Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 5, pp. 1323-1340, 1996

0957-4166/96 $15.00 + 0.00

S0957-4166(96)00149-8

Synthetic Studies on Zoapatanol: Construction of Oxepanes *via* an Intramolecular 1,3-Dipolar Cycloaddition Strategy

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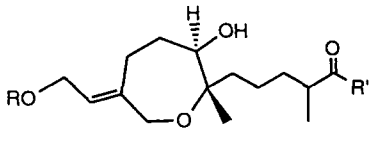
Abstract: The nitrones derived from β-allyloxyaldehydes with a β-quaternary centre cyclized to give six- instead of seven-membered *O*-heterocycles exclusively whereas a nitrile oxide derived from a γ-allyloxyaldehyde with a γ-quaternary centre cyclized to yield an oxepane ring as the sole product. Using the latter intramolecular nitrile oxide cycloaddition as the key step, optically active oxepane **5**, which is a suitable intermediate for a synthesis of zoapatanol **1**, has been constructed from D-glucose. Copyright © 1996 Elsevier Science Ltd

Zoapatanol **1**, Montanol **2**, Tomentanol **3**, and Tomentol **4** are novel diterpenoid oxepanes isolated from the leaves of Mexican zoapatle plant *Montanoa tomentosa* which Mexican women have been using for centuries to prepare "tea" to induce menses and labour, and to terminate early pregnancy.[1] Recent investigations suggested that zoapatanol and its bicyclic analogues might have potential use as antifertility agents.[2] Zoapatanol resembles prostaglandins in its anti-fertility effects but it was less active than the prostaglandin endoperoxide analogues.[3] Levine and his associates described the isolation and structure elucidation of zoapatanol in 1979.[4,5] The biological activity together with the intriguing structure prompted interests in the synthesis of zoapatanol. To date, six syntheses have been disclosed[6-11] together with the preparation of a number of analogues. The synthesis from Nicolaou *et al.* (16 steps, 12% overall yield)[8] and from Cookson *et al.* (17 steps, 5% overall yield)[6] are the most efficient. The key step of these approaches is the oxygen-carbon bond formation, leading to the *O*-heterocyclic ring and many syntheses[6-9] constructed the oxepane system in **1** by ring opening of an epoxide with an oxygen nucleophile under either basic or acidic conditions.[12] Most of the synthetic materials obtained were racemates and the first total synthesis of *optically active* zoapatanol **1** has only been recently reported.[11] In this asymmetric synthesis, the homochirality was introduced through Sharpless epoxidation[13] using L-diethyl tartrate as the chiral ligand. However, the formation of the oxepane ring system using novel palladium chemistry failed and the objective was eventually achieved based on a classical Williamson-type ether synthesis.



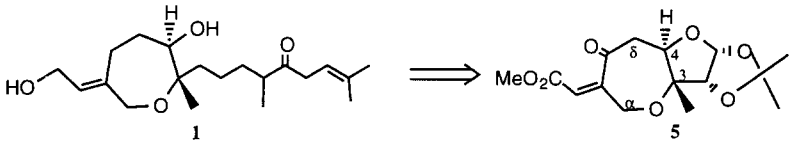
1 R = H, R' = $(CH_3)_2C\overset{E}{=}CHCH_2$

2 R = H, R' = $(CH_3)_2CH(CH_3)C=CH$

3 R = H, R' = $H_2C=C(CH_3)CH(CH_3)CH_2$

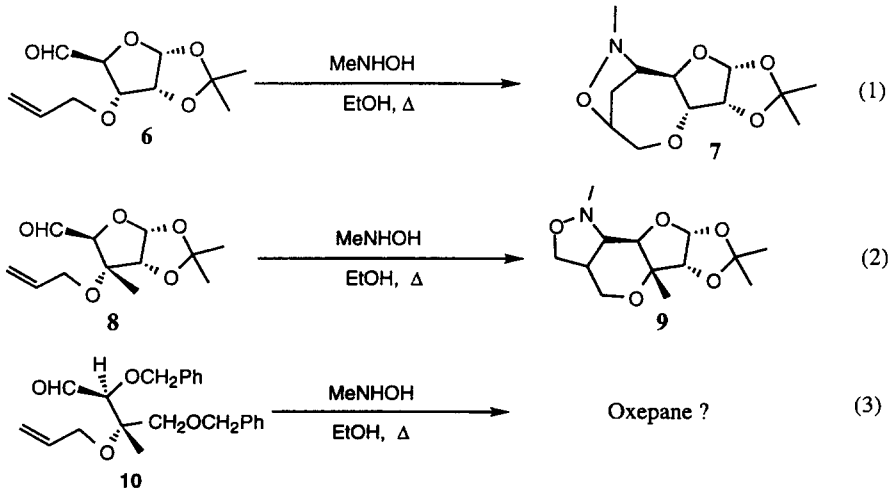
4 R = Ac, R' = $(CH_3)_2C(OH)C\overset{E}{H}=CH$

This paper now describes our efforts towards the fabrication of optically active zoapatanol from D-glucose and an advanced intermediate **5** containing the desired oxepane ring system has been synthesised *via* an intramolecular nitrile oxide cycloaddition (INOC)[14] strategy. The two endocyclic stereogenic centres in **5** were readily derived from C-3,4 of D-glucose, although the chirality of the quaternary carbon (C-3) required some synthetic manipulation. A preliminary account on part of the work has appeared.[15]

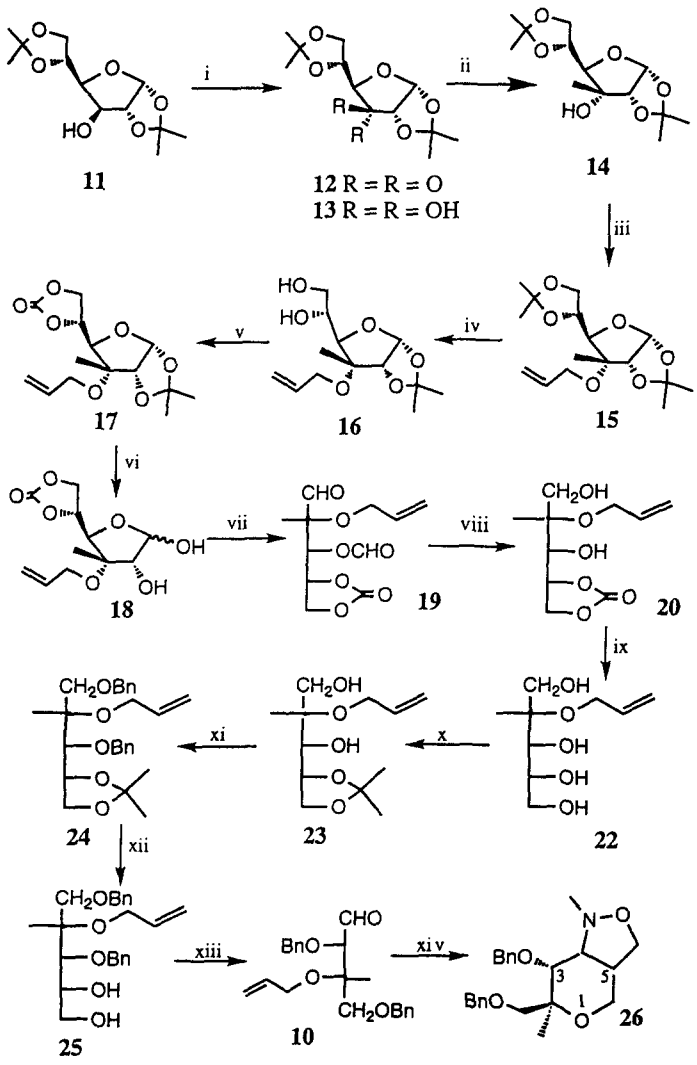


Results and Discussion

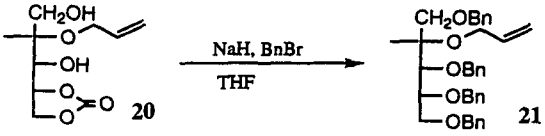
Our recent work has shown that intramolecular nitrone cycloaddition (INC) of nitrones derived from 3-*O*-allyl-1,2-*O*-isopropylidene-α-D-pentodialdo-furanoses afforded oxepanes or tetrahydropyrans (THPs) selectively whereas the intramolecular cycloadditions of nitrile oxides derived from the same aldehydes gave exclusively THPs.[16] For example, INC cyclisation of **6** gave high yields of the seven-membered *O*-heterocycle **7** [eqn (1)]. These encouraging results prompted us to investigate the feasibility of employing INC reactions to construct the oxepane ring system in **1**. We found that introducing a methyl group to C-3 in compound **6** to give aldehyde **8**, which now possesses the same endocyclic stereochemistry as that in zoapatanol, afforded an undesired THP **9** when **8** was subjected to the same reaction [eqn (2)]. We reasoned that the formation of the oxepane ring was disfavoured attributable to steric congestion in the corresponding transition state.[16] We speculated that conducting the INC experiment on an acyclic precursor such as β-allyloxyaldehyde **10** might have less steric demand on the reaction transition state that leads to the desired seven-membered *O*-heterocycle [eqn (3)]. We therefore set out to prepare aldehyde **10** to test our speculation.



