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# An Enantiospecific Approach to an Oxepane related to Zoapatanol *via* a 1,3-Dipolar Cycloaddition

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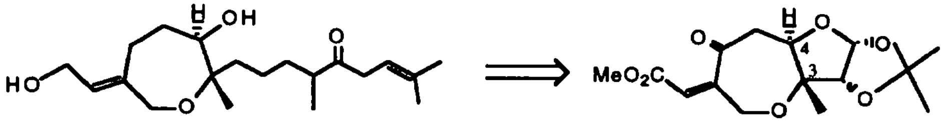
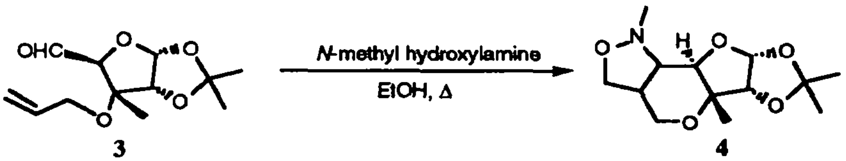
**Abstract:** The optically active oxepane **2**, which is a suitable intermediate for a synthesis of zoapatanol **1**, has been constructed from D-glucose involving an intramolecular nitrile oxide cycloaddition as the key step.

Zoapatanol **1** is one of the several 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 studies suggested that zoapatanol might have potential use as an antifertility agent.[2,3] The constitution of zoapatanol was determined in 1979,[4] and since then five syntheses have been reported.[5-9] The key step of these approaches is the oxygen-carbon bond formation, leading to the *O*-heterocyclic ring. All these syntheses,[5-8] except one,[9] constructed the oxepane ring in **1** by ring opening of an epoxide with an oxygen nucleophile under either basic or acidic conditions.[10] Disappointingly, all the synthetic materials obtained were racemates. This paper now discloses, starting from D-glucose, an approach to optically active zoapatanol in which the oxepane ring system **2** has been constructed *via* an intramolecular nitrile oxide cycloaddition (INOC)[11,12] strategy.



**1** **2**

Our recent work has shown that intramolecular nitrone cycloaddition (INC)[11,12] of nitrones formed 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.[13] Our initial attempts towards the oxepane ring system in **1** was to make use of the INC reaction. However, the aldehyde **3**, with the C-3,4 stereochemistry the same as that in zoapatanol, gave the undesired THP **4** attributable to steric reasons when subjected to an INC reaction.[13] Disappointingly, the acyclic aldehyde **5**[14] also afforded the undesired THP **6** *via* the same reaction.



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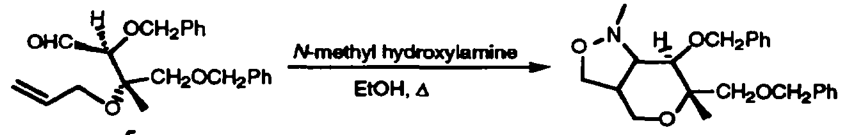
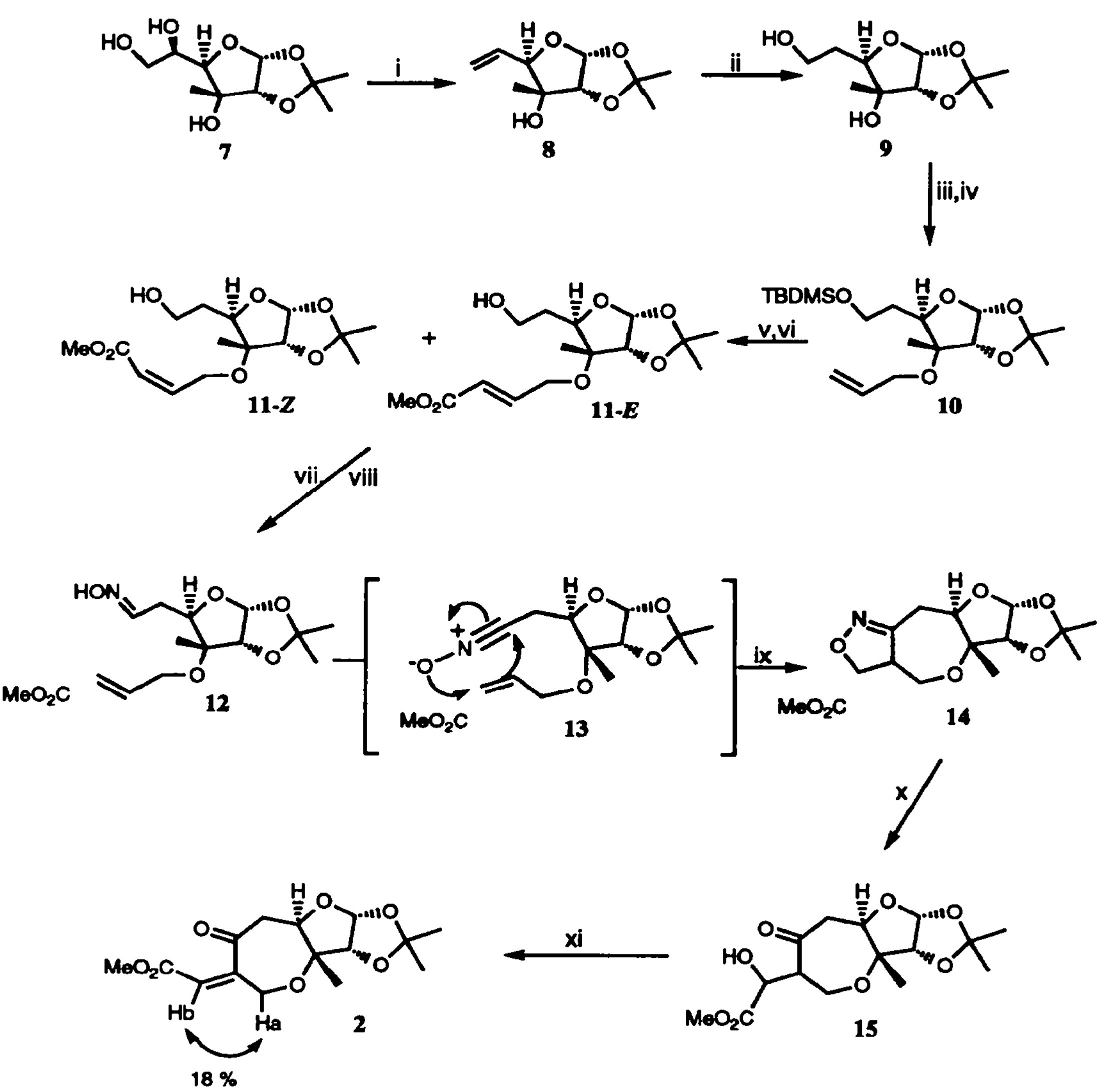


