A metal–oxo mediated approach to the synthesis of 21,22-diepi-membrarollin†

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A synthesis of 21,22-diepi-membrarollin (14) is described, which employed sequential metal–oxo mediated oxidative cyclisations to introduce six of the seven stereogenic centres.

The oxidative cyclisation of 1,5-dienes using metal–oxo complexes provides a powerful approach to 2,5-*bis*-hydroxyalkyl substituted tetrahydrofurans (THF diols), allowing control of relative stereochemistry at up to four newly formed stereogenic centres.[1–3] Enantiomerically enriched THF diols have been obtained directly from 1,5-dienes either by using chiral auxiliaries or chiral phase-transfer catalysts.[1d–i] As part of studies towards the synthesis of acetogenin natural products containing adjacent *bis*-THF motifs (Fig. 1),[4] we considered an approach involving two sequential oxidative cyclisations. Selective oxidative cyclisation of a dienyne would give THF diol **2** (Scheme 1), which retains a C–C multiple bond suitable for elaboration to the *bis*-THF **3** by semi-hydrogenation followed by a second directed oxidative cyclisation. In principle, the relative stereochemistry in the second THF ring in **3** could be controlled through choice of metal–oxo or metal–peroxo mediated cyclisation and by the starting olefin geometry.[5,6]

One key question central to the success of the strategy described above would be whether a powerful oxidant such as permanganate could be used in selective oxidations of multiply unsaturated substrates. To this end, the permanganate-promoted oxidation of dienyne **6** was investigated (Scheme 2). Oxidative cyclisation of the dienyne **6** in acetone and AcOH was found to proceed rapidly and selectively at low temperature, affording the THF diols **7** and **8** as a separable mixture of diastereoisomers (d.r. **7** : **8** = 6 : 1 from ^{1}H NMR of crude mixture). Significantly, products arising from alkyne oxidation were not evident.

The usefulness of product **7** was exemplified by elaboration of its 1-hydroxyprop-4-ynyl side-chain, generating the adjacent *bis*-THF motif found in cytotoxic anti-tumor acetogenin natural products.[4] Thus, alkyne **7** was reduced to give the (*Z*)-olefin **9** that underwent an acyl perrhenate-promoted hydroxyl-directed oxidative cyclisation reaction to afford a single isolated diastereoisomeric *bis*-THF **10** in excellent yield.[6] The stereochemistry of the *bis*-THF diol unit in **10** was assigned from analysis of the ^{1}H NMR spectra of the (*R*) and (*S*)-Mosher ester derivatives **16** and **17** of subsequent synthetic intermediates (Fig. 2).[7–9] A series of established steps was employed to complete the synthesis of an adjacent *bis*-THF acetogenin analogue 21,22-diepi-membrarollin (**14**),[1h,10] notably avoiding the use of any hydroxyl protecting groups.

The *trans*-stereoselectivity observed from the acyl perrhenate-mediated oxidative cyclisation of **7** can be rationalised by invoking a chair-like transition state **B** (Fig. 3).[9] An alternative transition state arrangement **A**, which would lead to the creation of the 2,5-*cis*-disubstituted THF, is presumably disfavoured due to steric interactions between the bulky hydroxyalkyl substituent on the first THF ring and the metal–oxo complex.

In summary, we have developed a short route into the adjacent *bis*-THF motif present in acetogenins. The strategy is notable in that metal–oxo mediated oxidative cyclisation reactions are used to create six of the seven stereogenic centres without the requirement for any hydroxyl protecting groups.

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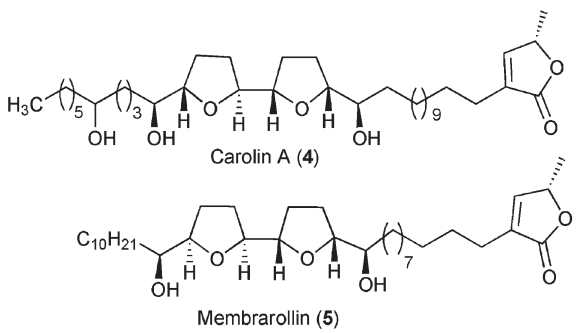
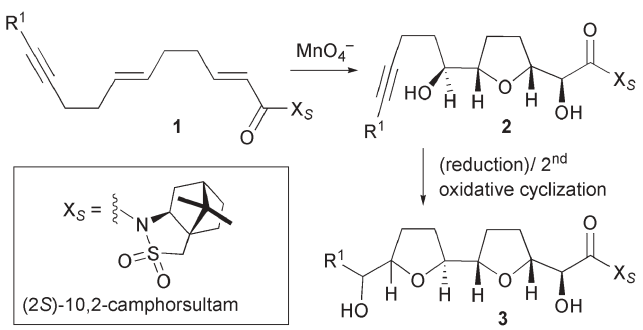


Fig. 1 Examples of adjacent *bis*-THF acetogenins.