The synthetic route, shown in Scheme 1, started from diacetone-D-glucose **11**[17] which was converted into the known alcohol **14**[18] *via* a modified protocol. Thus oxidation of the free alcohol in **11** with pyridinium dichromate (PDC) in the presence of acetic acid (AcOH)[19] gave the corresponding ketone **12**,[20] best isolated and stored as its crystalline hydrate **13**. The gem-diol **13** had to be dehydrated back to the ketone **12** before subjection to a Grignard reaction and the dehydration was conveniently carried out by azeotropic distillation with toluene. The ketone **12** was treated with methylmagnesium bromide which attacked the carbonyl group at the less hindered β-face, leading to tertiary alcohol **14**[18] with the desired stereochemistry. At this point of the synthetic excursion, the endocyclic stereochemistry corresponding to that in zoapatanol has been established. Alkylation of the free hydroxy group in **14** with allyl bromide furnished allyl ether **15**. The terminal acetonide in **15** was selectively hydrolysed to give diol **16** which was blocked with ethyl chloroformate to yield cyclic carbonate **17**. A strong absorption at 1803 cm^{-1} in the IR spectrum of **17** indicated the presence of the carbonate carbonyl function. The remaining acetonide in **17** was removed in the presence of 70% aqueous trifluoroacetic acid (TFA), leading to hemiacetal **18** which underwent sodium metaperiodate mediated glycol cleavage oxidation[21] to aldehyde **19**. Subsequent reduction of the crude aldehyde **19** formed the diol **20**. The resonances at δ_H 3.56 and 4.92-5.24 and strong IR absorptions at 1786 (carbonyl) and 3431 (hydroxy) cm^{-1} in the spectra of **20** supported its structure. Protection of the two hydroxy groups of **20** in the presence of the cyclic carbonate was a difficult task because the cyclic carbonate was rather unstable in basic medium. Initially, masking of the diol **20** as the corresponding benzyl (Bn) ethers was attempted. However, the carbonate was quickly cleaved under the basic conditions used (NaH), and all the hydroxy groups were converted into the unwanted tetrabenzyl ether **21** [eqn (4)]. Pivaloyl chloride and benzoyl chloride were then used to block the diols in the hope that the resultant esters would survive the basic conditions for the removal of the carbonate. Unfortunately, only the more reactive primary alcohol could be esterified by either of the two acylating reagents. As a result, an alternative strategy was pursued in order to solve this problem. Thus the cyclic carbonate in **20** was removed by using methanol-sodium methoxide to produce the tetraol **22**. The hydroxy groups at the 1,2-position were selectively blocked to form an isopropylidene **23** with acidified acetone under kinetic controlled conditions.[22] The remaining hydroxy groups in **23** were benzylated to afford the dibenzyl ether **24** from which the acetonide was hydrolysed to diol **25**. Gylcol cleavage oxidation[21] of **25** afforded an unstable aldehyde **10** which was used in the following INC experiment without purification. Thus the aldehyde **10** was condensed with the *N*-methylhydroxylamine in refluxing aqueous ethanol and the cycloaddition occurred smoothly to give **26** as the sole diastereoisomer whose structure was established as a THP by NMR spectroscopy. The resonances at δ 58.93, 68.04, 73.22, 74.21 and 74.88 in the ^{13}C (DEPT) NMR spectrum of **26** were assigned as the five methylene carbons attached to the oxygen atoms. The resonance from δ 2.91 to 2.95 in the ^{1}H NMR spectrum was assigned as the C-5 proton. This result induced us to believe that the nitrones derived from β-allyloxyaldehydes with a β-quaternary centre such as **8** and **10** would cyclise to give six- in stead of seven-membered *O*-heterocycles, attributable to the steric interaction between the methyl (or the alkenyl



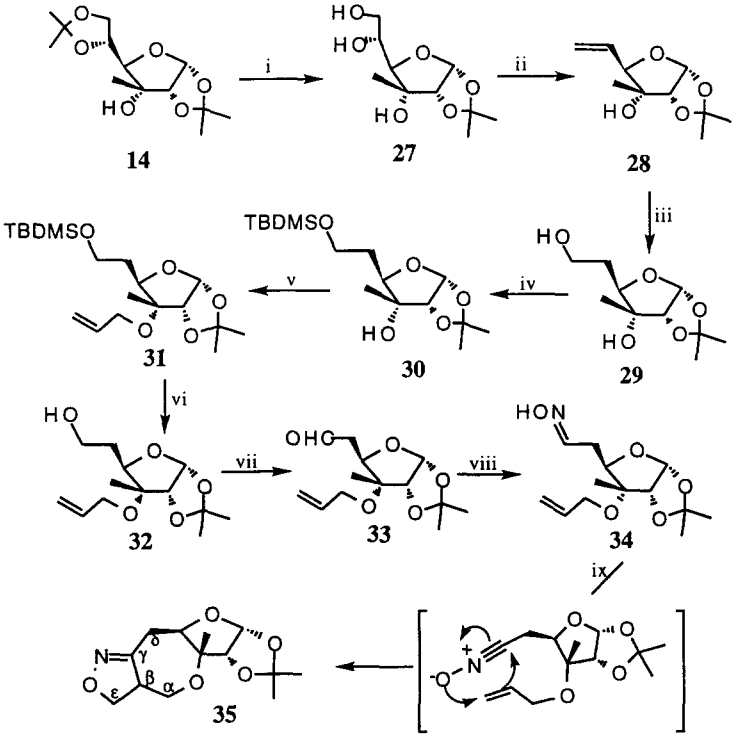
Scheme 1 *Reagents:* i, PDC, AcOH, 4Å molecular sieves, CH_2Cl_2 (98%); ii, MeMgBr, THF; iii, NaH, allyl bromide, THF (96%); iv, 90% aq. AcOH (87%); v, MeOCOCl, $(Et)_3N$, CH_2Cl_2 (78%); vi, 90% aq. TFA (87%); vii, $NaIO_4$, dioxane-water; viii, $NaBH_4$, MeOH-H_2O (76% from **18**); ix, MeOH, NaOMe (62%); x, acetone, CSA (86%); xi, BnBr, NaH, nBu_4NI, THF (80%); xii, 80% aq. AcOH (85%); xiii, $NaIO_4$, dioxane-water (82%); xiv, MeNHOH.HCl, $NaHCO_3$, 83% aq. EtOH (70%).



(4)

substituent) and the *N*-Me moiety in the transition state leading to the oxepane ring. The nitrone cycloaddition approach was therefore abandoned.

We then turned our attention to INOC reactions and envisaged that INOC reactions of oximes derived from γ-allyloxy aldehydes (five atoms between the aldehyde and the alkene moiety) should yield oxepane rings exclusively based on the arguments already proposed[16] for the exclusive formation of THPs from β-allyloxy oximes (four atoms between the oxime and the alkene moiety). Towards this end, we set out to prepare initially a relatively simple aldehyde **33** to test our reasoning (Scheme 2). The above described acetonide **14**[18] was selectively hydrolysed to triol **27** which then was transformed into the olefin **28** by the method of Garegg.[23] The resonances at δ 5.22, 5.33 and 5.66-5.80 in the ^{1}H NMR spectrum of **28** were assigned as the three olefinic protons. The alkene **28** underwent regioselective hydroboration in tetrahydrofuran (THF) and subsequent alkaline peroxide oxidation to furnish primary alcohol **29**. The upfield shift of the resonances from δ 5.22, 5.33 (terminal alkenic protons in **28**) to δ 3.86 (C-6 hydroxymethyl) and from δ 5.66-5.80 (C-5 alkenic proton in **28**) to δ 1.69-1.90 ppm (C-5 methylene) in the ^{1}H NMR spectrum of **29** provided evidence for the position of the hydroxy group.

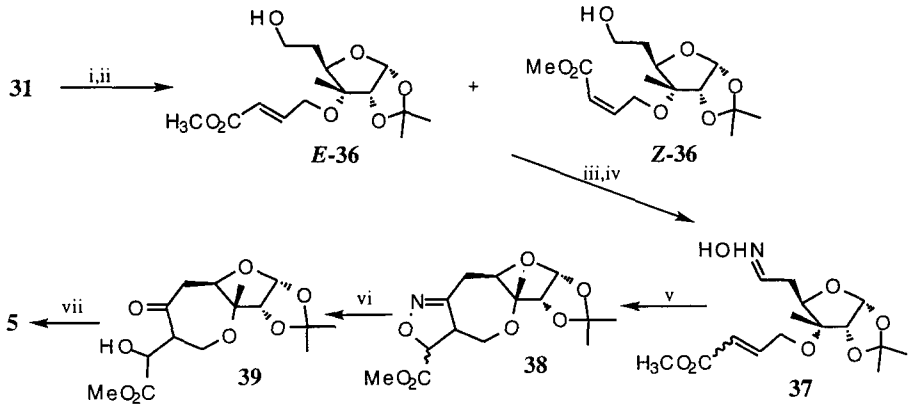


Scheme 2 *Reagents:* i, 80% aq. AcOH, (88%); ii, imidazole, Ph_3P, I_2, toluene (58%); iii, BH_3-Me_2S, then NaOH, H_2O_2, THF (84.5%); iv, imidazole, TBDMSCl, DMAP, CH_2Cl_2 (99%); v, NaH, THF, allyl bromide (77%); vi, nBu_4NF, THF, (96%); vii, PDC, AcOH, 4Å molecular sieves, CH_2Cl_2; viii, $NH_2OH.HCl$, Na_2CO_3, 80% aq. EtOH (65% overall from **32**); ix, 10% aq. NaOCl, CH_2Cl_2, cat. $(Et)_3N$ (61%).

