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Radical Reactions on Furanoside acetals : A Formal Synthesis of (-)-Canadensolide from D-mannose

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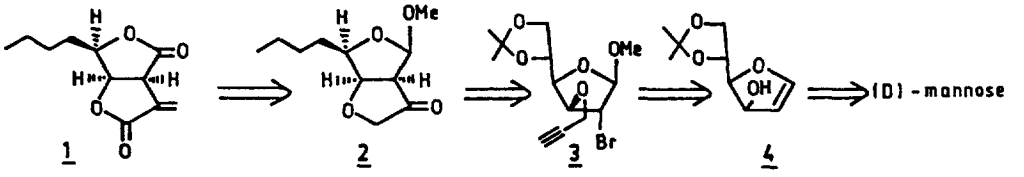
Abstract : By adaption of an intramolecular radical cyclisation protocol to the furanoid glycal derivative **3** derived from D-mannose, synthesis of the crucial bicyclo[3.3.0]octane system **6** is reported. A sequence of reactions on this key synthon **6**, leading to the formal synthesis of (-)-canadensolide (**1**) is described.

The utility of radical reactions[1] on carbohydrate[2] derived 'chiral templates' is highly fascinating owing to the mildness and high stereocontrol achieved, particularly for the creation of bicyclic systems. By adaption of a regio- and stereoselective[3] intramolecular radical cyclisation protocol to the 'chiron' derived from D-mannose, we herein, describe a formal synthesis of (-)-canadensolide (**1**). **1**, a fungal metabolite possessing antigerminative activity against fungi, was isolated[4] from Penicillium canadense. It's gross structure having an α-methylene bis(butyrolactone) moiety was defined by spectroscopic studies[4] and proved by synthesis[5]. The stereochemical assignments at the C-2, C-3 and C-4 stereocentres in **1** were derived by Fraser-Reid[6], starting from D-glucose. The unique structural features of **1** have resulted in several earlier syntheses[5-11]. We have previously reported the synthesis of **1**, using an intramolecular radical cyclisation approach on the 'chiron' derived from 'diacetone glucose'[12].

The disconnection approach for **1** (Scheme 1) revealed that it could be made from the bicyclic system **2**, which in turn would come from the halide **3** by a well defined intramolecular radical cyclisation reaction, while the acetonide moiety in **3** would help in incorporating the requisite C-4 side chain. The halide **3** in turn could conveniently be made by halo acetalisation reaction on the furanoid glycal **4** derived from D-mannose.