5 6

We then turned our attention to INOC reactions and reasoned that INOC reactions of oximes derived from β-allyloxy aldehydes should yield an oxepane ring exclusively based on the arguments already proposed[13] for the exclusive formation of THPs from γ-allyloxy oximes. In fact, this has been proved to be the case and the approach to the homochiral oxepane **2** is illustrated in Scheme 1.

The known triol **7**,[15] readily available from D-glucose in four steps, was converted into the olefin **8**,[16] m.p. 65—67 °C; $[\alpha]_D^{23}$ + 47° (*c* 0.6, $CHCl_3$), by the method of Garegg.[17] The alkene **8** underwent regioselective hydroboration in tetrahydrofuran (THF) and subsequent alkaline peroxide oxidation to afford the primary alcohol **9**, m.p. 83—85 °C; $[\alpha]_D^{23}$ + 49° (*c* 0.6, $CHCl_3$) The primary alcohol in **9** was selectively blocked with TBDMSCl as a silyl ether and the tertiary hydroxyl group was alkylated with allyl bromide to give the allyl ether **10**, $[\alpha]_D^{23}$ + 53° (*c* 0.8, $CHCl_3$). The terminal double bond in **10** 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 $CH_2Cl_2$ at room temperature to form a pair of isomers **11**-*Z* and **11**-*E* in a ratio of 1 to 3 respectively and in a combined overall yield of 94% from **10**. The two isomers **11**-*E* and **11**-*Z* were readily separated by chromatography as colourless oils and the geometry of the double bond was identified by measuring the coupling constant between the two vinylic protons in their $^1H$ NMR spectra. The alkene with the smaller coupling constant of 11.6 Hz was assigned to the *Z*-alkene, $[\alpha]_D^{23}$ + 128° (*c* 0.8, $CHCl_3$), and that with the large 15.6 Hz to the *E*-alkene, $[\alpha]_D^{23}$ + 45° (*c* 2.4, $CHCl_3$). It is noteworthy that the silyl blocking group was removed during ozonolysis and this unexpected desilylation is currently under investigation.

Oxidation of **11** as a mixture of geometric isomers afforded an aldehyde which was converted into the oxime **12** under standard conditions. The nitrile oxide **13** was then generated *in situ* during the biphasic oxidation of the oxime **12** in dichloromethane with aqueous sodium hypochlorite.[18] After stirring the reaction mixture vigorously at room temperature overnight, a pair of inseparable [3+2]-cycloadducts **14** (*ca.* 1:1 by $^1H$ NMR spectral analysis) were obtained. Hydrogenolysis of the mixture of isoxazolines **14** in an acidic medium with Raney-Ni[19] as the catalyst gave the hydroxy keto-esters **15** (*ca.* 1:1 mixture of diastereoisomers) which were then treated with methanesulfonyl chloride/triethylamine to give the α,β-unsaturated keto-ester **2** as white needles, m.p. 109.5—111 °C; $[\alpha]_D^{23}$ + 63° (*c* 0.8, $CHCl_3$). The resonance at δ 6.32 in the $^1H$ NMR



**Scheme 1.** *Reagents*: i, imidazole, triphenylphosphine, iodine, toluene, 58%; ii, borane-dimethylsulfide complex (2.0 M), THF, then $H_2O_2$, NaOH, 84.5%; iii, imidazole, TBDMSCl, cat. *N,N*-dimethylaminopyridine, $CH_2Cl_2$, 99%; iv, NaH, THF, then allyl bromide, 77%; v, $O_3$, $CH_2Cl_2$: MeOH (5:1), then dimethyl sulfide; vi, $Ph_3P{=}CHCO_2Me$, $CH_2Cl_2$, overall 94%; vii, PDC, 4Å molecular sieves, acetic acid, $CH_2Cl_2$; viii, hydroxylamine hydrochloride, pyridine, ethanol; ix, 10% aq. sodium hypochlorite, $CH_2Cl_2$, cat. triethylamine, overall 61%; x, Raney-Ni, $H_2$; xi, $MeSO_2Cl$, $CH_2Cl_2$, triethylamine, overall 52%.

spectrum of **2** indicated the presence of a single vinylic proton. The stereochemistry of the double bond in the oxepane **2** was ascertained from n.O.e. experiments. Thus irradiation of the methylene protons Ha resulted in a large n.O.e. enhancement (18%) of the vinylic proton Hb, thereby confirming that the two methylene protons Ha are at close proximity to Hb.

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.

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