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Diastereoselective synthesis of tetrahydrofuran-containing fragments by the permanganate oxidation of 1,5,9-trienes

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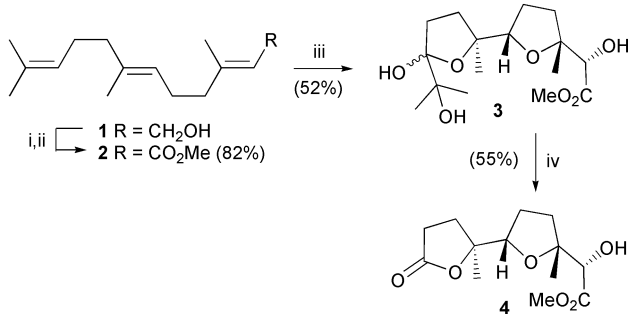
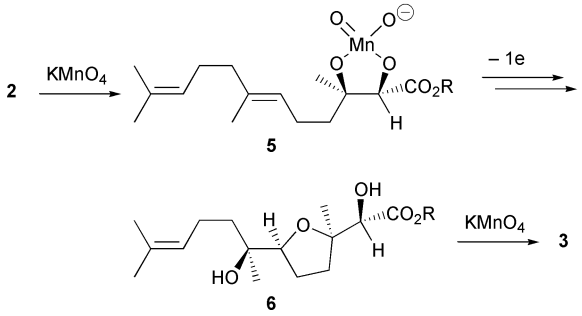
The permanganate oxidation of several readily accessible 1,5,9-trienes occurs regioselectively to provide very short diastereoselective routes to substituted octahydro-2,2′-bifuranyl systems.

Substituted tetrahydrofurans constitute important structural and functional sub-units of a variety of biologically active natural products including the polyether antibiotics and annonaceous acetogenins.[1,2] An attractive approach to the synthesis of *cis*-2,5-disubstituted tetrahydrofurans is the permanganate-promoted oxidative cyclisation of 1,5-dienes,[3–5] and there have been several elegant applications of oxidative cyclisation in the synthesis of polyether antibiotic fragments.[4,6,7] Unfortunately, modest yields and the non-availability of suitably functionalised isomerically pure 1,5-dienes have restricted more widespread application of oxidative cyclisation in natural product synthesis. Other metal oxo species have also been reported to effect oxidative cyclisation of 1,5-dienes,[8,9] although no overall advantage over the permanganate-promoted process is evident. Herein we report short diastereoselective syntheses of *cis*-2,5-disubstituted tetrahydrofuran-containing fragments that are suitably functionalised to permit further elaboration.

By exploiting the different reactivity of different types of olefin, regioselective oxidative cyclisation of certain 1,5,9-trienes can be achieved to provide rapid access to useful tetrahydrofuran building blocks. For example, oxidation of methyl (*E*,*E*)-farnesoate (**2**), obtained in 2 steps from (*E*,*E*)-farnesol (**1**),[10] by potassium permanganate in buffered aqueous acetone provides lactol **3** as an approximately 6:1 mixture of epimers (Scheme 1).[11] The formation of **3** can be explained by kinetically controlled attack at the C=C bond of the α,β-unsaturated ester,[12] leading to an intermediate hypomanganate diester **5**, which underwent extremely rapid oxidation to a manganate diester and cyclisation in line with the mechanism proposed by Baldwin (Scheme 2).[13] Independent oxidation of the remaining double bond present in **6** by permanganate afforded the observed product **3**. Lead tetraacetate cleavage of the vicinal diol completed the synthesis of the lactone **4** in an overall yield of 23% and in 4 steps from a commercial starting material.

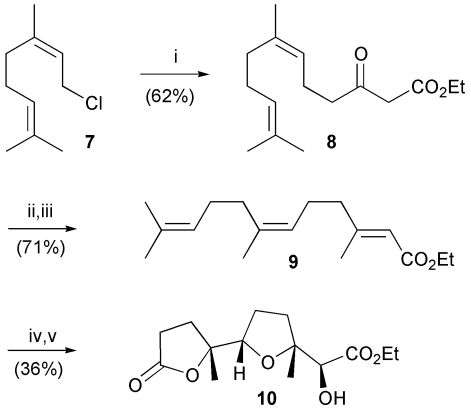


Scheme 1 *Reagents and conditions*: i, MnO_2, hexane; ii, MnO_4, KCN, AcOH, MeOH; iii, $KMnO_4$, AcOH, acetone, acetate buffer (pH 6.5); iv, $Pb(OAc)_4$, Na_2CO_3, CH_2Cl_2.