The primary hydroxy group in **29** was selectively blocked with *tert*-butyldimethylsilyl chloride (TBDMSCl)-*N*,*N*-4-dimethylaminopyridine (DMAP) as silyl ether **30** in which the tertiary hydroxy group was alkylated with allyl bromide to give the allyl ether **31**. The silyl group was removed with fluoride anion to the alcohol **32** in an excellent yield. The free hydroxy group in **32** was oxidized with PDC to form the required aldehyde **33** which, without purification, was converted into oxime **34** (as a 1.3:1 mixture of *syn*- and *anti*-isomers) under standard conditions in 65% overall yield from **32**. The two isomers of oxime **34** could not be separated by column chromatography, but the geometry of the C=N bond could be identified by the $J_{NH,6}$ in its ^{1}H NMR spectrum. The one with a smaller coupling constant of 4.9 Hz at δ 6.90 was assigned the *syn*-oxime and that with the larger 6.2 Hz at δ 7.48 the *anti*-oxime. The ratio of the two isomers could be determined by measuring the integrals of the two signals. The mixture of oximes **34** was oxidized to the corresponding nitrile oxide *in situ* during the biphasic reaction in dichloromethane with aqueous sodium hypochlorite (triethylamine as the catalyst).[24] The reaction mixture was stirred vigorously at room temperature overnight. All the starting material disappeared and TLC indicated that only one product had formed. The structure of this substance was established to be **35** by NMR spectral analyses. The resonances at δ 26.69 and 52.14 in the ^{13}C (DEPT) NMR spectrum of **35** were assigned as C-δ and C-β on the oxepane ring whereas the signals at δ 65.41 and 70.38 indicated the two methylene carbons, C-α and C-ε, attaching to the oxygen atoms. The resonance at δ 3.40 in the ^{1}H NMR spectrum of **35** was assigned to the C-β proton whereas the resonances at δ 3.67, 3.88, 4.62 and 4.34 indicated the four protons on C-α and C-δ. The desired seven-membered bicycloisoxazoline **35** was thus obtained in 65% yield. Encouraged by this favourable result, we believed that the INOC reaction was the reliable protocol for the synthesis of seven-membered *O*-heterocycles. We then proceeded to assemble oxepane **5** which is a suitable intermediate for a synthesis of homochiral zoapatanol.

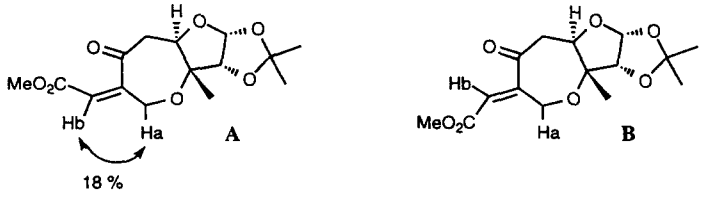
The double bond of the allyl ether moiety in **31** (Scheme 3) was cleaved by ozonolysis and then worked up with dimethyl sulfide to give an aldehyde intermediate which was immediately subjected to the Wittig alkenation with (methoxycarbonyl)methylenetriphenylphosphorane in dichloromethane at room temperature to form a pair of diastereoisomers ***Z*-36** and ***E*-36** in a ratio of 1 to 3 respectively and in a combined overall yield of 94% from **31**. The two isomers ***Z*-36** and ***E*-36** were readily separated by column chromatography as colourless oils and the geometry of the double bond was elucidated by measuring the coupling constant between the two alkenic protons in their ^{1}H NMR spectra. The alkene with the smaller coupling constant of 11.6 Hz was assigned to the *Z*-alkene, and that with the larger *J* of 15.6 Hz to the *E*-alkene. It is noteworthy that the silyl blocking group was removed during ozonolysis. We speculated that a small amount of methoxide might be generated during the ozonolysis and played an important role in the cleavage of the silyl ether. This unexpected ozone mediated desilylation was a bonus to our strategy since the desilylation had been scheduled to follow ozonolysis in our synthetic excursion. Oxidation of the primary alcohol in **36** as a mixture of geometric isomers afforded the corresponding aldehydes which were converted into the oxime **37** by reacting with hydroxylamine in refluxing ethanol. The nitrile oxide was generated *in situ* during the

biphasic oxidation of the oxime **37** in dichloromethane with aqueous sodium hypochlorite. After stirring the reaction mixture vigorously at room temperature overnight, a pair of inseparable [3+2]-cycloadducts **38** (*ca.* 1:1 by integrating the ester methyl groups in the ^1H NMR spectrum) were obtained.



Scheme 3 *Reagents:* i, O_3, CH_2Cl_2: MeOH (5:1), then Me_2S; ii, $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, (overall 94%); iii, PDC, 4Å molecule sieve, AcOH, CH_2Cl_2; iv, $NH_2OH.HCl$, pyridine, ethanol; v, 10% aq. NaOCl, CH_2Cl_2, cat. Et_3N (overall 61% from **36**); vi, Raney-Ni, H_2; vii, $MeSO_2Cl$, CH_2Cl_2, Et_3N, overall 52%.

Hydrogenolysis of the mixture of isoxazolines **38** in an acidic medium with Raney-Ni[25] as the catalyst gave hydroxy keto-esters **39** (*ca.* 1:1 mixture of diastereoisomers) which were then treated with methanesulfonyl chloride-triethylamine to give α,β-unsaturated keto-ester **5** as white needles. The resonance at δ 6.32 in the ^1H NMR spectrum of **5** indicated the presence of a single vinylic proton. Furthermore, the resonances at δ 2.78 and 2.92 were assigned as the C-δ protons and the signals at δ 4.49 and 5.37 as the C-α protons of **5**. Absorptions at 1690 (α,β-unsaturated carbonyl moiety), 1724 (α,β-unsaturated ester carbonyl) and 1640 cm^{-1} (C=C) in the IR spectrum of **5** also provided evidence for an α,β-unsaturated keto-ester moiety. The stereochemistry of the double bond in the oxepane **5** was ascertained from NOE experiments. Irradiation of the methylene protons Ha resulted in a large NOE enhancement (18%) of the vinylic proton Hb, indicating that the two methylene protons Ha should be at close proximity to Hb. Structure **A** instead of **B** was therefore assigned to **5**.



In conclusion, we have demonstrated that the INOC strategy was successful for the synthesis of an oxepane ring system containing two stereogenic centres. We believe that the oxepane **2**

would be a key intermediate suitable for further elaboration into optically active zoapatanol. The research in this direction is in progress.

Experimental Section

Melting points were determined with a Reichert apparatus and are reported in degrees Celsius uncorrected. Optical rotations were measured with a JASCO, DIP-370 automatic digital polarimeter, operating at 589 nm. $[\alpha]_D^t$-Values are given in units of 10^{-1} deg cm^{-1} g^{-1}. Infrared (IR) spectra were recorded on a Nicolet 205 FT-IR spectrometer. Nuclear magnetic resonance (NMR) spectra were measured on a Bruker WM250 spectrometer at 250.13 MHz (^1H) or at 62.89 MHz (^{13}C). All chemical shifts were recorded in ppm downfield from tetramethylsilane on the δ scale. Spin-spin coupling constants (J) were measured directly from the spectra and are given in Hz. EIMS were recorded on a VG 7070F mass spectrometer. HRMS or elemental analyses were performed at either the Shanghai Institute of Organic Chemistry, The Chinese Academy of Sciences, China or the MEDAC Ltd, Department of Chemistry, Brunel University, Uxbridge, U. K. All reactions were monitored by analytical thin-layer chromatography (TLC) on aluminum precoated with silica gel $60F_{254}$ (E. Merck). Visualization was achieved by UV irradiation or by immersion in either a 10% solution of dodecamolybdophosphoric acid in EtOH or a 10% solution of H_2SO_4 in EtOH, with subsequent heating. All columns were packed wet using E. Merck silica gel 60 (230–400 mesh) as the stationary phase and eluted using flash chromatographic technique. THF was dried by refluxing over and distilling from sodium metal under a nitrogen atmosphere, using benzophenone as an indicator. All solvents were reagent grade. Reagents were purchased from commercial suppliers and used without purification. Where appropriate, reactions were performed under a nitrogen atmosphere and for all the reactions described, stirring was performed magnetically or mechanically.