Scheme - 1

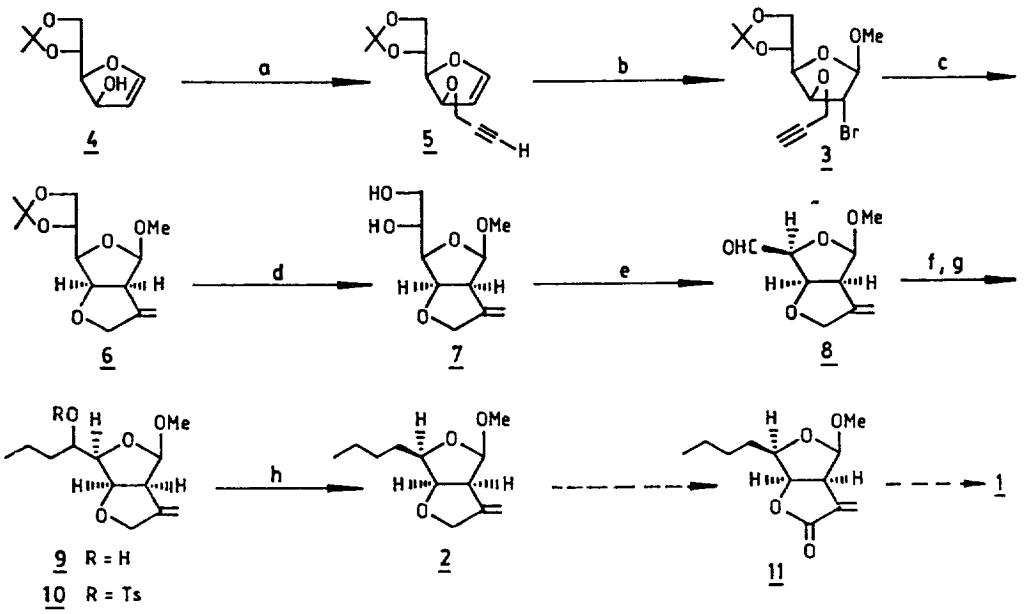


Thus, the basic strategy in the synthesis of **1** starting from D-mannose involves a) conversion of glycal **4** to halide **3**, b) radical cyclisation of halide **3** to the bicyclic system with correct stereochemistry, c) extension of side chain at C-5 in **6** and d) finally oxidation

at C-1 and allylic carbon centres.

Accordingly 1,2:5,6-di-O-isopropylidene-D-mannose[13], by a known sequence of reactions viz. a) treatment with Ph_3P in CCl_4 and b) base catalysed fragmentation under Ireland conditions[14] using lithium in liquid ammonia and quenching with anhydrous ammonium chloride, was converted into the requisite furanoid glycal **4**. Alkylation of C-3 hydroxy group in **4** (Scheme 2) with propargyl bromide (NaH, THF) gave **5** (92%), $[\alpha]_D$ -85.8 (c 1, $CHCl_3$). The stereo-

Scheme - 2



a) NaH, C_3H_3Br, THF; b) NBS, MeOH, CH_3CN, 0°C, c) Bu_3SnCl, AIBN, $NaCNBH_3$, t-BuOH, 85°C; d) 60% aq. AcOH, RT; e) $NaIO_4$, MeOH; f) n-C_3H_7MgBr, THF; g) TsCl, Pyridine; h) Zn, NaI, dimethoxyethane, 83°C.

selective halo acetalisation[15] of **5** with 1 eq. of NBS in the presence of 10 eq. of methanol in CH_3CN afforded 1,2-trans-β-D-glycoside **3**[16,17] (82%), $[\alpha]_D$ -60.8 (c 1, $CHCl_3$) along eiyh minot α-D-glycoside **3a** (7%), $[\alpha]_D$ +35 (c 1.0, $CHCl_3$. The β-anomeric configuration of **3** was evident both from the negative specific rotation value as well as the ^{1}H-NMR spectrum from the appearence of H-1 at δ 5.19 as a singlet, and the acetylenic proton at δ 2.56 as a triplet.

The 2-bromo sugar **3** underwent the crucial regio- and stereoselective radical cyclisation[1,3] on treatment with catalytic amount of Bu_3SnCl[18] and AIBN in presence of 2 eq. of sodium cyanoborohydride[19] in refluxing t-butanol to afford the bicyclo[3.3.0]octane system **6** in 78% yield, $[\alpha]_D$ -44 (c 1, $CHCl_3$), where the requisite stereochemistry in **6** was derived[3] from the C-3 carbon bearing the propargylic appendage. The ^{1}H NMR spectrum of **6** indicated the presence of exo-methylene protons (2H) at δ 4.99 (brs), the H-6 proton at δ 4.92 as a doublet ($J_{5,6}$ 6.15 Hz), along with the absence of acetylenic proton, thus giving evidence

for the formation of **6**. The cyclisation reaction also resulted in the formation of methyl 2-deoxy-5,6-O-isopropylidene-3-O-(3'-propynyl)- β-D-arabino-hexofuranoside **(6a)** in 8% yield.