Scheme 2

The scope of the triene oxidation is increased by the availability of other double bond isomers of ethyl farnesoate, which can be prepared conveniently using methodology developed by Weiler.[14] For example, the dianion of ethyl acetoacetate was alkylated with neryl chloride (**7**) to afford β-ketoester **8** (Scheme 3), which underwent stereoselective conversion to the corresponding (*Z*)-enolphosphate. Treatment of the enolphosphate with lithium dimethylcuprate† gave the desired triene **9** as a single isomer‡ in good overall yield. Permanganate oxidation of ethyl (2*E*,6*Z*)-farnesoate (**9**) under the usual conditions provided an epimeric mixture of lactols, which was cleanly converted to a single diastereomeric lactone **10** upon brief exposure to lead tetraacetate. In principle, all four possible diastereoisomers of lactones **4** and **10** could be prepared from geraniol or nerol using this approach.[15]



Scheme 3 *Reagents and conditions*: i, ethyl acetoacetate, NaH (1 eq.), n-BuLi (1 eq.); ii, LiHMDS, $(EtO)_2POCl$; iii, Me_2CuLi, Et_2O; iv, $KMnO_4$, AcOH, acetone, phosphate buffer (pH 6.2); v, $Pb(OAc)_4$, Na_2CO_3, CH_2Cl_2.

Our interest in the synthesis of annonaceous acetogenins such as Asiminenin A led us to consider use of the triene oxidation to generate a suitable lactone precursor **12** (Scheme 4). The requisite triene **11** was synthesised following a route described by Hoye.[16] Oxidation of **11** with potassium permanganate afforded an apparently complex mixture of products, from which compounds **13** (9%), **14** (23%) and unexpectedly **12**

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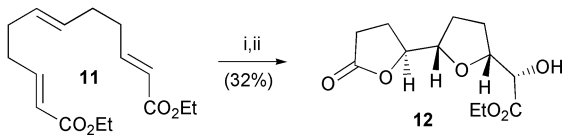
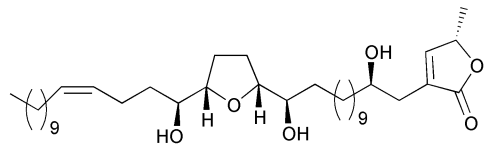
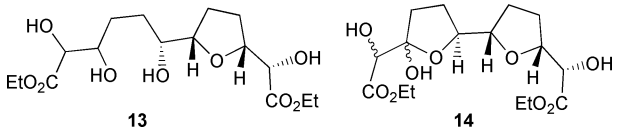


Scheme 4 *Reagents and conditions*: i, $KMnO_4$, AcOH, phosphate buffer (pH 6.2), acetone; ii, $NaIO_4$, acetone, H_2O.



Asiminenin A



(10%) were identified. Rigorous assignment of the proton NMR spectra of the major component **14** was complicated by the presence of a number of isomers. Further indirect evidence for the structure of **14** came from its oxidative cleavage to yield the desired lactone **12** using sodium metaperiodate. Alternatively, the crude reaction mixture obtained from the permanganate oxidation of **11** could be treated with sodium metaperiodate to afford the lactone **12** in 32% yield over the two steps. The *cis*-relationship of the side chains on the tetrahydrofuran ring was confirmed by means of NOE experiments.

In summary, we have presented a very short diastereoselective synthesis of potentially useful tetrahydrofuran-containing fragments from readily accessible 1,5,9-trienes. The use of a chiral auxiliary in the oxidative cyclisations would provide the corresponding optically enriched tetrahydrofurans.[6,7] Future work will focus on the application of the oxidative cyclisation in the synthesis of the annonaceous acetogenin natural products and synthetic ionophores.

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Notes and references

† We found it essential that methyllithium in ether was used in this reaction. On one occasion when a THF solution of methyllithium containing cumene was used a mixture of the desired product and the reduced *E*-disubstituted olefin was obtained (ratio of 5:1 estimated from the 300 MHz ^{1}H NMR spectrum).

‡ Only one isomer was observed in the 300 MHz ^{1}H NMR spectrum of **9**.

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