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# STEREOSELECTIVE SYNTHESIS OF (-)-CANADENSOLIDE FROM D-GLUCOSE

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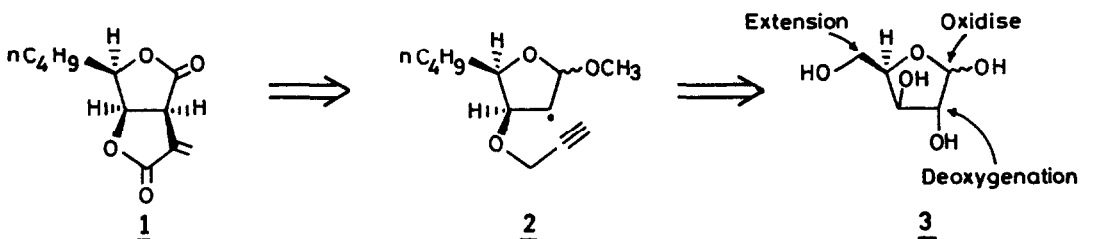
**Abstract:** A simple and stereoselective synthesis of (-)-canadenosolide starting from D-glucose, through a radical mediated cyclisation, has been described.

(-)Canadensolide (1), a naturally occurring mould metabolite was isolated from Penicillium canadense and found to show antigerminative activity against fungi[1]. It's gross structural assignment was carried out by McCorkindale[1] using spectral and degradative studies, while Yoshioki et al[2] established its relative stereochemistry by a racemic synthesis. Fraser-Reid et al[3] have assigned its absolute stereochemistry as 2S,3R and 4R by its stereoselective synthesis from a carbohydrate precursor. The unusual and unique α-methylene bis(butyrolactone) system present in 1 has attracted much attention which resulted in several total syntheses[2-7]. Herein we report a total synthesis of 1 from easily available D-glucose employing a regio- and stereoselective C-C bond formation by a radical mediated cyclisation.

A synthetic design for this interesting system involves the stereoselective construction of the required skeleton and the introduction of exomethylene group. As can be envisaged from the retrosynthetic analysis the radical intermediate (2) would lead[8] to the regio- and stereoselective formation of the C-C bond, while simultaneously incorporating the exomethylene group. 2 could be obtained by transformations such as extension of side-chain at C-5 and radical generation at C-2 on sugar, 3 as shown in Sceme 1.

