

## 2,5-Dihydroxy-3,4-*O*-isopropylidene-tetrahydrofuran for the synthesis of heterocycles

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**Dedicated to Professor Otto Meth-Cohn on the occasion of his 65<sup>th</sup> birthday**

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### Abstract

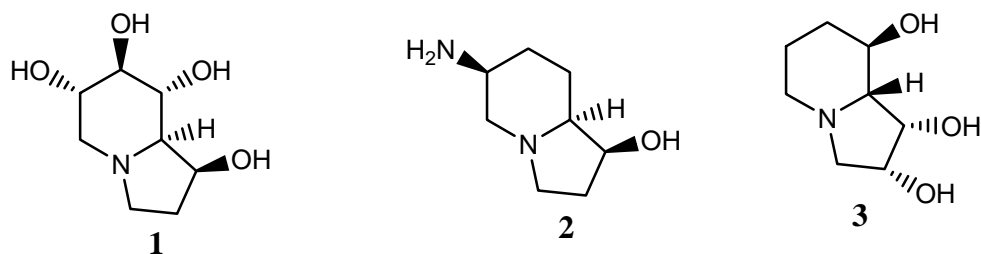
2,3-*O*-isopropylidene-D-ribose was cleaved with sodium metaperiodate to give 1,4-dihydroxy-2,3-*O*-isopropylidene-tetrahydrofuran, which underwent a double Wittig reaction on treatment with carboethoxymethylene(triphenyl)phosphorane to give the corresponding dienes. The latter were found to be excellent Michael acceptors and allowed the preparation of pyrrolizidine and tetrahydrothiophene.

**Keywords:** Pyrrolizidine, tetrahydrothiophene, Wittig reaction, heterocycles

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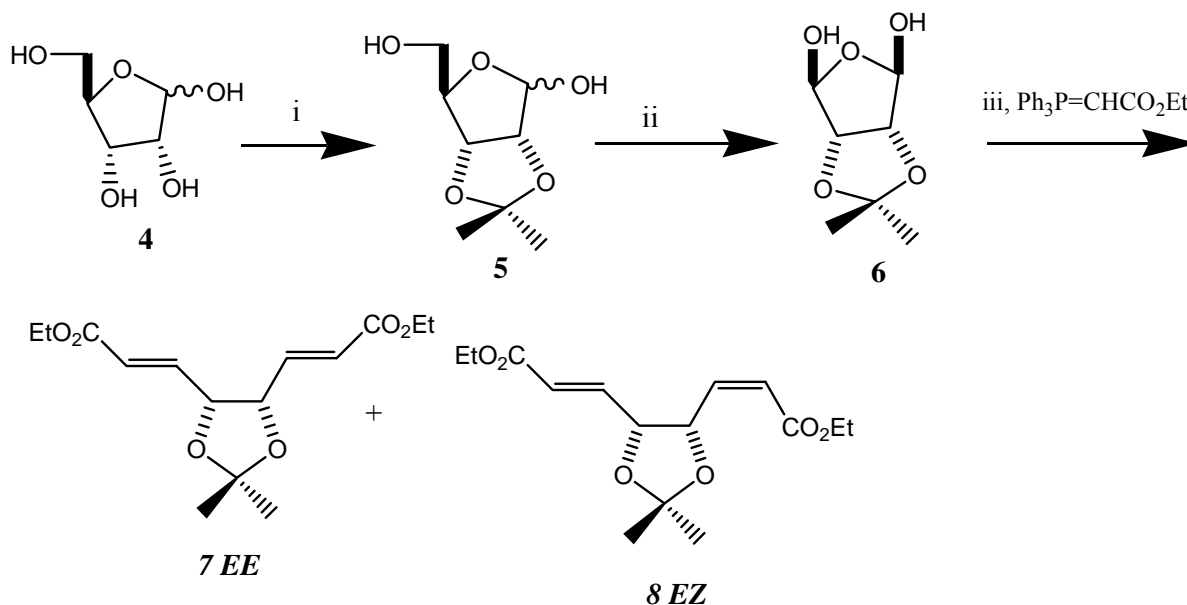
### Introduction

The pyrrolizidine alkaloids continue to attract the attention of synthetic chemists and of biologists due to their potent biological effects and the synthetic challenges they represent. In parallel there has been heightened interest in the synthesis of the indolizidine alkaloids<sup>1</sup> due to the discovery of their antiviral and antitumor activity. The alkaloids castanospermine 1, salafamine 2, and swainsonine 3 are representatives of this class of compound,<sup>2</sup> and elegant synthetic have been developed to them giving both racemic and, more recently, enantiospecific forms.<sup>2</sup>



