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Stereoselective synthesis of *cis*-2,6-bis-hydroxyalkyl-tetrahydropyrans by the permanganate promoted oxidative cyclisation of 1,6-dienes

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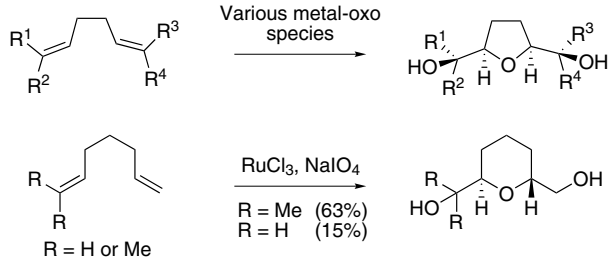
Abstract—The first examples of permanganate promoted oxidative cyclisations of 1,6-dienes are described, providing exclusively *cis*-2,6-bis-hydroxyalkyl-tetrahydropyrans. In addition, good levels of asymmetric induction have been attained using dienoyl sultam substrates.

Tetrahydrofuran (THF) and tetrahydropyran (THP) rings are key structural and functional features present in many biologically active natural products, such as polyether antibiotics and *Annonaceous* acetogenins.[1,2] A powerful method for the synthesis of *cis*-2,5-bis-hydroxyalkyl-tetrahydrofurans (THF diols) is by oxidative cyclisation of 1,5-dienes using transition metal-oxo species (Mn, Os, Ru, Scheme 1).[3,4] When MnO_4^- is used as the oxidising agent, high levels of asymmetric induction may be attained using either chiral auxiliaries or a chiral phase-transfer catalyst.[3f–j,5]



Scheme 1. Oxidative cyclisation of 1,5-dienes and 1,6-dienes to provide THF diols and THP diols, respectively.

Recently, Piccialli has demonstrated that ruthenium oxo species may be used to catalyse the stereoselective oxidative cyclisation of 1,6-dienes to afford racemic *trans*-2,6-bis-hydroxyalkyl-tetrahydropyrans (THP diols, Scheme 1).[6] In contrast, the 1,6-diene, linalyl acetate, had been reported not to undergo cyclisation in the presence of permanganate.[3b] Here we report our preliminary results detailing the first examples of permanganate promoted oxidative cyclisation of 1,6-dienes to afford THP diols with the controlled creation of up to four new stereogenic centres.

Previous work established that 1,5-dienoyl compounds and 1,5-dienones were excellent substrates for permanganate promoted oxidative cyclisation, therefore the homologous 1,6-dienes were prepared following established methods (Scheme 2). Swern oxidation of alcohols **1** and **2** gave the corresponding aldehydes **3** and **4**,[7] which were converted to the desired α,β-unsaturated arylketones **7** and **8** by a sequence involving aldol reaction and dehydration.[8] Dienoyl sultams **10** and **11** were prepared directly from the aldehydes **3** and **4** using the Horner–Emmons reagent **9**.[3j,9]

Permanganate mediated oxidative cyclisation was first carried out on the dienone **7** using the AcOH:acetone conditions previously reported by us (Scheme 3).[3j] Pleasingly, THP-diol **12** (17%) was obtained as one of two isolated products, the other being 4-methoxybenzoic acid (15%). In an effort to improve the yield of THP diol **12**, oxidation under phase-transfer conditions was