At this stage, the incorporation of C-4 side chain was envisaged by the transformation of the acetonide moiety in **6**. Accordingly, acid catalysed hydrolysis (60% aq. AcOH) of **6**, followed by oxidative cleavage ($NaIO_4$, MeOH) of **7** furnished the aldehyde **8** (68%). Treatment of **8** with freshly prepared n-propyl magnesium bromide in THF at room temperature gave the carbinol **9** (76%). **9** on tosylation with TsCl in pyridine, followed by reductive detosylation of resulting tosylate **10** with 10 eq. of zinc in presence of 5 eq. of NaI[20] (dimethoxyethane, 85°C) gave the required furan **2** in 58% yield. The specific rotation value -161 (c 0.5, $CHCl_3$) and the ^1H NMR spectroscopic data of **2** were in full agreement with the values reported in literature[5]. Since the conversion of **2** to **1** through the lactone **11** has been earlier reported by us[5], synthesis of **2** formally constitutes the total synthesis of **1**.

In conclusion, it is pertinent to mention that a formal synthesis of **1** has been achieved through the synthesis of **2** by the adaption of an intramolecular radical cyclisation protocol on the carbohydrate derived chiron. This approach should be of use for the synthesis of several other related natural products.

Experimental :

General Methods : NMR spectra were recorded for solutions in $CDCl_3$ (internal Me_4Si) with a Varian 200 Gemini spectrometer (^1H, 200 MHz). Optical rotations were measured with a JASCO DIP 360 or 370 polarimeter. Silica gel (60-120 and finer than 200 mesh, Aceme) was used for column chromatography. TLC was performed on silica gel 60 F_{254} (Merck) with detection using a solution of 2% of phosphomolybdic acid and 1% $Ce_2SO_4.4H_2O$ in aq. 20% H_2SO_4 at 130°C. All reactions were carried out in dry solvents under anhydrous conditions unless otherwise stated.

1,4-Anhdro-2-deoxy-5,6-O-isopropylidene-3-O-(3'-propynyl)-D-arabino-hex-1-enitol (5).- To a stirred suspension of sodium hydride (2.4 g, 50 mmol, 50% suspension) in dry THF (50 ml) at 0°C, a solution of **4** (4.65 g, 25 mmol) in THF (10 ml) was added. After stirring at room temperature for 30 min, propargyl bromide (3.57 g, 30 mmol) was added and stirred the reaction mixture for 4 h. It was quenched with aq. ammonium chloride solution and extracted with ether. Ethereal layer was washed with water, dried (Na_2SO_4), evaporated and the residue obtained purified by column chromatography (Si-gel, 9:1 pet.ether:EtOAc) to afford **5** (5.14 g, 92%) as a syrup; $[\alpha]_D$ -85.8 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.39, 1.42 (2s, 6H), 2.42 (t, 1H, $J_{2'',3''}$ 1.9 Hz, H-3''), 3.95, 4.1 (dd, 1H each, H-6,6'), 4.18 (t, 2H, 1'',1''a), 4.35-4.6 (m, 2H, H-4,5), 4.75 (dd, 1H, $J_{3,4}$ 6.2 Hz, H-3), 5.3 (t, 1H, $J_{2,3}$ 2.49 Hz, H-2), 6.62 (d, 1H, $J_{1,2}$ 2.49 Hz, H-1). Elemental Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.04; H, 7.79. Found: C, 64.26; H, 7.92.

Methyl 2-bromo-2-deoxy-5,6-O-isopropylidene 3-O-(3'-propynyl)-β-D-glucofuranoside (3).- A solution of **5** (5 g, 22.3 mmol) and methanol (7.14 g, 223 mmol) in acetonitrile (75 ml) was treated with N-bromosuccinimide (3.92 g, 22.3 mmol) at 0°C and stirred at room temperature for 1h. Solvent was removed, residue taken in dichloromethane and washed with water, hypo and water. It was dried (Na_2SO_4), evaporated and residue obtained was chromatographically

purified (Si-gel, 5:1 pet.ether:EtOAc) to furnish **3** (6.13 g, 82%) as a syrup; $[\alpha]_D$ -60.8 (c 1.0, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ 1.39, 1.45 (2s, 6H), 2.56 (t, 1H, $J_{1'',3''}$ 1.98 Hz, H-3''), 3.41 (s, 3H), 4.0-4.15 (m, 2H, H-6,6'), 4.21 (s, 1H, H-2), 4.29 (d, 2H, H-1',1''a), 4.3-4.4 (m, 2H, H-3,5), 4.52 (dd, 1H, H-4), 5.19 (s, 1H, H-1). Elemental Anal. Calcd. for $C_{13}H_{19}BrO_5$: C, 46.53; H, 5.68. Found: C, 46.57; H, 5.71.