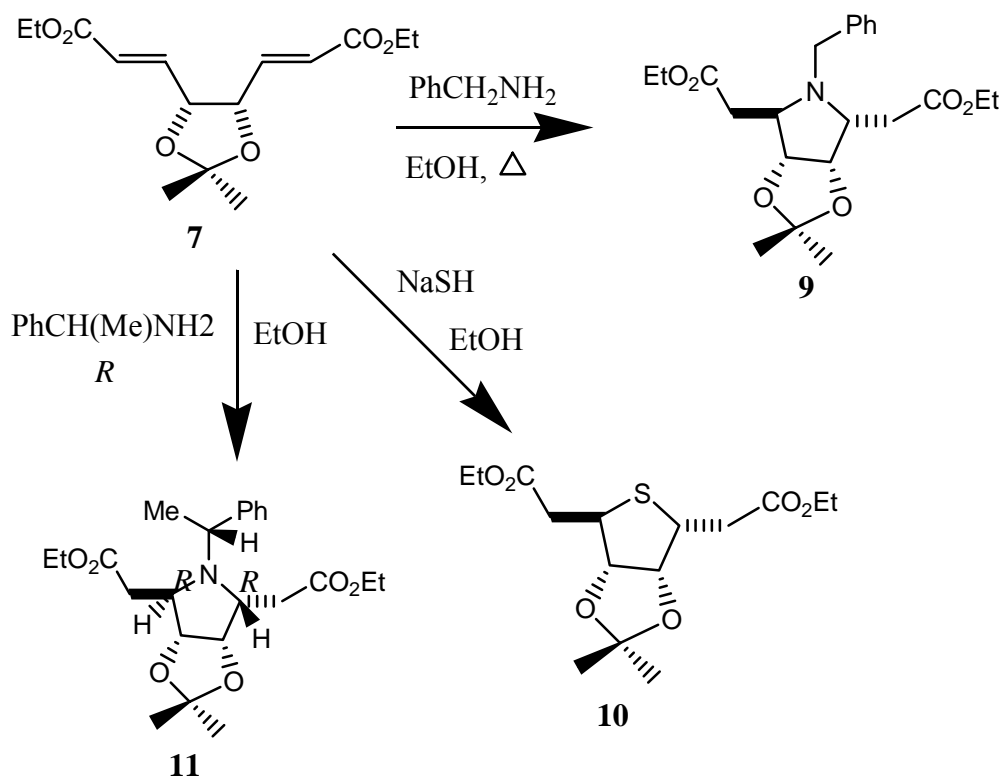
Our interest in the chemistry of carbohydrates led us to consider their use for the synthesis of heterocyclic systems related to these alkaloids. At the forefront of our thinking was the desire to use Wittig chemistry on a carbohydrate derived dialdehyde, and we chose readily available 2,3-*O*-isopropylidene-D-ribose as the starting material, a compound that has been used for the synthesis of *C*-glycosyl compounds.<sup>3</sup> Furthermore relevant chemistry involving Wittig reactions upon 2,3-*O*-isopropylidene-D-erythrose have been surveyed by Buchanan.<sup>4</sup>

The acetonide **5** was easily prepared by treatment of D-ribose in acetone with a catalytic amount of hydrochloric acid in 85 % yield, after chromatography. The acetonide was cleaved with sodium metaperiodate in water to give the furanose **6** in 60 % yield, after crystallisation from dichloromethane, m.p. 91-92 °C. The furanose **6** exists primarily in the *b*-form in DMSO solution accompanied by a small amount, 5%, of the all *cis*-isomer.



*Reagents and Conditions:* i, acetone, cat. HCl, RT, 4h; ii, NaIO<sub>4</sub>, H<sub>2</sub>O, RT, 3h; iii, EtN(<sup>i</sup>Pr)<sub>2</sub> (2.2 eq.), 3 Å mol. sieves, DCM, RT, 4h.

The dihydroxyfuranose **6** was reacted with ethoxycarbonylmethylene(triphenyl)phosphorane in dichloromethane to give a mixture of *EE* and *EZ* alkenes, which were separated by chromatography in a combined yield of 75% in a ratio of 4:1. Analysis of the above crude reaction mixture by  $^1\text{H}$  n.m.r. and tlc also indicated the presence of the *ZZ* isomer, however we were unable to obtain any of the isomers in the pure state. The *EE* geometry of the major component **7** was assigned by  $^1\text{H}$  n.m.r. spectroscopy. The signals due to 2-H and 3-H showed  $J_{2,3}$  15.6 Hz characteristic of a *trans*-relationship, in addition the spectrum as a whole was simplified as the compound has a plane of symmetry. In the spectrum of the *EZ* isomer **8** two alkenic spin-spin systems are exhibited showing coupling interactions  $J_{2,3} = 15.5$  Hz and  $J_{6,7} = 11.6$  Hz. In addition, the H-4 signal ( $\delta$  5.67) appears at a considerably lower field compared to that of H-4 signal in the *EE* isomer **7** ( $\delta$  4.81) due to deshielding by the ester carbonyl group.