**Scheme I**

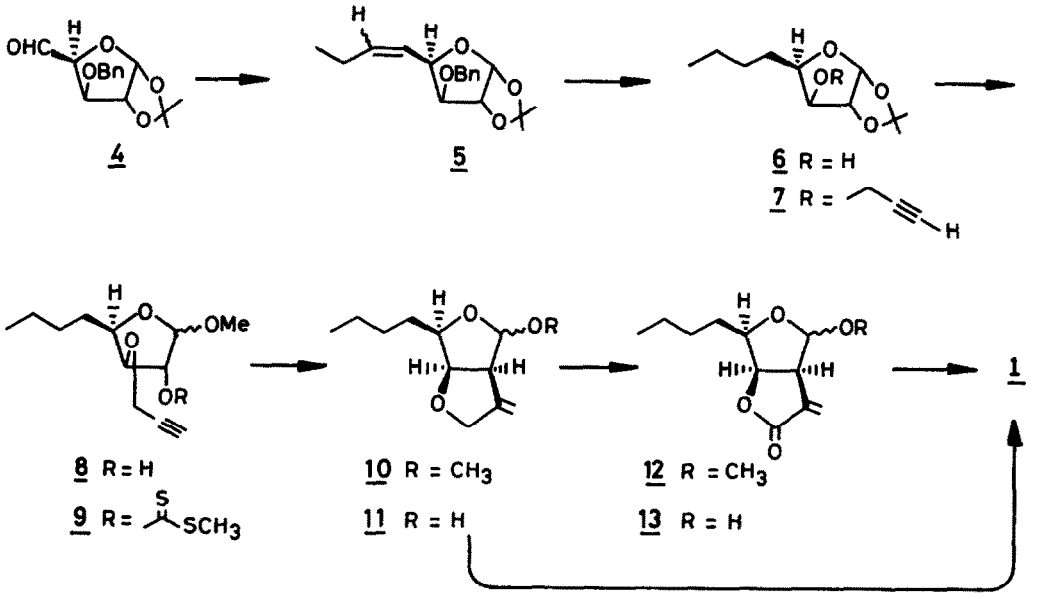



1 2 3

For the present purpose, aldehyde 4[9], with a benzyl ether at C-3 position was chosen as the appropriate starting unit because the C-5 aldehyde functionality would serve as a handle in the chain extension while hydrogenation of olefinic bond in 5 simultaneously lead to saturation of olefin site as well as liberation of free hydroxy at C-3. Thus, the first objective of side-chain extension on aldehyde 4, obtained in 4 steps from D-glucose, was achieved by a Wittig olefination reaction with n-propyltriphenylphosphonium bromide and n-BuLi in THF to afford 5 as an E/Z

mixture in 51% yield (Scheme 2). Catalytic hydrogenation of resultant olefin **5** with 10% Pd-C in ethanol afforded **6**, where debenzylation also occured simultaneously at C-3 to give a free

**Scheme II**




hydroxy compound, required for further transformations. C-3 hydroxyl group in **6** was protected as its propargyl ether derivative, on reaction with NaH and propargyl bromide in THF to afford **7**. This propargyl group at C-3, would be taken to our advantage at later stages, to perform two different functions viz. as a protecting group during the transformations at C-1, C-2 and to provide the required carbon skeleton of **1** through the intramolecular radical cyclisation.

At this stage it was aimed at the generation of radical intermediate **2** obtainable from C-2 hydroxy of sugar, which would lead to the cis-fused bicyclo[3.3.0]octan[10] system **10**, leading to **1**.

Accordingly the liberation of free hydroxyl at C-2 was achieved by methanolysis of **7** with Amberlite $H^+$ resin at reflux to afford **8** in 74% yield, which on treatment with NaH, $CS_2$ and MeI was converted to the xanthate ester **9** in 80% yield. As anticipated compound **9** underwent the crucial radical cyclisation[11,12] with n-$Bu_3SnH$ and cat. amount of AIBN in refluxing benzene to afford the desired cis-fused bicyclic compound **10** as a single stereoisomer in 84% yield.

Having obtained the bicyclic compound **10** in pure form, it was next aimed at the introduction of bis(1,4-butyrolactone) system leading to **1**. According to the plan, acid hydrolysis of **10** with conc. HCl in 50% aq. AcOH and simultaneous oxidation of the resultant lactol (**11**) with $CrO_3$-pyridine in $CH_2Cl_2$ at 40°C afforded a complex mixture along with **1** in very poor yield. Alternatively a stepwise oxidation of **10** was undertaken. Accordingly **10** was subjected to oxidation with $CrO_3$-pyridine in $CH_2Cl_2$ at 40°C to afford **12** in 74% yield. Hydrolysis of the lactone **12**

with conc. HCl in 50% aq. AcOH and oxidation of resultant lactol (**13**) with PCC furnished **1** in 70% yield, whose spectral data were in full agreement with reported values[3].

## Experimental

$^1$H NMR spectra were recorded on Varian FT 80-A, Jeol PMX 90 or Bruker WH 300 instruments using deutero chloroform as solvent with TMS as internal standard. IR spectra were recorded on Perkin-Elmer 683 or 1310 spectrophotometer. Optical rotations were measured on a JASCO DIP 360 or 370 polarimeter. Mass spectra were recorded on Finnigan Mat 1210 double focussing spectrometer and VG Micromass 7070H instrument.