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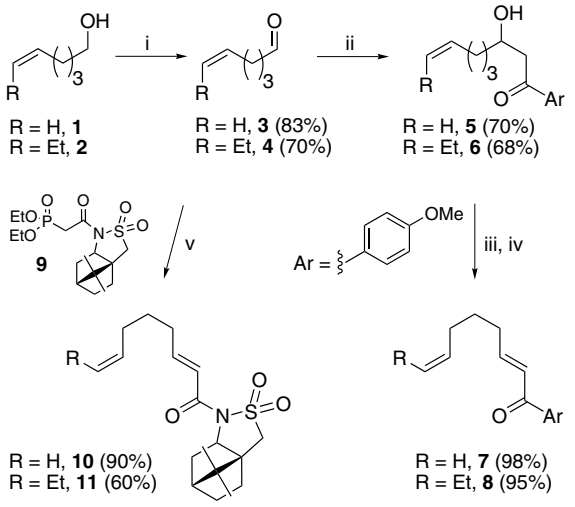
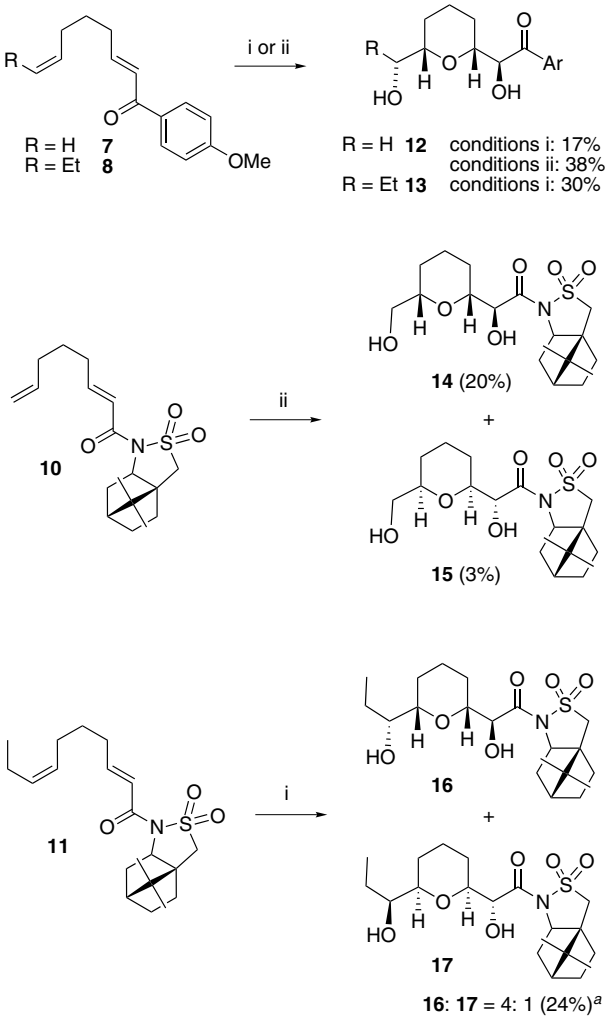


Scheme 2. Reagents and conditions: (i) DMSO, $(COCl)_2$, CH_2Cl_2, −60 °C, then Et_3N; (ii) 4-methoxy acetophenone, LDA, THF, −60 °C; (iii) MsCl, Et_3N, CH_2Cl_2; (iv) DBU, CH_2Cl_2; (v) NaH, CH_2Cl_2, then **3** or **4**, 0 °C.

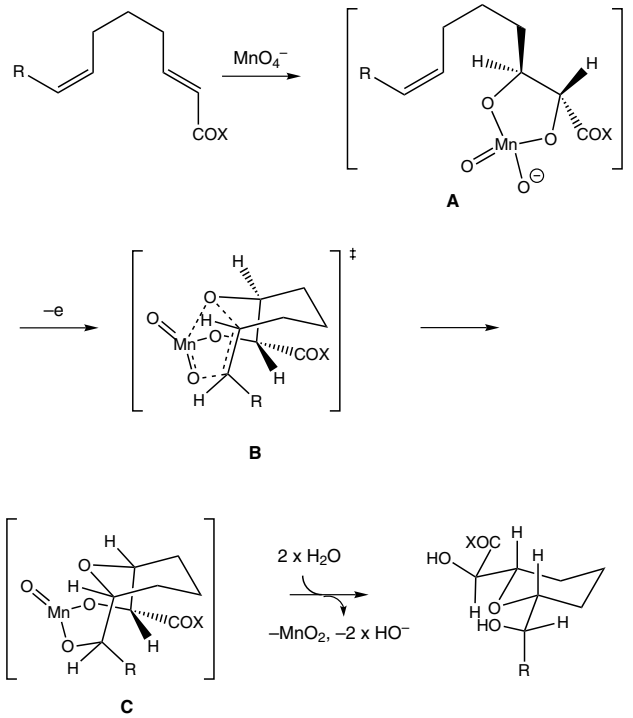


Scheme 3. Reagents and conditions: (i) $KMnO_4$ (1.4 equiv), AcOH:acetone (2:3), −15 °C; (ii) $KMnO_4$ (1.4 equiv), adogen 464 (10 mol%), AcOH (16 equiv), CH_2Cl_2, −60 °C. [a]Ratio estimated from the ^1H NMR spectrum of the inseparable mixture of diastereoisomers after column chromatography.