1,2:5,6-*Di*-O-*isopropylidene*-α-D-ribo-*hexofuranos*-3-*ulose hydrate* **13**.—To a stirred solution of diacetone-D-glucose **11**[17] (3.12 g, 12.1 mmol) in dry CH_2Cl_2 (80 cm^3) was added slowly pyridinium dichromate (6.85 g, 18.2 mmol), powdered 4Å molecular sieves (9 g), and glacial acetic acid (0.5 cm^3). A silica gel drying tube was placed on the flask and the mixture was stirred at room temperature. The reaction was exothermic, refluxing gently initially and the orange colour of the solution turned to dark brown within 5 min. The solution was allowed to stir for 24 h and then Celite (3 g) was added and the mixture stirred for 10 more min. The mixture then was suction filtered through a bed of silica gel (about 4 cm in length) on a sintered-glass funnel and the residue washed with $CHCl_3$ (3 × 25 cm^3). The solvent was then removed from the filtrate under reduced pressure, yielding the ketone as a colourless syrup (3.05 g, 98%). The ketone was hydrated after addition of several drops of distilled water, giving the *hydrate* **13** as white needles, m.p. 100—101 °C (lit.,[20] m.p. 111—112 °C); $[\alpha]_D^{23}$ + 45 (*c* 1.0, $CHCl_3$), {lit.,[20] $[\alpha]_D^{25}$ + 44 (*c* 1.0, ethanol)}; R_f 0.6 [diethyl ether-hexanes (1:1 v/v)]; ν_{max} (film)/cm^{-1} 3425 (OH), 1770 (C=O); δ_H (250 MHz) 1.35 (6H, s), 1.45 (3H, s), 1.47 (3H, s), 1.75 (2H, s), 4.05 (2H, d, *J* 7.0), 4.30-4.50 (3H, m), 6.13 (1H, d, *J* 3.7); *m/z* (EI) 245 (53%, M^+ - Me).

1,2:5,6-*Di*-O-*isopropylidene*-3-C-*methyl*-α-D-*allofuranose* **14**.—The hydrate **13** (3.0 g, 11.62 mmol) was dried by evaporation with dry toluene several times and was then dissolved in dry THF (60 cm^3). Grignard reagent, 3 M solution of MeMgBr (8.1 cm^3, 24.4 mmol) was added at 0 °C slowly with vigorous stirring. After the addition, the solution was stirred from 0 °C to room temperature within 3 h. Saturated ammonium chloride (40 cm^3) was added to the cooled solution slowly. The resulting mixture was filtered and the filtrate was extracted with chloroform (3 × 50 cm^3), dried with anhydrous $MgSO_4$, and filtered. The filtrate was concentrated to give white crystals which was recrystallised with a minimum quantity of hot hexane, yielding the *tertiary alcohol* **14** as white needles (3,06 g, 96%), m.p. 103 °C (lit.,[18] 105—107 °C); $[\alpha]_D^{23}$ + 20 (*c* 1.0, $CHCl_3$) {lit.,[18] $[\alpha]_D$ + 22 (*c* 1.0, $CHCl_3$)}; R_f 0.17 [diethyl ether-hexanes (1:1 v/v)]; ν_{max} (film)/cm^{-1} 3481 (OH); δ_H (250 MHz) 1.29 (3H, s), 1.35 (3H, s), .45 (3H, s), 1.59 (3H, s), 2.68 (1H, s), 3.77 (1H, d, *J* 7.0), 3.93 (1H, dd, *J* 8.5, 10.9), 4.10-4.14 (2H, m), 4.18 (1H, d, *J* 3.6); 5.70 (1H, d, *J* 3.7); *m/z* (EI) 259 (5.5%, M^+ - Me).

3-O-*Allyl*-1,2;5,6-*di*-O-*isopropylidene*-3-C-*methyl*-α-D-*allofuranose* **15**.—Sodium hydride (0.5 g, 20.8 mmol) was washed with dry hexane (5 cm^3) and suspended in dry THF (20 cm^3) under nitrogen at 0 °C. A solution of the alcohol **14** (1.7 g, 6.0 mmol) in THF (10 cm^3) was added dropwise and the reaction mixture was left to stir at room temperature for half an hour. Allyl bromide (1.1 cm^3, 12.0 mmol) was added dropwise and the mixture was refluxed for 12 h. Methanol (1.0 cm^3) was then added slowly followed by the addition of water (5 cm^3). The aqueous layer was extracted with chloroform (5 × 20 cm^3). The combined extracts were washed with brine, dried over $MgSO_4$, and filtered. Concentration of the filtrate followed by flash chromatography [hexanes-diethyl ether (1:1 v/v)] afforded the *allyl ether* **15** as a pale yellow oil (1.6 g, 80%) (Found: C, 61.3; H, 8.3. $C_{16}H_{26}O_6$ requires C, 61.1; H, 8.3%); $[\alpha]_D^{23}$ + 69 (*c* 0.9, $CHCl_3$); R_f 0.45 [diethyl ether-hexanes (1:1 v/v)]; ν_{max} (film)/cm^{-1} 1456 (C=C); δ_H (250 MHz) 1.27 (3H, s), 1.33 (3H, s), 1.35 (3H, s), 1.43 (3H, s), 1.57 (3H, s), 3.94-4.16 (7H, m), 4.25 (1H, d, *J* 3.7), 5.12 (1H, dq, *J* 1.8, 10.0), 5.32 (1H, dq, *J* 1.8, 24.7); 5.67 (1H, d, *J* 3.7), 5.88-6.03 (1H, m); *m/z* (EI) 299 (59.4%, M^+ - Me).

3-O-*Allyl*-1,2-O-*isopropylidene*-3-C-*methyl*-α-D-*allofuranose* **16**.—3-*O*-Allyl-1,2;5,6-di-*O*-isopropylidene-3-*C*-methyl-α-D-allofuranose **15** (1.0 g, 3.18 mmol) was dissolved in 90% aqueous acetic acid (20 cm^3) and the solution was stirred at room temperature for 12 h. The acetic acid was removed in *vacuo*, giving a yellow syrup. The crude product was purified by flash chromatography to yield the *diol* **16** as a pale yellow syrup (0.8 g, 90%) (Found: C, 57.0; H, 8.1. $C_{13}H_{22}O_6$ requires C, 56.9; H, 8.1%); $[\alpha]_D^{23}$ + 88 (*c* 1.8, $CHCl_3$); R_f 0.26 [diethyl ether-hexanes (3:1 v/v)]; ν_{max} (film)/cm^{-1} 3508 (OH); δ_H (250 MHz) 1.32 (3H, s), 1.34 (3H, s), 1.58 (3H, s), 3.64-3.85 (5H, m), 3.98 (1H, d, *J* 8.5), 4.29 (1H, d, *J* 3.7), 5.14-5.20 (1H, dq, *J* 1.5, 10.0) 5.24-5.33 (1H, dq, *J* 1.5, 17.2), 5.69 (1H, d, *J* 3.7), 5.87-6.02 (1H, m); *m/z* (EI) 245 (7.6%, M^+ - Me).

3-O-*Allyl*-1,2-O-*isopropylidene*-3-C-*methyl*-α-D-*allofuranose*-5,6-*carbonate* **17**.—A solution of the diol **16** (2.0 g, 7.3 mmol), triethylamine (2.9 g, 29.1 mmol) in CH_2Cl_2 (50 cm^3) was stirred at 0 °C followed by dropwise addition of a solution of ethyl chloroformate (6.2 g, 56.7 mmol) in CH_2Cl_2 (10 cm^3). The reaction mixture was left to stir at room temperature for 3 h. Water (10

cm^3) was added to destroy the excess of ethyl chloroformate. The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (5 × 20 cm^3). The combined organic extracts were washed with brine and dried over $MgSO_4$, filtered, and solvent removed from the filtrate under reduced pressure. The crude residue was purified by flash chromatography [diethyl ether-hexanes (3:1 v/v)] to afford the *cyclic carbonate* **17** as a yellow solid (1.7 g, 78%), recrystallised from ethyl acetate-hexanes to give white needles, m.p. 64.5—65.0 °C; (Found: C, 55.6; H, 6.9. $C_{14}H_{20}O_7$ requires C, 56.0; H, 6.7%); $[\alpha]_D^{23}$ + 32 (*c* 1.2, $CHCl_3$); R_f 0.3 [diethyl ether-hexanes (4:1 v/v)]; ν_{max} (film)/cm^{-1} 1803 (C=O); δ_H (250 MHz) 1.10 (3H, s), 1.27 (3H, s), 1.50 (3H, s), 4.02 (1H, d, *J* 4.9), 4.20 (1H, d, *J* 4.9), 4.23 (1H, d, *J* 3.6), 4.40 (1H, d, *J* 4.5), 4.43 (2H, dd, *J* 6.2, 11.5), 4.68-4.76 (1H, m), 5.10 (1H, dd, *J* 1.6, 11.25), 5.27 (1H, dd, *J* 1.6, 10.3), 5.66 (1H, d, *J* 3.6), 5.79-5.94 (1H, m); m/z (EI) 300 (3.2%, M^+).

3-O-*Allyl*-3-C-*methyl*-D-*allofuranose*-5,6-*carbonate* **18**.—Cyclic carbonate **17** (1.7 g, 5.7 mmol) was dissolved in 90% aqueous TFA (10 cm^3) and the solution stirred at room temperature for 8 h. TFA was removed *in vacuo*, giving a syrupy residue which was purified by flash chromatography [ethyl acetate-hexanes (4:1 v/v)] to give the *hemiacetal* **18** as a pale yellow syrup (1.3 g, 90%) (Found: C, 50.5; H, 6.2. $C_{11}H_{16}O_7$ requires C, 50.8; H, 6.2%); $[\alpha]_D^{23}$ + 5 (*c* 5.6, $CHCl_3$); R_f 0.32 [diethyl ether-hexanes (4:1 v/v)]; ν_{max} (film)/cm^{-1} 3450 (OH) 1800 (C=O); δ_H (250 MHz) 1.38 (3H, s), 3.79-4.15 (4H, m), 4.34-4.52 (3H, m), 5.12-5.30 (3H, m), 5.77-5.92 (1H, m); *m/z* (EI) 232 (36.8%, M^+ - CO).