**3-O-Benzyl-5,6-dideoxy-6-C-ethyl-1,2-O-isopropylidene-α-D-xylo-hex-5-enofuranose (5):**

A stirred and cooled (0°) suspension of n-propyltriphenylphosphonium bromide (5.8 g, 15 mmol) in dry THF (30 mL) under $N_2$ atmosphere was treated with n-BuLi (5.3 mL, 15 mmol; 2.8N hexane solution) and stirred at room temperature for 30 min. A solution of aldehyde **4** (3 g, 14.3 mmol) in dry THF (10 mL) was added dropwise and stirred for an additional 1 h. The reaction mixture was quenched with aq. ammonium chloride solution and extracted with ether. Organic layer was washed with water, brine, dried ($Na_2SO_4$) and evaporated. Purification of the residue by column chromatography (silica gel, 5% EtOAc in pet.ether) resulted **5** (2.2 g) in 51% yield as an E:Z mixture. $^1$H NMR($CDCl_3$): δ 0.99 (t, 3H, $CH_3$), 1.36 (s, 3H, $CH_3$), 1.56 (s, 3H, $CH_3$), 1.90-2.44 (m, 2H, allylic), 3.92 (d, 1H, H-3), 4.8 (s, 3H, $PhC\underline{H}_2$, H-2), 5.01 (m, 1H, H-4), 5.60-5.90 (m, 2H, olefinic), 6.01 (d, 1H, H-1), 7.40 (brs, 5H, Ph). $M^+$ 289 ($M^+$-$CH_3$). $[\alpha]_D$ -99.4 (c 1.17, $CHCl_3$).

**5-Deoxy-1,2-O-isopropylidene-5-C-(n-propyl)-α-D-xylofuranose (6):**

A suspension of 10% Pd-C (0.2 g) and olefin (**5**, 2 g) in ethanol (20 mL) was subjected to hydrogenation at 40 psi and room temperature for 7 h. The reaction mixture was filtered and filtrate on evaporation furnished **6** (1.22 g) in 86% yield. $^1$H NMR($CDCl_3$): δ 0.98 (t, 3H, $CH_3$), 1.20-1.64 (m, 12H), 2.00 (brs, 1H, OH), 3.95-4.24 (m, 2H, H-3 and H-4), 4.48 (d, 1H, H-2), 5.88 (d, 1H, H-1). IR(Neat): 3450 $cm^{-1}$ (OH). $M^+$ 20 ($M^+$-$CH_3$). $[\alpha]_D$ -12.5 (c 0.91, $CHCl_3$).

**5-Deoxy-1,2-O-isopropylidene-5-C-(n-propyl)-3-O-(3'-propynyl)-α-D-xylofuranose (7):**

A solution of **6** (1.2 g, 5.5 mmol) in dry THF (10 mL) was added to a suspension of sodium hydride (0.480 g, 10 mmol, 50% suspension) in dry THF (10 mL) at 0° and stirred at room temperature. After 30 min. propargyl bromide (0.726 g, 6 mmol) was added at 0°C and stirred for 1 h. The reaction mixture was quenched with aq. ammonium chloride solution and extracted with ether. Organic layer was washed with water, brine and dried ($Na_2SO_4$). Evaporation of solvent and purification of residue by column chromatography (silica gel, 5% EtOAc in pet. ether) afforded **7** (1.1 g) in 78% yield as a liquid. $^1$H NMR($CDCl_3$): δ 0.98 (t, 3H, $CH_3$), 1.24-1.76 (m, 12H), 2.88 (t, 1H), 3.90 (d, 1H), 4.10-4.24 (m, 3H), 4.64 (d, 1H), 5.90 (d, 1H, H-1). IR(Neat): 3430 (C≡C-H) and 2120 $cm^{-1}$ (C≡C). $M^+$ 239 ($M^+$-15). $[\alpha]_D$ -52.5 (c 1.2 g, $CHCl_3$).

Analysis calcd. for $C_{11}H_{22}O_4$: C, 60.52; H, 10.16. Found: C, 60.30; H, 10.3%.

**Methyl—5-deoxy—5-C-(n-propyl)-3-O-(3'-propynyl)-α,β-D-xylo furanoside (8):**

A mixture of **7** (1 g, 3.9 mmol) and Amberlite $H^+$ resin (0.6 g) in methanol (15 mL) was heated at reflux for 8 h. The reaction mixture was cooled, filtered and washed with methanol.

Filtrate was evaporated and residue purified by column chromatography (silica gel) to give **8** in two fractions in 79% yield.