With the dienes **7** and **8** to hand we reacted the *EE* diene **7** with benzylamine and isolated the racemic pyrrolidines **9** in 69% yield as colourless needles. This product has a *trans* C-2 - C-5 relationship as evidenced by its fully decoupled  $^{13}\text{C}$  nmr spectrum. This shows resonances at 50.60, 54.62, 60.11, 79.07, whereas for the isomer with a *cis* orientation at C-2 and C-5 only two resonances in this region would be anticipated. Similarly the  $^1\text{H}$  nmr spectrum of the *cis* product should also be much simplified.

Following on from this we investigated the reaction of sodium hydrosulfide with 7, and this resulted in the formation of the racemic tetrahydrothiophene 10 in 53% yield. Analysis of the  $^1\text{H}$  and  $^{13}\text{C}$  nmr of this product also suggested that it had a *trans* relationship of the hydrogen atoms at C-2 and C-5. Armed with these findings we sought to reintroduce the chirality into these heterocyclic systems. Both enantiomers of 1-phenylethylamine are commercially available at modest prices. Treatment of the diene 7 with *R*-phenylethylamine resulted in the formation of the pyrrolizidine 11 in a yield of 50 % after chromatographic purification. Once again the relative stereochemistry was found to be *trans* at C-2 and C-5. Treatment of the *S*-enantiomer gave the corresponding enantiomeric pyrrolizidine.

In conclusion we have demonstrated that the furanose 6 can be transformed to pyrrolizidines that are capable of elaboration to naturally occurring alkaloids.

## Experimental Section

**General methods.**  $^1\text{H}$  NMR spectra were recorded in  $\text{CDCl}_3$  on Bruker WH 400 (400 MHz) NMR spectrometer and are reported as follows: chemical shifts  $\delta$  (ppm), [number of protons, multiplicity, coupling constants  $J$  (Hz), and assignment]. Residual protic solvent  $\text{CHCl}_3$  ( $\delta_{\text{H}} = 7.26$  ppm) was used as the internal reference.  $^{13}\text{C}$  NMR spectra were recorded in  $\text{CDCl}_3$ , at 22.5 MHz on JEOL EX 90 NMR spectrometer using central resonance of  $\text{CDCl}_3$  ( $\delta_{\text{C}} = 77.0$  ppm) as the internal reference. Infra-red spectra were recorded on a UNICAM series FTIR spectrometer. Mass spectra were obtained on a AEI MS 902 or VG ZAB-E spectrometer. Microanalyses were performed by MEDAC Ltd, Surrey. Melting points were determined on a Gallenkamp capillary melting point apparatus and are uncorrected. Optical rotations were measured in chloroform solution using Bellingham & Stanley ADP 220 polarimeter. Flash chromatography was carried out using Fluka silicagel 60 (230-400 mesh) unless otherwise indicated. Analytical thin layer chromatography (TLC) was performed using precoated aluminium plates (Merck Kieselgel 60  $\text{F}_{254}$ ) and visualised by UV, phosphomolybdic acid or basic aqueous potassium permanganate solutions. Petrol refers petroleum ether bp 40-60  $^{\circ}\text{C}$  which was distilled prior to use and ether ( $\text{Et}_2\text{O}$ ) refers to diethyl ether.

All reactions were carried out under an argon or nitrogen atmosphere in oven-dried glassware unless otherwise stated.  $\text{CH}_2\text{Cl}_2$  and DMF were distilled from calcium hydride and stored over 4Å molecular sieves. Aqueous solutions are saturated unless otherwise specified.