2-O-*Allyl*-3-O-*formyl*-2-C-*methyl-aldehydo*-D-*ribose*-4,5-*carbonate* **19**.—To a stirred solution of the hemiacetal **18** (1.3 g, 5.1 mmol) in dioxane-water (3:2 v/v, 30 cm^3) at room temperature was added sodium metaperiodate (1.3 g, 6.1 mmol). The solution was allowed to stir at room temperature. Sodium iodate precipitated out of the solution during the reaction and then was filtered off. The filtrate was extracted with chloroform (5 × 20 cm^3), dried over $MgSO_4$, and filtered. Solvent was removed from the filtrate under reduced pressure, leaving a pale yellow syrup which was used in the next stage without purification, R_f 0.67 [ethyl acetate-hexanes (4:1 v/v)].

4-O-*Allyl*-4-C-*methyl*-L-*ribitol*-1,2-*carbonate* **20**.—To a stirred solution of the crude aldehyde **19** in ethanol-water (3:1 v/v, 20 cm^3) at 0 °C, was added sodium borohydride (194 mg, *ca.* 1 equivalent- assuming *ca.* 5.1 mmol of aldehyde present). After 4 h, glacial acetic acid (0.5 cm^3) was added to destroy the excess of the borohydride and then all the solvents were removed under reduced pressure, leaving a yellow syrup. The crude product was purified by flash chromatography [diethyl ether-hexanes (3:1 v/v)] to afford the *diol* **20** as a pale yellow syrup (0.8 g, 76% from the diol **18**) (Found: C, 51.6 ; H, 7.1. $C_{10}H_{16}O_6$ requires C, 51.7; H, 7.0%); $[\alpha]_D^{23}$ + 52 (*c* 2.5, $CHCl_3$); R_f 0.17 [diethyl ether-hexanes (3:1 v/v)]; ν_{max} (film)/cm^{-1} 1786 (C=O) 3431 (OH); δ_H (250 MHz) 1.10 (3H, s), 3.56 (2H, s), 3.94 (2H, d, *J* 3.6), 4.02-4.27 (1H, m), 4.39 (1H, dd, *J* 8.4, 16.8), 4.59 (1H, t, *J* 8.0, 16.0), 4.92—5.24 (3H, m), 5.75-5.90 (1H, m); *m/z* (EI) 204 (36.8%, M^+ - CO).

2-O-*Allyl*-2-C-*methyl*-D-*ribitol* **22**.—To a stirred solution of the cyclic carbonate **20** (50 mg, 0.2 mmol) in methanol (3 cm^3) was added potassium carbonate (180 mg, 0.3 mmol) and left to stir at room temperature for half an hour, after which time the reaction was complete. The methanol was removed under reduced pressure and the product was extracted from the residue with CH_2Cl_2 (5 × 5 cm^3) and dried over $MgSO_4$ and filtered. The filtrate was concentrated and the residue was purified by flash chromatography [ethyl acetate-methanol (4:1 v/v)] to afford the *tetraol* **22** as a colourless oil (27.8 mg, 62%) (Found: C, 52.5; H, 8.8. $C_9H_{18}O_5$ requires C, 52.4; H, 8.8%); $[\alpha]_D^{23}$ + 12 (*c* 1.5, $CHCl_3$); R_f 0.6 [ethyl acetate-methanol (4:1 v/v)]; ν_{max} (film)/cm^{-1} 3450 (OH), 1640 (C=C); δ_H (250 MHz) 1.76 (3H, s), 3.63 (2H, s), 3.77-3.86 (3H, m), 4.00 (1H, d, *J* 5.5), 4.61 (1H, d, *J* 8.8), 5.14 (1H, d, *J* 10.0), 5.25 (1H, d, *J* 17.2), 5.80-5.96 (1H, m); *m/z* (EI) 175 (12.1%, M^+ - CH_2OH).

4-O-*Allyl*-1,2-O-*isopropylidene*-4-C-*methyl*-L-*ribitol* **23**.—To a stirred solution of the tetraol **22** (27.8 mg, 0.1 mmol) in dry acetone (2 cm^3), (±)-10-camphorsulfonic acid (spatula tip) was added. The solution was left to stir at room temperature for half an hour, after which time the reaction was complete. Concentrated NH_3 (0,5 cm^3) was added to neutralise the sulfonic acid and the acetone was removed under reduced pressure, leaving a yellow syrup. The crude residue was purified by flash chromatography [hexanes-ethyl acetate (2:1 v/v)] to afford the *acetonide* **23** as a colourless oil (28.7 mg, 86%) (Found: C, 58.1; H, 9.1. $C_{12}H_{22}O_5$ requires C, 58.5; H, 9.0%); $[\alpha]_D^{23}$ + 26 (*c* 2.8, $CHCl_3$); R_f 0.24 [hexanes-ethyl acetate (2:1 v/v)]; ν_{max} (film)/cm^{-1} 3459 (OH), 1650 (C=C); δ_H (250 MHz) 1.19 (3H, s), 1.30 (3H, s), 1.35 (3H, s), 3.55 (1H, t, *J* 7.0), 3.62 (2H, d, *J* 4.5), 3.94 (2H, d, *J* 7.3), 4.06 (1H, dd, *J* 6.2, 10.0), 4.20 (1H, q, *J* 6.8), 5.09 (1H, dd, *J* 1.3, 10.0), 5.21 (1H, dd, *J* 1.8, 20.0), 5.77-5.91 (1H, m); *m/z* (EI) 231 (17.3%, M^+ - Me).

4-O-*Allyl*-3,5-*di*-O-*benzyl*-1,2-O-*isopropylidene*-4-C-*methyl*-L-*ribitol* **24**.—Sodium hydride (161.4 mg, 6.7 mmol) was washed with dry hexane (5 cm^3) and suspended in dry THF (20 cm^3) under nitrogen at 0 °C. A solution of the diol **23** (373.2 mg, 1.5 mmol) in THF (10 cm^3) was added dropwise and the reaction mixture was left to stir at room temperature for half an hour. Benzyl bromide (1.1 cm^3, 12.0 mmol) was added dropwise and the mixture was heated under reflux for 12 h. Methanol (1.0 cm^3) was added slowly, and was followed by the addition of water (5 cm^3). The mixture was extracted with chloroform (5 × 20 cm^3). The combined extracts were washed with brine, dried over $MgSO_4$, and filtered. Concentration of the filtrate followed by flash chromatography [hexanes-diethyl ether (1:1 v/v)] afforded the *dibenzyl ether* **24** as a pale yellow syrup (414 mg, 80%) (Found: C, 73.3; H, 8.2. $C_{26}H_{34}O_5$ requires C, 73.2; H, 8.0%); $[\alpha]_D^{23}$ + 4 (*c* 4.7, $CHCl_3$); R_f 0.35 [hexane-diethyl ether (1:1 v/v)]; ν_{max} (film)/cm^{-1} 1650, 2985 (C=C); δ_H (250 MHz) 1.26 (3H, s), 1.34 (3H, s), 1.43 (3H, s), 3.40 (2H, s), 3.86-4.02 (4H, m), 4.14 (1H, d, *J* 1.4), 4.46 (2H, d, *J* 1.8), 4.42-4.52 (1H, m), 4.56 (1H, d, *J* 11.3), 4.90 (1H, d, *J* 11.3), 5.05 (1H, dd, *J* 1.5, 10.5), 5.19 (1H, dd, *J* 1.8, 13.9), 5.76-5.92 (1H, m), 7.14-7.26 (10H, m); *m/z* (EI) 305 (7.4%, M^+ - $CH_2C_6H_5$ - 2Me).

2-O-*Allyl*-1,3-*di*-O-*benzyl*-2-C-*methyl*-D-*ribitol* **25**.—Acetonide **24** (400 mg, 1.0 mmol) was dissolved in aqueous 80% acetic acid (10 cm^3) and the solution was stirred at room temperature for 1 h. The acetic acid and water were removed in *vacuo*, giving a yellow syrup. The crude

product was purified by flash chromatography [hexanes-ethyl acetate (3:1 v/v)] , yielding the *diol* **25** as a pale yellow syrup (336 mg, 85%) (Found: C, 71.6; H, 7.9. $C_{23}H_{30}O_5$ requires C, 71.5; H, 7.8); $[\alpha]_D^{23}$ - 0.3 (*c* 12.1, $CHCl_3$); R_f 0.29 [hexanes-ethyl acetate (3:1 v/v)]; ν_{max} (film)/cm^{-1} 3441 (OH); δ_H (250 MHz) 1.26 (3H, s), 3.55 (2H, s), 3.69—3.99 (1H, m), 3.96 (2H, s), 4.04 (2H, d, *J* 8.3), 4.51 (2H, dd, *J* 12.1, 19.6), 4.53 (2H, s), 4.59 (1H, d, *J* 11.2), 4.72 (1H, d, *J* 11.2), 5.15 (1H, d, *J* 11.1), 5.29 (1H, d, *J* 18.5), 5.82-5.98 (1H, m), 7.21—7.34 (10H, m); *m/z* (EI) 265 (4.6%, M^+ - $CH_2C_6H_5$-CHOH).