Fraction A: [α-anomer **8a**, 0.4 g, 8% EtOAc in pet. ether). $^1$H NMR($CDCl_3$): δ 0.98 (t, 3H, $CH_3$), 1.20-1.73 (m, 6H), 2.44 (t, 1H), 2.82 (brs, 1H), 3.44 (s, 3H), 3.9 (m, 1H), 4.06-4.31 (m, 3H), 4.92 (d, 1H). IR(Neat): 3420-3450 (OH), 3130 (C ≡C-H) and 2120 $cm^{-1}$ (C≡C). $M^+$ 197 ($M^+$-$OCH_3$). $[\alpha]_D$ +68.4 (c 1.03, $CHCl_3$).

Fraction B: β-anomer **8b**, 0.31o g, 9% EtOAc in pet. ether). $^1$H NMR($CDCl_3$): δ0.98 (t, 3H), 1.22-1.76 (m, 12H), 2.47 (t, 1H), 3.44 (s, 3H), 4.0 (m, 1H), 4.25-4.70 (m, 3H), 4.79 (s, 1H). $[\alpha]_D$ -70° (c 1.15, $CHCl_3$).

**Methyl-5-deoxy-2-O-[(S-methylthio)thiocarbonyl]-5-C-(n-propyl)-3-O-(3-propynyl)-α,β-D-xylofuranoside (9):**

A stirred suspension of sodium hydride (0.0576 g, 1.2 mmol, 50% dispersion) in dry THF (5 mL) at 0° under $N_2$ atmosphere was treated with a solution of **8** (0.22 g, 1 mmol) in THF (5 mL) and stirred at room temperature for 30 min. Carbondisulphide (0.691 g, 1.2 mmol) was added at 0°, stirred at room temperature and after 1 h it was cooled to 0°, treated with methyl iodide and stirred for 1 h at room temperature. Reaction mixture was quenched with aq. ammonium chloride and extracted with ether. Ethereal layer was washed with water, brine and dried ($Na_2SO_4$). Solvent was evaporated and residue was purified by column chromatography (silica gel, 4% EtOAc in pet ether) to afford **9** (0.254 g) in 80% yield.

α-Anomer: $^1$H NMR($CDCl_3$): δ 0.91 (t, 3H), 1.20-1.70 (m, 6H), 2.25 (t, 1H), 2.57 (s, 3H), 3.22 (s, 3H), 4.20-4.53 (m, 4H), 5.21 (d, 1H), 5.66 (t, 1H). IR(Neat): 3130 (C ≡C-H) and 2130 $cm^{-1}$ (C≡C). $M^+$ 287 ($M^+$-$OCH_3$). $[\alpha]_D$ +78.4 (c 0.575, $CHCl_3$).

β-anomer: $^1$H NMR($CDCl_3$): δ 0.9 (t, 3H), 1.20-1.80 (m, 6H), 2.39 (t, 1H), 2.48 (s, 3H), 3.4 (s, 3H), 4.10-4.25 (m, 2H), 4.46 (d, 2H), 4.97 (s, 1H), 5.8 (s, 1H). $[\alpha]_D$ -120.5 (c 2.52, $CHCl_3$).

**Cyclization of 9**

A solution of **9** (0.159 g, 0.5 mmol) in dry benzene (5 mL) containing catalytic amount of AIBN under $N_2$ atmosphere was heated at reflux and treated with n-$Bu_3SnH$ (0.174 g, 0.6 mmol). After 30 min. benzene was evaporated and residue chromatographed (silica gel, 5% EtOAc in pet. ether) to afford **10** (0.089 g) in 84% yield.

α-anomer $^1$H NMR($CDCl_3$): δ 0.90 (t, 3H), 1.10-1.80 (m, 6H), 3.21-3.54 (m, 3H), 3.8-3.95 (m, 2H), 4.50 (m, 1H), 4.6-4.85 (m, 2H), 5.0-5.1 (m, 2H). $M^+$ 212 $[\alpha]_D$ -8.31 (c 0.89, $CHCl_3$).

Analysis calcd. for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.77; H, 9.27%.

β-anomer: $^1$H NMR($CDCl_3$): δ 0.91 (t, 3H), 1.20-1.85 (m, 6H), 3.32-3.53 (m, 4H), 3.82-3.95 (m, 1H), 4.20-4.61 (m, 3H), 4.9 (d, 1H), 5.1 (m, 1H). $[\alpha]_D$ -160.5 (c, 1.015, $CHCl_3$).