1,4-dihydroxy-2,3-*O*-isopropylidene tetrahydrofuran 6 2,3-*O*-Isopropylidene-D-ribose (4.88g, 25.7 mmol) in water (80 ml) was treated with sodium periodate (6.6 g, 30.8 mmol) and the resulting mixture stirred vigorously for 3h at room temperature. The mixture was extracted with

ethyl acetate (3 x 100 ml), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford a white solid. Crystallisation from dichloromethane gave the title compound as colourless needles 2.85g, (60% yield), m. p. 91-92 °C.  $\nu_{\max}$  (KBr) 3452, 1386 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (400 MHz; d<sub>6</sub>-DMSO) 1.22 (3H, s), 1.33 (3H, s), 4.51 (2H, s), 5.20 (2H, d, *J* 5.3), 6.36 (2H, d, *J* 5.3);  $\delta_{\text{H}}$  (400 MHz; d<sub>6</sub>-DMSO) minor *cis* isomer, 1.25 (3H, s), 1.39 (3H, s), 4.51 (2H, s), 5.26 (2H, d, *J* 3.4), 6.32 (2H, d, *J* 4.2);  $\delta_{\text{C}}$  (22.5 MHz; d<sub>6</sub>-DMSO) 24.8, 26.9, 85.2 (2C), 103.3(2C), 111.4; m/z (EI) Found 176.0686 C<sub>7</sub>H<sub>12</sub>O<sub>5</sub> requires 176.0685; micro analysis; Found C, 47.81; H, 6.90 C<sub>7</sub>H<sub>12</sub>O<sub>5</sub> requires C, 47.73; H, 6.87 %.

**(2E,6E)-Diethyl-4,5-O-isopropylidene-4,5-dihydroxy-2,6-octadienedioate (7), (2Z,6Z)-diethyl-4,5-O-isopropylidene-4,5-dihydroxy-2,6-octadienedioate (8).** To a solution of the tetrahydrofuran 6 (1.04 g, 6 mmol) in dichloromethane (100 ml) was added *N,N*-diisopropylethylamine (1.68g, 2.2 eq.) and ethoxycarbonylmethylene-(triphenyl)phosphorane (4.76g, 2.2 eq.) and 3 Å mol. Sieves (10g). The resultant mixture was stirred at RT for 4h. The solvent was removed in *vacuo* and the resultant crude material purified by flash chromatography, silica; (petrol, ether; 2:1) eluent. This afforded the title compound in a combined yield of (1.34g), 75 %, ratio (*EE:ZZ*, 4:1).

**(2E, 6E)-Diethyl-4,5-O-isopropylidene-4,5-dihydroxy-2,6-octadienedioate (7).**  $\nu_{\max}$  (neat) 1720, 1659 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 1.24 (6H, t, *J* 7.1), 1.38 (3H, s), 1.53 (3H, s), 4.15 (4H, q, *J* 7.1), 4.81 (2H, appt dd, *J* 2.6, 1.6), 6.04 (2H, d, *J* 15.6), 6.67 (2H, dd, *J* 15.6, 1.6);  $\delta_{\text{C}}$  (22.5 MHz; CDCl<sub>3</sub>) 13.75, 24.9, 27.2, 60.1, 77.0, 109.8, 123.2, 141.7, 165.1;  $l_{\max}$  (EtOH, c = 1.31 mg / ml) 268 nm, (e 1.7 x 10<sup>2</sup>); m/z (EI) Found. 298.1424 C<sub>15</sub>H<sub>22</sub>O<sub>6</sub> requires 298.1416; microanalysis; Found C, 60.35, H, 7.21; C<sub>15</sub>H<sub>22</sub>O<sub>6</sub> requires C, 60.39; H, 7.43%.

**(2Z, 6Z)-Diethyl-4,5-O-isopropylidene-4,5-dihydroxy-2,6-octadienedioate (8).**  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 1.23 (6H, 2 appt. t, *J* 6.8), 1.36 (3H, s), 1.50 (3H, s), 4.13 (4H, m), 5.02 (1H, ddd, *J* 7.4, 5.6, 1.5), 5.63 (1H, dt, *J* 7.3, 1.6), 5.85 (1H, ddd, *J* 11.6, 1.7), 6.00 (1H, dd, *J* 15.5, 1.5), 6.10 (1H, dd, *J* 11.6, 7.1), 6.62 (1H, dd, *J* 15.6, 5.6);  $\delta_{\text{C}}$  (22.5 MHz; CDCl<sub>3</sub>) 14.2(2C), 25.1, 60.3, 60.5, 76.0, 77.4, 109.8, 12.9, 122.6, 143.7, 146.0, 165.5, 165.9.