3-O-*Allyl*-2,4-*di*-O-*benzyl*-3-C-*methyl*-*aldehydo*-L-*erythrose* **10**.—To a stirred solution of the diol **25** (260 mg, 1.1 mmol) in dioxane-water (3:2 v/v, 30 cm^3) at room temperature was added sodium metaperiodate (286.6 mg, 1.3 mmol). The solution was allowed to stir at room temperature. Sodium iodate precipitated out of the solution during the reaction and was filtered off. The filtrate was extracted with chloroform (5 × 20 cm^3), dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure, leaving a pale yellow syrup which was immediately used in the next stage without purification, R_f 0.44 [hexanes-ethyl acetate (3:1 v/v)] .

Isoxazolidine **26**. — Aldehyde **10** (100 mg, 0.4 mol) and *N*-methylhydroxylamine hydrochloride (0.1 g, 1.3 mmol) were dissolved in 83% aqueous ethanol (10 cm^3). Sodium hydrogen carbonate was added unit pH 8 (universal pH paper) was reached. The solution was heated under reflux for 4 h. It was filtered and extracted with chloroform (3 × 30 cm^3), dried over anhydrous $MgSO_4$, filtered and the filtrate was concentrated. The crude product was purified by flash chromatography, yielding the *THP* **26** as a pale yellow syrup (78 mg, 70%) (Found: C, 71.8; H, 7.8. $C_{23}H_{29}O_4N$ requires C, 72.1; H, 7.6%); $[\alpha]^{23}$ - 10 (*c* 1.2, $CHCl_3$); R_f 0.34 [hexanes-diethyl ether (1:3 v/v)]; ν_{max} (film)/cm^{-1} 1453 (C=N); δ_H (250 MHz) 1.09 (3H, s), 2.54 (2H, s), 2.86-2.92 (1H, m), 3.20 (1H, dd, *J* 7.6, 15.8), 3.40 (1H, d, *J* 3.0), 3.52 (1H, dd, *J* 10), 3.71 (1H, dd, *J* 8.8), 3.76 (1H, dd, *J* 7.7, 15.4), 3.84 (1H, d, *J* 3.0), 3.90 (1H, dd, *J* 4.2, 12.6), 4.20 (1H, dd, *J* 7.5, 9.42), 4.53 (2H, dd, *J* 12.2, 22.5), 4.55 (1H, d, *J* 11.6), 5.00 (1H, d, *J* 11.6), 7.15-7.21 (10H, m); *m/z* (EI) 292 (22.4%, M^+- $CH_2C_6H_5$), 256 (28.0%, M^+ - Me).

1,2-O-*Isopropylidene*-3-C-*methyl*-α-D-*allofuranose* **27**.[18]—3-*O*-Allyl-1,2:5,6-di-*O*-isopropylidene-3-*C*-methyl-α-D-allofuranose **14** (1.0 g, 3.7 mmol) was dissolved in 80% aqueous acetic acid (20 cm^3) were stirred at room temperature for 10 h. The acetic acid was removed *in vacuo* to give a white solid. The crude product was purified by flash chromatography [ethyl acetate-methanol (95:5 v/v)] to give the *diol* **27** (0.8 g, 88%). Recrystallisation from chloroform and ether afforded white small needless, m.p. 110—111 °C; (lit.,[18] 132.5—133.5 °C) (Found: C, 51.6; H, 8.1. $C_{10}H_{18}O_6$ requires C, 51.3; H, 7.8%); $[\alpha]_D^{23}$ + 35 (*c* 0.9, $CHCl_3$) {lit.,[18] $[\alpha]_D$ + 23 (*c* 0.4, $CHCl_3$)}; R_f 0.32 [ethyl acetate-methanol (95:5 v/v)]; ν_{max} (film)/cm^{-1} 3357 (OH); δ_H (250 MHz) 1.29 (3H, s), 1.32 (3H, s), 1.56 (3H, s), 3.65 (1H, dd, *J* 4, 12.5), 3.90—3.95 (3H, m), 4.14 (1H, d, *J* 3.7), 5.68 (1H, d, *J* 3.7); *m/z* (EI) 219 (3.2%, M^+ - Me).

5,6-*Deoxy*-1,2-O-*isopropylidene*-3-C-*methyl*-α-D-ribo-*hex*-5-*enofuranose* **28**.—A solution of the triol **27** (100 mg, 0.4 mmol), imidazole (116 mg, 1.7 mmol) and triphenylphosphine (448

mg, 1.7 mmol) in toluene (15 cm^3) was heated under reflux while iodine (324 mg, 1.3 mmol) was added to the boiling mixture in small portions over 1 h. After the addition, TLC analysis indicated that the reaction was complete. Saturated sodium thiosulfate solution (5 cm^3) and NaOH solution (3.0 M, 5 cm^3) were then added to the cooled reaction mixture in a separatory funnel. The organic layer was separated, washed with brine (10 cm^3) water (10 cm^3), dried over $MgSO_4$, and filtered. The solvent was removed from the filtrate under reduced pressure to give a yellow solid. The crude product was purified by flash chromatography [hexanes-ethyl acetate (3:1 v/v)] to afford the *alkene* **28** as a white solid (49.1 mg, 58%). Recrystallisation from diethyl ether-hexanes furnished colourless needles, m.p. 65—67 °C (Found: C, 59.6; H, 8.1. $C_{10}H_{16}O_4$ requires C, 60.0; H, 8.05%); $[\alpha]_D^{23}$ + 47 (*c* 0.6, $CHCl_3$); R_f 0.24 [hexanes-ethyl acetate (3:1 v/v)]; ν_{max} (film)/cm^{-1} 3480 (OH), 1640 (C=C); δ_H (250 MHz) 1.04 (3H, s), 1.30 (3H, s), 1.60 (3H, s), 4.10 (1H, d, *J* 3.8), 4.15 (1H, d, *J* 5.8), 4.22 (1H, t, *J* 6.8), 5.22 (1H, d, *J* 10.6), 5.33 (1H, d, *J* 17.3), 5.66-5.80 (1H, m), 5.72 (1H, d, *J* 4.0); *m/z* (EI) 185 (3.5%, M^+ - Me).

5-*Deoxy*-1,2-O-*isopropylidene*-3-C-*methyl*-α-D-ribo-*hexofuranose* **29**.—To a solution of the alkene **28** (47.2 mg, 0.2 mmol) in dry THF was added a 2.0 M solution of borane-dimethyl sulfide in THF (0.1 cm^3, 0.2 mmol) at room temperature. The mixture was stirred for 3 h and then was treated with a solution of NaOH solution (3.0 M, 1 cm^3) and aqueous H_2O_2 (30% v/v, 1 cm^3) at 0 °C. The solution was raised to room temperature and stirred overnight. The solvent was removed and the residue was extracted with chloroform (5 × 5 cm^3). The organic extracts were combined and dried over anhydrous $MgSO_4$, filtered and the filtrate was concentrated under reduced pressure to give a white solid. The crude product was purified by flash chromatography [hexanes-ethyl acetate (1:5 v/v)] to afford the *alcohol* **29** as a white solid (50.8 mg, 84.5%), which was recrystallised from ethyl acetate-hexanes to give white needles, m.p. 83—85 °C; (Found: C, 54.8; H, 8.1; $C_{10}H_{18}O_5$ requires C, 55.0 H, 8.2%); $[\alpha]_D^{23}$ + 49 (*c* 0.6, $CHCl_3$); R_f 0.18 [hexanes-ethyl acetate (1:3 v/v)]; ν_{max} (film)/cm^{-1} 3457 (OH); δ_H (250 MHz) 1.18 (3H, s), 1.35 (3H, s), 1.58 (3H, s), 1.69-1.90 (2H, m), 3.78 (1H, t, *J* 5.7), 3.86 (2H, dd, *J* 5.8, 12.9), 4.15 (1H, d, *J* 3.9), 5.74 (1H, d, *J* 3.9); *m/z* (EI) 203 (14.3%, M^+ - Me).

5-*Deoxy*-6-O-t-*butyldimethylsilyl*-1,2-O-*isopropylidene*-3-C-*methyl*-α-D-ribo-*hexofuranose* **30**.—To a stirred solution of the diol **29** (50.8 mg, 0.2 mmol) in CH_2Cl_2 (3 cm^3) were added, imidazole (47 mg, 0.7 mmol), *t*-butyldimethylsilyl chloride (71.8, 0.5 mmol) and a catalytic amount of DMAP at 0 °C. The reaction mixture was then left to stir at room temperature for 4 h after which time the reaction was complete. Water (2 cm^3) was added to the reaction mixture and then the mixture was extracted with CH_2Cl_2 (5 × 5 cm^3). The combined extracts were washed with brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated and the residue was purified by flash chromatography [hexanes-ethyl acetate (5:1 v/v)]; to afford the *silyl ether* **30** as a colourless oil (75.6 mg, 99%) (Found: C, 57.7; H, 9.9. $C_{16}H_{32}O_5Si$ requires C, 57.8 H, 9.7%); $[\alpha]_D^{23}$ - 36 (c 4.7, $CHCl_3$); R_f 0.2 [hexanes-ethyl acetate (6:1 v/v)]; ν_{max} (film)/cm^{-1} 3457 (OH), 1084 (Si-O); δ_H (250 MHz) 0.05 (6H, s), 0.88 (9H, s), 1.13 (3H, s), 1.33 (3H, s), 1.55 (3H, s), 1.59-1.81 (2H, m), 3.65-3.84 (2H, m), 3.90 (1H, dd, *J* 5, 7.5), 4.13 (1H, dd, *J* 3.9), 5.70 (1H, dd, *J* 3.8); *m/z* (EI) 217 (13.4%, M^+ - TBDMS).