Scheme 1 Oxidative cyclisation approach to adjacent *bis*-THFs.

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† Electronic supplementary information (ESI) available: details of the stereochemical assignment in **16** and **17**. See DOI: 10.1039/b512126d
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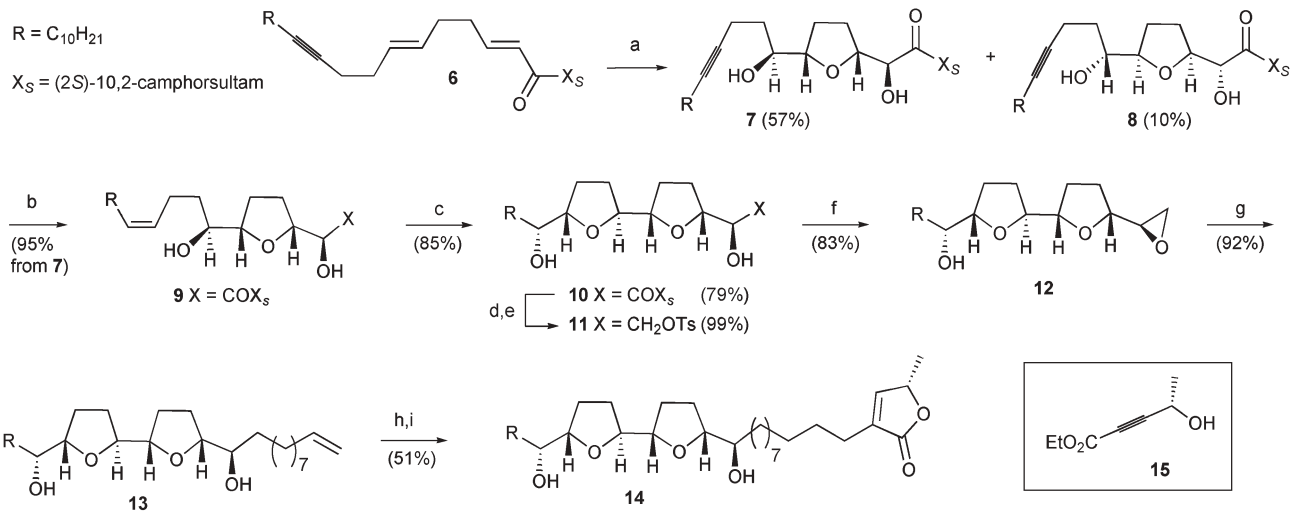

Scheme 2 *Reagents and conditions*: a) $KMnO_4$, acetone–AcOH (1 : 1); b) H_2, $Pd/BaSO_4$, quinoline, hexane; c) Re_2O_7, THF, TFAA; d) $NaBH_4$, THF, H_2O; e) Bu_2SnO, benzene, TsCl, TBAB; f) DBU, CH_2Cl_2; g) $CH_2{=}CH(CH_2)_7MgBr$, CuI, THF; h) **15**, CpRu(COD)Cl, CH_3OH; i) $TsNHNH_2$, THF, NaOAc, H_2O.

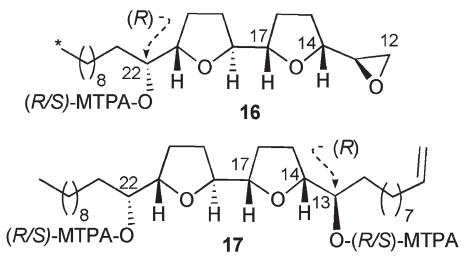

Fig. 2 Mosher's ester derivatives used to determine the stereochemistry at C21 and C22.

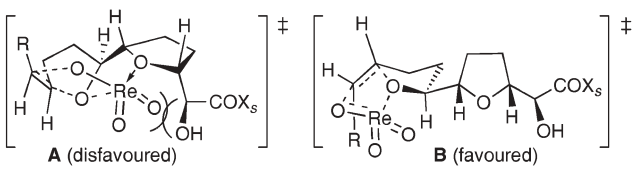

Fig. 3 Possible transition states **A** and **B** for the perrhenate-mediated oxidative cyclisation of **9**, leading to *cis*,*cis* or *cis*,*trans bis*-THF motifs respectively.

Notes and references

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8 For further details of the stereochemical assignment see supporting information.

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