**(5-Ethoxycarbonyl-1-phenylethyl-3,4-O-isopropylidene-pyrrolidin-2-yl)acetic acid ethyl ester (9).** To the diene 7 (0.76g, 2.5 mmol) in ethanol (5 ml) was added benzylamine (0.297g, 2.77 mmol). The was stirred at RT for 0.5 h and then heated at reflux for 6h. The volatiles were removed in *vacuo* to give a pale yellow oil. Dissolution of the residual oil in 10 ml of petrol/ether (2:1) commenced crystallisation of the title compound. The resulting white needles were filtered and dried in *vacuo* at 30-40 °C. Yield 0.72g, 69%; m.p. 95-97 °C.  $\nu_{\max}$  (CHCl<sub>3</sub>) 1732 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 1.19 (6H, t, *J* 7.1), 1.28 (3H, s), 1.50 (3H, s), 2.41 (2H, appt. dd, *J* 16.91, 4.0), 2.72 (2H, appt. dd, *J* 16.9, 4.6), 2.85 (2H, m), 3.67 (2H, s), 4.09 (4H, q, *J* 7.1), 4.69 (2H, dd,

$J$  4.5, 1.4), 7.25 (5H, m);  $\delta_C$  (100 MHz;  $CDCl_3$ ) 13.92 (2C), 25.50, 26.06, 33.00, 50.60, 54.62, 60.11, 79.07, 110.94, 128.09, 128.16, 128.41, 171.81;  $m/z$  (CI,  $NH_3$ ) 406 ( $M^+ + H$ ); microanalysis; Found C, 65.31; H, 7.89; N, 3.40;  $C_{22}H_{31}NO_6$  requires C, 65.17; H, 7.71; N, 3.45%.

**(5-Ethoxycarbonylmethyl-3,4-*O*-isopropylidene-tetrahydro-thiopheny-2-yl)acetic acid ethyl ester (10).** To a solution of the diene 7 (1.05g, 3.52 mmol) in ethanol (10 ml) was added NaSH (0.21g, 1.1 eq). The mixture was stirred at RT for 5 h. The solvent was removed in *vacuo* and the residue chromatographed using silica, (petrol: ether; 4:1) to afford the title compound as a white solid. Yield 0.62g; 53%.  $\nu_{max}$  ( $CHCl_3$ ) 1732  $cm^{-1}$ ;  $\delta_H$  (400 MHz;  $CDCl_3$ ) 1.24 (6H, t,  $J$  7.1), 1.26 (3H, s), 1.45 (3H, s), 2.58 (2H, appt. dd,  $J$  16.78, 8.34), 2.81 (2H, appt. dd,  $J$  16.79, 6.34), 3.51-3.59 (2H, m), 4.11-4.19 (4H, m), 4.76 (1H, d,  $J$  3.76), 4.77 (1H, d,  $J$  1.6);  $\delta_C$  (22.5 MHz;  $CDCl_3$ ) 13.99 (2C), 24.85, 26.79, 32.69, 33.50, 43.14, 45.73, 60.50, 60.65, 84.49, 85.77, 111.31, 170.53, 171.31; microanalysis; Found C, 54.34; H, 7.42; S, 6.06;  $C_{15}H_{24}O_6S$  requires C, 54.20; H, 7.28; N, 9.64%.

**(5-Ethoxycarbonyl-1-methyl-(1R)-phenylethyl-3,4-*O*-isopropylidene-pyrrolidin-2-yl)acetic acid ethyl ester (11).** To the diene 7 (0.76g, 2.55 mmol) in ethanol (5 ml) was added *R*-(1)-phenylethylamine 0.4ml (0.376g, 3.1mMol). The solution was stirred at RT for 0.5 h and then heated at reflux for 18h. The volatiles were removed in *vacuo* to give a pale yellow oil. The solvent was removed under reduced pressure and the residue chromatographed, silica; (petrol/ether; 2:1). This gave the title compound as a pale yellow oil, decomposition was observed during the purification procedure. Yield 0.53g, 50%;  $[\alpha]_D^{+41}$  (c = 0.4,  $CHCl_3$ ).  $\nu_{max}$  ( $CHCl_3$ ) 1732  $cm^{-1}$ ;  $\delta_H$  (90 MHz;  $CDCl_3$ ) 1.16-1.24 (6H, m), 1.29 (3H, s), 1.49 (3H, s), 1.55 (3H, s), 2.00-2.45 (3H, m), 2.70 (1H, dd,  $J$  15.4, 4.8), 3.15 (1H, m), 4.02-4.25 (5H, m), 4.43-4.69 (2H, m), 7.21-7.38 (5H, m);  $\delta_C$  (22.5 MHz;  $CDCl_3$ ) 14.08, 18.31, 25.59, 26.10, 34.04, 34.46, 52.86, 53.49, 58.43, 59.99, 60.47, 79.30, 80.37, 111.28, 126.62, 127.00, 128.05, 128.29, 171.94, 172.29;  $m/z$  (CI,  $NH_3$ ) Found. 437.2657  $C_{23}H_{37}NO_6$  requires 437.2652.

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