3-O-*Allyl*-6-O-t-*butyldimethylsilyl*-5-*deoxy*-1,2-O-*isopropylidene*-3-C-*methyl*-α-D-ribo-*hexofuranose* **31**.—Sodium hydride (10 mg, 0.4 mmol) was washed with dry hexane (2 cm^3) and suspended in dry THF (5 cm^3) under nitrogen at 0 °C. A solution of alcohol **30** (28.3 mg, 0.1 mmol) in THF (3 cm^3) was added dropwise and the reaction mixture was left to stir at room temperature for half an hour. Allyl bromide (30.5 mg, 0.3 mmol) was added dropwise and the mixture was refluxed for 12 h. Methanol (0.5 cm^3) was added slowly followed by addition of water (1 cm^3). The aqueous layer was extracted with chloroform (5 × 5 cm^3). The combined extracts were washed with brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated and the crude product was purified by flash chromatography [hexanes-ethyl acetate (8:1 v/v)] to afford the *allyl ether* **31** as a pale yellow syrup (24.4 mg, 77%) (Found: C, 62.2; H, 10.0. $C_{19}H_{36}O_5Si$ requires C, 61.2; H, 9.7%); $[\alpha]_D^{23}$ + 53 (*c* 0.8, $CHCl_3$); R_f 0.58 [hexanes-ethyl acetate (5:1 v/v)]; ν_{max} (film)/cm^{-1} 1090 (Si-O), 1650 (C=C); δ_H (250 MHz) 0.37 (6H, s), 0.87 (9H, s), 1.11 (3H, s), 1.24 (3H, s), 1.54 (3H, s), 1.58-1.68 (2H, m), 3.67—3.80 (2H, m), 4.04-4.09 (3H, m), 4.22 (1H, d, *J* 3.9), 5.09-5.31 (2H, m), 5.66 (1H, d, *J* 3.85), 5.85-6.00 (1H, m); *m/z* (EI) 257 (8.3%, M^+ - TBDMS).

3-O-*Allyl*-5-*deoxy*-1,2-O-*isopropylidene*-3-C-*methyl*-α-D-ribo-*hexofuranose* **32**.— To a stirred solution of the silyl ether **31** (24.4 mg, 0.1 mmol) in THF (3 cm^3) was added a solution of n-Bu_4NF (56.5 μl, 0.2 mmol) at room temperature. The mixture was left to stir at room temperature for 2 h after which time reaction was complete. The solvent was removed under reduced pressure to give a yellow oil. The crude product was purified by flash chromatography [hexanes-ethyl acetate (1:2 v/v)] to provide the *alcohol* **32** as a pale yellow syrup (16.1 mg, 96%) (Found: C, 60.3; H, 8.8. $C_{13}H_{22}O_5$ requires C, 60.5; H, 8.6%); $[\alpha]_D^{23}$ + 65 (*c* 1.0, $CHCl_3$); R_f 0.33 [hexanes-ethyl acetate (1:2 v/v)]; ν_{max} (film)/cm^{-1} 3459 (OH), 1640 (C=C); δ_H (250 MHz) 1.20 (3H, s), 1.34 (3H, s), 1.58 (3H, s), 1.78-1.86 (2H, m), 3.87 (2H, bs), 4.11-4.17 (3H, m), 4.28 (H, d, *J* 3.8), 5.17 (1H, dd, *J* 1.2, 5.2), 5.29 (1H, dd, *J* 1.4, 15.8), 5.70 (1H, d, *J* 3.8), 5.87-6.02 (1H, m); *m/z* (EI) 243 (3.9%, M^+ - Me).

3-O-*Allyl*-5-*deoxy*-1,2-O-*isopropylidene*-3-C-*methyl*-α-D-*ribo-hexodialdo*-1,4-*furanose* **33**.— To a stirred solution of the alcohol **32** (400 mg, 1.6 mmol) in CH_2Cl_2 (30 cm^3), powdered 4Å molecule sieves (1.29 g), PDC (1.01 g, 2.3 mmol) and acetic acid (1.6 cm^3) were added in sequence at room temperature. The reaction mixture was left to stir at room temperature for 2 h after which time the reaction was complete. Celite (250 mg) and diethyl ether (10 cm^3) were added to the reaction mixture and the solid was filtered off through a thin bed of silica gel. The filtrate was concentrated under reduced pressure to give the *aldehyde* **33** as a pale yellow syrup which was immediately used in the next stage, R_f 0.44 [hexanes-ethyl acetate (1:1 v/v)].

3-O-*Allyl*-5-*deoxy*-1,2-O-*isopropylidine*-3-C-*methyl*-α-D-*ribo-hexodialdo*-1,4-*furanose Oxime* **34**.—Hydroxylamine hydrochloride (323.1 mg, 4.7 mmol) and then sodium carbonate (440 mg, 7.0 mmol) were added to a solution of the crude aldehyde **33** in ethanol (40 cm^3) and water (5 cm^3). The reaction mixture was heated under reflux for 1 h, after which time the reaction was complete. The reaction mixture was cooled and the ethanol was removed under reduced pressure. The residue was extracted with CH_2Cl_2 (3 × 15 cm^3) and the combined extracts were

washed with brine, dried over anhydrous $MgSO_4$ and filtered. After CH_2Cl_2 was removed from the filtrate under reduced pressure, the residue was purified by flash chromatography [diethyl ether-hexanes (4:3 v/v)] to afford a 1.3:1 *syn-anti* mixture (by NMR analysis) of the *title oxime* **34** as a pale yellow oil (273 mg, 65% base on **32**) (Found: C, 57.9 ; H, 8.0; N, 5.0. $C_{13}H_{21}NO_5$ requires C, 57.6; H, 7.8; N, 5.2%); $[\alpha]_D^{23}$ + 60 (*c* 0.9, $CHCl_3$); R_f 0.28 [hexanes-ethyl acetate (1:1 v/v)]; ν_{max} (film)/cm^{-1} 3410 (OH), 1650 (C=C), 1450 (C=N); δ_H (250 MHz) 1.16 (3H, s), 1.44 (3H, s), 1.82 (3H, s), 2.38-2.72 (2H, m), 4.08 (1H, d, *J* 5.8), 4.18 (1H, dd, *J* 8.3, 12.2), 4.59 (1H, d, *J* 5.9), 4.27 (1H, d, *J* 3.6), 5.08 (1H, dd, *J* 1.3, 10.3), 5.22 (1H, dd, *J* 1.3, 17.2), 5.70 (1H, d, *J* 3.6), 5.80-5.95 (1H, m), 6.90 (0.53H, t, *J* 4.9), 7.48 (0.42H, t, *J* 6.2); *m/z* (EI) 257 (2.4%, M^+).

Isoxazoline **35**.—To a solution of oxime **34** (250 mg, 0.9 mmol) in CH_2Cl_2 (20 cm^3), at room temperature, was added a catalytic amount of triethylamine (5 μl) and was followed by the dropwise addition of 10% aqueous sodium hypochlorite (685 mg, 9.2 mmol). The reaction mixture was heated under reflux overnight and then cooled. The product was extracted with CH2Cl2 (3 × 20 cm^3). The combined organic extracts were dried over anhydrous $MgSO_4$, and filtered. The solvent was removed from the filtrate under reduced pressure. The crude residue was purified by flash chromatography [hexanes-ethyl acetate (1:2 v/v)] to afford the *isoxazoline* **35** as a white solid (117.7 mg, 61%). Recrystallisation from hexanes-ethyl acetate afforded colourless needles, m.p. 139—140 °C; (Found: C, 57.7; H, 7.0; N, 5.1. $C_{13}H_{19}NO_5$ requires C, 58.0; H, 7.1; N, 5.2%); $[\alpha]_D^{23}$ - 16 (*c* 1.0, $CHCl_3$); R_f 0.23 [hexanes-ethyl acetate (4:3 v/v)]; ν_{max} (film)/cm^{-1} 1400 (C=N); δ_H (250 MHz) 1.21 (3H, s), 1.37 (3H, s), 1.62 (3H, s), 2.67 (1H, dd, *J* 11.9, 17.6), 3.01 (1H, dd, *J* 6, 17.6), 3.41-3.47 (1H, m), 3.67 (1H, dd, *J* 11.0, 12.4), 3.79 (1H, dd, *J* 4.4, 12.4), 3.88 (1H, dd, *J* 6.0, 7.7), 4.25 (1H, d, *J* 3.1), 4.26 (1H, dd, *J* 10.6, 12.4), 4.34 (1H, dd, *J* 6.0, 11.9), 5.86 (1H, d, *J* 3.4); δ_C (250 MHz) 13.63, 25.78, 26.06, 26.69, 52.14, 65.14, 65.41, 70.38, 75.92, 82.22, 85.45, 103.3, 113.2, 155.23; *m/z* (EI) 254 (4.4%, M^+ - Me).