**Methyl-2-C-(carboxymethylene methyl)-2,5-dideoxy-5-C-(n-propyl)-D-lyxofuranoside-2,3-γ -lactone (12):**

A mixture of **10** (β-anomer, 0.060 g, 0.28 mmol) $CrO_3$ (0.4 g, 4 mmol) and pyridine (0.4 mL, 5 mmol) in $CH_2Cl_2$ (5 mL) was heated at reflux for 3 h. It was cooled to room temperature and decanted. Residue was dissolved in aq. $NaHCO_3$ solution and extracted with $CH_2Cl_2$. Combined organic layers were washed sequentially with aq. $NaHCO_3$ solution, water, 2N aq. HCl and brine.

It was filtered through a small pad of silica gel and evaporated. Residue obtained was purified by column chromatography (silica gel, 10% EtOAc in pet. ether) to furnish **12** (0.04 g) in 74% yield. $^1$H NMR($CDCl_3$): δ 0.80 (t, 3H), 1.10-1.25 (m, 6H), 3.31 (s, 3H), 3.8-4.10 (m, 2H), 4.63-4.92 (m, 2H), 5.57 (d, 1H), 6.22 (d, 1H). IR(Neat): 1780 cm$^{-1}$ (CO). $M^+$ 212. $[\alpha]_D$ -80.5 (c 0.745, $CHCl_3$).

**2-C-(Carboxymethylene methyl)-2,5-dideoxy-5-C-(n-propyl)-D-lyxono-1,4-lactone-2,3-lactone (canadensolide) (1):**

**Method A**

Compound **10** (0.030 g, 0.14 mmol, -anomer) in 50% aq. acetic acid (2 mL) containing 2 drops of conc. HCl was heated at 60° for 30 min. Reaction mixture was cooled to room temperature, treated with solid $NaHCO_3$, ether and water. Aqueous layer was separated and extracted with ether. Combined ether layers were washed aq. $NaHCO_3$, water and dried ($Na_2SO_4$). Solvent was evaporated to afford the lactol **11** (0.028 g) in quantitative yield.

A mixture of **11** (0.028 g, 0.4 mmol), $CrO_3$ (0.4 g, 4 mmol) and pyridine (0.4 mL, 5 mmol) in $CH_2Cl_2$ (5 mL) was heated at reflux for 3 h. It was cooled to room temperature and decanted. Residue was dissolved in aq. $NaHCO_3$ solution and extracted with $CH_2Cl_2$. Combined organic layers were washed sequentially with aq. $NaHCO_3$ solution, water, 2N aq. HCl and brine. It was filtered through a small pad of silica gel and evaporated to give a complex mixture of products.

**Method B:**

Compound **12** (0.038 g, 0.168 mmol) in 50% aq. AcOH (2 mL) containing 2 drops of conc. HCl was heated at 60° for 30 min. Reaction mixture was cooled to room temperature, treated with solid $NaHCO_3$, ether and water. Aqueous layer was separated and extracted with ether. Combined ether layers were washed aq. $NaHCO_3$ solution, water and dried ($Na_2SO_4$). Solvent was evaporated to afford the lactol **13** (0.032 g) in quantitative yield.

A solution of the above lactol (**13**, 0.032 g, 0.150 mmol) in $CH_2Cl_2$ (2 mL) was treated with PDC (0.3 g) and NaOAc (0.020 g) at room temperature for 1 h. The reaction mixture was diluted with ether and filtered through a small pad of silica gel. Evaporation of solvent and purification of residue by column chromatography (silica gel, 10% EtOAc in pet. ether) afforded **1** (0.022 g) in 70% yield. $^1$H NMR($CDCl_3$): δ 0.92 (t, 3H), 1.42 (m, 4H), 1.81-1.90 (m, 2H), 4.05 (dt, 1H, H-2), 4.69 (dt, 1H, H-4), 5.18 (d, 1H, H-3), 6.14 (dq, 1H, H-A), 6.48 (dq, 1H, H-B). IR(Neat): 1780 and 1670 cm$^{-1}$. $M^+$ 124, $[\alpha]_D$ -160 (c 0.1, $CHCl_3$. lit.[3] $[\alpha]_D$ -162 (c 3.2, $CHCl_3$).

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