NMR:(7) 5.96 (d, $J_{1,2}$=3.8, 1H, H-1), 5.02 (d, $J_{4,5}$=6.7, 1H, H-5), 4.56 (d, $J_{2,3}$=0, 1H, H-2), 4.25 (dd, $J_{3,4}$=3.2, 1H, H-4), 3.96 (d, 1H, H-3), 4.46 and 4.67 (2xd, J=11.5, 2H, benzylic CH_2), 1.28 and 1.43 (2xs, 2x3H, acetonide methyls).

Elemental Analysis: $C_{21}H_{24}O_5$ requires C, 70.78; H, 6.74. Found: C, 70.2; H, 6.69.

3,5-Di-O-benzyl-1,2-O-isopropylidene-5-C-phenyl-α-D-glucopentofuranose (8):

To a slurry of pentane-washed NaH (0.053 g, 2.2 mmol) in dry DMF, a solution of 3-O-benzyl-1,2-O-isopropylidene-5-C-phenyl-α-D-glucopentofuranose (7) (0.6 g, 1.68 mmol) in 5 ml of dry DMF was added at 0°C. To this suspension, benzyl bromide (0.32 g, 0.23 ml, 1.87 mmol) was added dropwise and stirring was continued for an additional one hour. Excess NaH was quenched by slow addition of MeOH and the reaction mixture was poured into ice-cold water and extracted with CH_2Cl_2. Combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure which afforded a white solid (0.7 g, 93.3%). Recrystallised from CH_2Cl_2/hexane (1:20 v/v) m.p. 85-86°C, $[\alpha]_D$ =49.2, Rf = 0.72 (solvent-B).

^1H NMR: 5.86 (d, $J_{1,2}$=3.8, 1H, H-1), 4.73 (d, $J_{4,5}$=8.3, 1H, H-5), 4.59 (d, $J_{2,3}$=0, 1H, H-2), 4.36 (dd, $J_{3,4}$ =2.09, 1H, H-4), 4.24 (d, 1H, H3), 4.66 (dd, J=11.7, 2H, benzylic CH_2), 4.37 (dd, J=11.1, 2H, other benzylic CH_2), 1.41 and 1.21 (2xs, isoprop. methyls). ^{13}C NMR: 111.4, 104.9, 82.85, 82.1, 81.8, 78.2, 72.3, 70.2, 26.7 and 26.2.

Elemental Analysis: $C_{28}H_{30}O_5$ requires C, 75.33; H, 6.72. Found: C, 74.93; H, 6.67

3,5-Di-O-benzyl-5-C-phenyl-α-D-glucopentofuranose (9):

3,5-Di-O-benzyl-1,2-O-isopropylidene-5-C-phenyl- α-D-glucopentofuranose (8) (0.7 g, 1.57 mmol) was dissolved in 3 ml of trifluoroacetic acid/water (2:1 mixture) and stirred at room temperature for 4 h. The reaction mixture was neutralised with saturated $NaHCO_3$ solution and extracted with ethyl acetate. Combined extracts were washed with brine and dried over Na_2SO_4. Evaporation of the solvent under vacuo furnished the lactol (8) as anomeric mixture (0.4 g, 62.8%). Recrystallised from CH_2Cl_2/hexane m.p. 98-99°C, $[\alpha]_D$=-8.2°, Rf = 0.85 (solvent-C).

^1H NMR data was not discernable because of overlap of signals due to two anomers.

^{13}C NMR data: α-Anomer; 96.24, 83.23, 81.41, 78.40, 74.15, 72.24, 70.15. β-Anomer; 103.07, 84.04, 81.99, 79.24, 76.99, 72.93, 70.15.

Elemental Analysis: $C_{25}H_{26}O_5$ requires C, 73.89; H, 6.4. Found: C, 73.37; H, 6.28.

6,8-Di-O-benzyl goniofufurone (12):

3,5-Di-O-benzyl-5-C-phenyl- α-D-glucopentofuranose (8) (0.2 g, 0.49 mmol) in methanol (5 ml) was cooled to -20°C and ethoxycarbonylmethylenetriphenylphosphorane (0.26 g, 0.76 mmol) was added and stirred for 8 h at the same temperature. The solvent was removed under vacuo and purified by column chromatography to obtain 150 mg (70.8%) of 6,8-di-O-benzyl goniofufurone (12) as colourless syrup. $[\alpha]_D$:-5.8°, Rf = 0.62 (solvent-B).

^1H NMR: 4.82 (m, 2H, H-4 and H-8), 4.65 (m, 3H, benzylic CH_2 and H-5), 4.4 (m, 2H, benzylic CH-A and H-6), 4.15 (dd, J=4.1 and 12, 1H, H-7), 4.21 (d, J=13.0, 1H, benzylic CH-B), 2.55 (dd, J=3.8 and 18.1, 1H, H-3A), 2.45 (d, J=18.1, 1H, H-3B). ^{13}C-NMR: 85.0, 83.5, 81.1, 78.2, 77.0, 73.3, 70.3 and 35.9.

Elemental Analysis: $C_{27}H_{26}O_5$ requires C, 75.33; H, 6.09. Found: C, 74.96; H, 6.03.

(+)-Goniofufurone (1):

6,8-Di-O-benzyl goniofufurone **(12)** (100 mg, 0.23 mmol) was dissolved in 5 ml of MeOH to which 20 mg of 10% Pd-C was added and magnetically stirred under hydrogen atmosphere for 12 h. The catalyst was filtered off and the solvent removed under vacuo. The residue was recrystallised from CH_2Cl_2/hexane (1:20 v/v) yield 0.05 g (86.2%). m.p. 149-150°C. $[\alpha]_D$ = +10.5 (c 0.6, EtOH). lit.[1] $[\alpha]_D$ +9.0 (c, 0.5 in EtOH). Rf: 0.3 (solvent-C).
^1H NMR: 2.76 (dd, J=18.6, 5.9, 1H, H-3a), 2.66 (br.d, J=18.6, 1H, H-3b), 5.15 (m, 1H, H-4), 4.9 (d, J=4.2, 1H, H-5), 4.4 (d, J=2.7, 1H, H-6), 4.12 (dd, J=4.8, 2.7, 1H, H-7), 5.21 (d, J=4.8, 1H, H-8). ^{13}C NMR: 175.3, 87.4, 83.0, 77.3, 74.5, 73.5 and 36.1.
Elemental Analysis: $C_{13}H_{14}O_5$ requires C, 62.4; H, 5.6. Found: C, 62.21; H, 5.54

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