Eluted second was methyl 2-bromo-2-deoxy-5,6-O-isopropylidene-3-O-(3'-propynyl)-α-D-glucofuranoside (**3a**) (0.52 g, 7%) as a syrup; $[\alpha]_D$ +35 (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ1.35, 1.4 (2s, 6H), 2.5 (t, 1H, H-3'), 3.45 (s, 3H), 3.9-4.50 (m, 8H, H-2,3,4,5,6,6',1',1'a), 4.98 (d, 1H, $J_{1,2}$ 2.4 Hz, H-1).

(1R,4'R,5R,8S)-8-(2',2'-Dimethyl-1',3'-dioxolan-4'-yl-6-O- β-methyl-4-methylene-2,7-dioxabicyclo-[3.3.0]octane (6).- A mixture of **3** (6 g, 17.9 mmol), tributyltin chloride (0.1 mmol) and sodium cyanoborohydride (2.24 g, 35.8 mmol) in t-butanol (150 ml) was heated at reflux and treated with AIBN (0.1 mmol). After 24 h, solvent was removed residue purified by column chromatography (Si-gel, 4:1 pet.ether:EtOAc) first to give methyl 2-deoxy-5,6-O-isopropylidene-3-O-(3'-propynyl)-β-D-arabinohexofuranoside (**6a**) (0.36 g, 8%) as a syrup; $[\alpha]_D$ -89 (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ1.32, 1.42 (2s, 6H), 2.12 (brt, 2H, H-2), 2.35 (brt, 1H, H-3'), 3.32 (s, 3H), 3.9-4.4 (m, 8H, H-3,4,5,6,6',1',1'a), 5.0 (d, 1H, $J_{1,2}$ 4.9 Hz, H-1). Elemental Anal. Calcd. for $C_{13}H_{20}O_5$: C, 60.78; H, 7.83. Found: C, 60.91; H, 7.86.

Eluted second was **6** (3.57 g, 78%) as a syrup; $[\alpha]_D$ -44 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.37, 1.42 (2s, 6H), 3.3-3.4 (m, 1H, H-1), 3.35 (s, 3H), 3.45-4.5 (m, 6H, H-3,3a,4',5,5',5'a), 4.62 (dd, 1H, $J_{1,8}$ 3.28 Hz, $J_{4',8}$ 4.9 Hz, H-8), 4.92 (d, 1H, $J_{5,6}$ 6.15 Hz, H-6), 4.99 (brs, 2H, vinylic). Elemental Anal. Cacld. for $C_{13}H_{20}O_5$: C, 60.78; H, 7.81. Found: C, 60.91; H, 7.86.

(1R,5R,8S)-8-Formyl-6-O- β-methyl-4-methylene-2,7-dioxabicyclo[3.3.0]octane (8).- A solution of **6** (3.1 g, 12.1 mmol) in 60% aq. AcOH was stirred at rom temperature for 12 h. It was diluted with water and extracted into ethyl acetate. Organic layer was washed with water, sodium bicarbonate solution and water. It was dried (Na_2SO_4) and evaporated to give **7** (1.77 g, 68%) as a syrup.

A mixture of the above diol **7** (1.5 g, 6.94 mmol) and sodium periodate (2.97 g, 13.88 mmol) in methanol (20 ml) containing few drops of water was stirred at room temperature for 3 h. It was filtered and methanol removed. Purification of the residue obtained by column chromatography (Si-gel, 2:3 pet.ether:EtOAc) gave **8** (0.86 g, 68%) as a syrup; $[\alpha]_D$ -78 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 3.28-3.42 (m, 1H, H-5), 3.37 (s, 3H), 3.9-4.5 (m, 3H, H-1,3,3a), 4.7-5.22 (m, 4H, H-6,8 2 vinylic) 9.7 (s, 1H, CHO). Elemental Anal. Cacld. for $C_9H_{12}O_4$: C, 58.54; H, 6.49. Found: C, 58.68; H, 6.56.