5-*Deoxy*-1,2-O-*isopropylidene*-3-O-(3'-*methoxycarbonyl*-2'-*propenyl*)-3-C-*methyl*-α-D-ribo-*hexofuranose* **36**.—The silyl ether **31** (1.0 g, 2.7 mmol) was suspended in CH_2Cl_2-MeOH (20 cm^3, 5:1, v/v) in a dry ice-acetone bath at - 78 °C. The mixture was ozonolysed for an hour and by then, all the starting material disappeared. Oxygen was continued to bubble through the solution in order to exclude the excess of O_3. The reaction mixture was raised to room temperature and dimethyl sulfide was added and the resulting mixture continued to stir for 8 h. Solvent removal gave an oil which was dissolved in CH_2Cl_2 (10 cm^3) and $Ph_3P{=}CHCO_2Me$ (2 gm, mmol) was added. The reaction mixture was stirred at room temperature for 3 h. The solvent was then evaporated and the product was purified by flash column chromatography [hexanes-ethyl acetate (2:3 v/v)] to give a 1:3 *cis-trans* mixture of the *enoate* **36** as a colourless oil (Found: C, 56.9; H, 7.5. $C_{15}H_{24}O_7$ requires C, 57.0; H, 7.65%); ν_{max} (film)/cm^{-1} 3450 (OH), 1720 (C=O), 1640 (C=C).

Z-36: $[\alpha]_D^{23}$ + 128 (*c* 0.8, $CHCl_3$); R_f 0.33 [hexanes-ethyl acetate (1:2 v/v)]; δ_H (250 MHz) 1.19 (3H, s), 1.27 (3H, s), 1.56 (3H, s), 1.80 (2H, q, *J* 6.6), 3.72 (3H, s), 3.76 (2H, t, *J* 5.6), 3.41-3.47 (1H, m), 3.67 (1H, dd, *J* 11.0, 12.4), 3.79 (1H, dd, *J* 4.4, 12.4), 3.88 (2H, t, *J* 5.6), 4.10 (1H, t, *J* 6.7), 4.29 (1H,

d, *J* 3.8), 4.56-4.65 (1H, m), 4.76-4.86 (1H, m), 5.69 (1H, d, *J* 3.8), 5.81 (1H, tt, *J* 2.2, 9.3), 6.39 (1H, tt, *J* 4.8, 11.7); *m/z* (EI) 301 (1.6%, M^+ - Me).

***E*-36**: $[\alpha]_D^{23}$ + 45 (*c* 2.4, $CHCl_3$); R_f 0.30 [hexanes-ethyl acetate (1:2 v/v)]; δ_H (250 MHz) 1.11 (3H, s), 1.25 (3H, s), 1.50 (3H, s), 1.76 (2H, q, *J* 5.8), 3.70 (3H, s), 3.75 (2H, t, *J* 5.7), 4.06 (1H, t, *J* 6.6), 4.18-4.27 (3H, m), 5.65 (1H, d, *J* 3.9), 6.02 (1H, tt, *J* 2.0, 15.6), 6.91 (1H, tt, *J* 4.3, 15.7); *m/z* (EI) 301 (1.6%, M^+ - Me).

Isoxazoline **38**.—The mixture of geometric isomers **36** (430 mg, 1.4 mmol) was suspended in dry CH_2Cl_2 (20 cm^3) and PDC (473 mg, 883.9 mmol), powdered 4Å molecular sieves (113,4 mg) and glacial acetic acid (0.2 cm^3) were added slowly. A silica gel drying tube was place at the flask and the mixture was stirred at room temperature. The reaction was exothermic, refluxing gently initially and the orange colour of the solution turned to dark brown within 5 min. The solution was allowed to stir for 2 h and then Celite (0.5 g) was added and stirred for 10 more min. The solution was suction filtered through a bed of silica gel and the solvent was removed under reduced pressure, yielding the corresponding aldehyde. Hydroxylamine hydrochloride (142 mg, 2.4 mmol) and then pyridine (142 mg, 1.8 mmol) were added to a solution of the crude aldehyde in ethanol (20 cm^3). The reaction mixture was heated under reflux for 1 h, after which time the reaction was complete. The reaction mixture was cooled and the ethanol was removed under reduced pressure. The residue was extracted with CH_2Cl_2 (3 × 15 cm^3). The combined extracts were washed with brine, dried over anhydrous $MgSO_4$, and filtered. After the CH_2Cl_2 was removed from the filtrate under reduced pressure, the residue was purified by flash chromatography [hexanes-ethyl acetate (1:1 v/v)] to give the oxime **37**, R_f 0.32 [hexanes-ethyl acetate (1:1 v/v)]. To a solution of oxime **37** in CH_2Cl_2 (20 cm^3) at room temperature, was added a catalytic amount of Et_3N (5 μl) followed by a dropwise addition of 10% aqueous sodium hypochlorite (340 mg, 4.1 mmol). The reaction mixture was stirred at room temperature overnight. The organic materials was extracted with CH_2Cl_2 (3 × 20 cm^3). The combined organic extracts were dried over anhydrous $MgSO_4$ and filtered. The solvent was concentrated under reduced pressure. The crude residue was purified by flash chromatography [hexanes-ethyl acetate (1:2 v/v)] to afford a 1:1 stereoisomeric mixture (by NMR) of the *isoxazoline* **38** as a colourless oil (271.3 mg, 61%) (Found: C, 54.2; H, 7.5; N, 4.3. $C_{15}H_{25}NO_7$ requires C, 54.4; H, 7.6; N, 4.2%); $[\alpha]_D^{23}$ - 47 (*c* 1.2, $CHCl_3$); R_f 0.32 [hexanes-ethyl acetate (1:2 v/v)]; ν_{max} (film)/cm^{-1} 1735 (C=O ester), 1650 (C=N), 1450 (C=C); δ_H (250 MHz) 1.18 (3H, s), 1.23 (3H, s), 1.38 (3H, s), 1.62 (3H, s), 1.64 (3H, s), 2.73 (2H, ddd, *J* 2.8, 11.9, 17.8), 3.08 (2H, dt, *J* 6.1, 17.8), 3.69-3.89 (3H, m), 4.07 (1H, dd, *J* 2.9, 14.3), 4.33 (1H, d, *J* 3.3), 4.38 (1H, dd, *J* 6.2, 12.0), 4.51 (1H, d, *J* 5.0), 4.99 (1H, d, *J* 7.4), 5.72 (1H, d, *J* 3.3); *m/z* (EI) 312 (23.2%, M^+ - Me).

3,8-*Anhydro*-5,7-*dideoxy*-1,2-O-*isopropylidene*-7-(Z-*methoxycarbonylmethylidene*)-3-C-*methyl*-α-D-ribo-*octofuranos*-6-*ulose* **5**.—To a solution of the isoxazoline **38** (150 mg, 0.5 mmol), 3 mole % equivalent of acetic acid, CH_2Cl_2-methanol-water (10 cm^3, 10 : 5 :1 v/v) was added a catalytic amount of Raney-Ni. The system was evacuated and purged three time with H_2 using a 3-way stopcock with a H_2 balloon. The mixture was then stirred vigorously under H_2 at 25 °C for 3 h. CH_2Cl_2 (20 cm^3) was added, and the solution was then dried over anhydrous

$MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure to give hydroxyester **39**. The crude hydroxyester **39** was dissolved in a solution of triethylamine (232 mg, 2.3 mmol) in CH_2Cl_2 (10 cm^3) at 0 °C and MsCl (157.6 mg, 1.3 mmol) was added dropwise to the solution. After 8 h at 0 °C the mixture was raised to room temperature and the mixture was washed with water (2 × 10 cm^3) and brine (10 cm^3). The organic layer was dried over anhydrous $MgSO_4$, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography [ethyl acetate-hexanes (1:1 v/v)] to give a white solid **5** (74 mg, 52%) which was recrystallised from ethyl acetate-hexanes to give *the oxepane* **5** as colourless needles, m.p. 109.5—111 °C; (Found: C, 57.4; H, 6.4. $C_{15}H_{20}O_7$ requires C, 57.7; H, 6.5%); $[\alpha]_D^{23}$ + 63 (*c* 0.8, $CHCl_3$); R_f 0.38 [ethyl acetate-hexanes (1:1 v/v)]; ν_{max} (film)/cm^{-1} 1724 (C=O, ester), 1690 (C=O, aldehyde), 1640 (C=C); δ_H (250 MHz) 1.12 (3H, s), 1.28 (3H, s), 1.53 (3H, s), 2.78 (1H, dd, *J* 12.5, 16.9), 2.92 (1H, dd, *J* 4.1, 16.9), 3.70 (3H, s), 4.29 (1H, d, *J* 3.5), 4.33 (1H, dd, *J* 12.5, 4.1), 4.49 (1H, d, *J* 15.8), 5.37 (1H, d, *J* 15.8), 5.64 (1H, d, *J* 3.5), 6.32 (1H, s); *m/z* (EI) 312 (1.1%, M^+).

Acknowledgments: We thank the Hong Kong UPGC Direct Grant for financial support.

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(*Received in Japan* 13 *February* 1996; *accepted* 19 *March* 1996)