(1R,5S,8S)-8-(1'R,S-Hydroxybutyl)-6-O- β -methyl-4-methylene-2,7-dioxabicyclo[3.3.0]octane (9).- A freshly preapred solution of n-propyl magnesium bromide [made from n-propyl bromide (0.52 g, 4.29 mmol) and magnesium (0.105 g, 4.29 mmol)] in dry THF (10 ml) was added to a stirred solution of **8** (0.7 g, 4.29 mmol) in dry THF (10 ml) at 0°C under N_2 atmosphere. After 4 h, it was quenched with ammonium chloride solution and extracted into chloroform. Organic layer was washed withwater, dried (Na_2SO_4) evaporated and residue obtained

was purified by column chromatography (Si-gel, 3:1 pet.ether:EtOAc) to afford **9** (0.74 g, 76%) as a syrup; $[\alpha]_D$ -93 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 0.8-0.98 (m, 3H), 1.2-1.7 (m, 4H), 3.22-3.38 (m, 4H), 3.57-4.45 (m, 4H), 4.62-4.78 (m, 1H), 4.9 (s, 1H, H-1), 5.07, 5.13 (2s, 2H, vinyclic). Elemental Anal. Calcd. for $C_{12}H_{20}O_4$: C, 63.08; H, 8.7°. Found: C, 63.13; H, 8.83.

(1R,5S,8R)-8-(1'-Butanyl)-6-O- β -methyl-4-methylene-2,7-dioxabicyclo[3.3.30]octane (2).- A mixture of **9** (0.6 g, 2.63 mmol) and p-TsCl (0.6 g, 3.156 mmol) in pyridine (2 ml) was stirred at room temperature for 30 h. The reaction mixture was diluted with chloroform, washed with water, cold dil. 5% HCl and water. Organic layer was dried (Na_2SO_4) and evaporated to furnish (1R,5S,8S)-6-O-β-methyl-4-methylene-8-(1'-p-toluenesulfonyloxybutyl)-2,7-dioxabicyclo-[3.3.0]octane (**10**) (0.79 g, 79%). ^1H NMR ($CDCl_3$): δ 0.9 (t, 3H), 1.25-2.05 (m, 6H), 2.4 (s, 3H), 3.15-4.3 (m, 4H, H-5, OCH_3), 3.85-4.45 (m, 4H, H-1, 3, 3a, 4), 4.75 (s, 1H, H-1), 4.95-5.15 (m, 3H, H-1', vinylic), 7.25 (d, 2H, ArH), 7.9 (d, 2H, ArH).

A mixture of **10** (0.65 g, 1.70 mmol) sodium iodide (1.27 g, 8.5 mmol) and activated zinc (1.1 g, 17 mmol) in DME (5 ml) was heated at reflux for 3 h. The reaction mixture was cooled to room temperature, filtered through celite and diluted with chloroform. The organic layer was washed with water, hypo, water, dried (Na_2SO_4) and evaporated. The residue obtained was purified by column chromatography (Si-gel, 15:1 pet.ether-EtOAc) to afford **2** (0.209 g, 58%) as a syrup. $[\alpha]_D$ -161 (c 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 0.9 (t, 3H), 1.15-1.6 (m, 6H), 3.32 (brt, 1H, H-5), 3.38 (s, 3H), 4.2-4.35 (m, 2H, H-3, 3a), 4.42 (dd, 1H, H-1), 4.61 (dd, 1H, H-8), 4.85 (s, 1H, H-6), 5.05, 5.15 (2s, 2H, vinylic). Elemental Anal. Calcd. for $C_{12}H_{20}O_3$: C, 67.99; H, 9.38. Found: C, 67.89; H, 9.5.

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