investigated.[5] Carrying out the reaction in CH_2Cl_2 at −60 °C led to a significant improvement, increasing the yield of **12** to 38%. Aqueous permanganate conditions were also applied but this provided the cyclised product in only 5% yield. The corresponding 2,6-*trans*-disubstituted THP was not observed in any of the reactions.

The oxidative cyclisations of the three additional 1,6-dienes (**8**, **10** and **11**) were performed using the conditions described above, returning the desired THP diols in moderate yields but good diastereoselectivity (Scheme 3).[10] It is noteworthy that the camphor sultam auxiliary may be used to obtain enantiomerically enriched THP diol-containing fragments, which will be useful in target synthesis.

The relative stereochemistry of the 2,6-disubstituted THP diol product **12** was assigned as *cis* on the basis of ^1H NMR coupling constant data from the C2 and C6 protons. Assignment of the relative stereochemistry in THP diol **12** was ultimately confirmed by X-ray crystallography.[11] The observed relative stereoselectivity within the THP diol moiety may be accounted for by initial suprafacial [3+2] cycloaddition of MnO_4^- with the more electron deficient olefin to generate an intermediate Mn(V) diester **A** (Scheme 4). By analogy to the proposed mechanism for oxidative cyclisation of 1,5-dienes;[3b,12] oxidation of Mn(V) to Mn(VI) precedes cyclisation through a chair-like transition state **B** to afford Mn(IV) diester **C**. Hydrolysis of intermediate **C** will then lead to the THP diol product. Control of absolute stereochemistry results from the camphor sultam directing the initial attack of MnO_4^- to one face of the more reactive enoyl olefin bond.[3f,j]



Scheme 4. Proposed mechanism for the permanganate-mediated oxidative cyclisation of 1,6-dienes.

In conclusion, we have developed a simple permanganate-mediated oxidative cyclisation of 1,6-dienes to provide *cis*-2,6-disubstituted THP diols with excellent control of relative stereochemistry. Furthermore, we have demonstrated the potential of this reaction for the synthesis of enantiomerically enriched THP fragments containing up to four new stereocentres. Further work is underway to improve the chemical efficiency of this new oxidative cyclisation, and to illustrate its utility in target synthesis.

Acknowledgements

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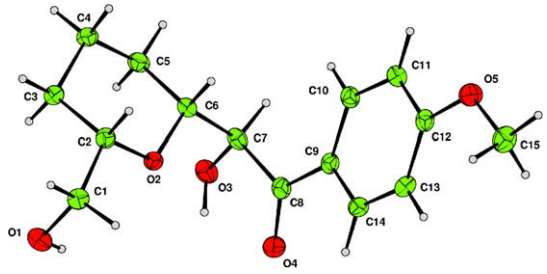
References and notes

1. Polyether antibiotics: (a) Dutton, C. J.; Banks, B. J.; Cooper, C. B. *Nat. Prod. Rep.* **1995**, *12*, 165–181; Marine polyether triterpenes: (b) Fernandez, J. J.; Souto, M. L.; Norte, M. *Nat. Prod. Rep.* **2000**, *17*, 235–246; Annonaceous acetogenins: (c) Alali, F. Q.; Liu, X. X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504–540.
2. For reviews covering synthetic routes to THFs and THPs: (a) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309–3362; (b) Harmange, J.-C.; Figadere, B. *Tetrahedron: Asymmetry* **1993**, *4*, 1711–1754; (c) Elliott, M. C.; Williams, E. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2303–2340; (d) Faul, M. M.; Huff, B. E. *Chem. Rev.* **2000**, *100*, 2407–2473.
3. $KMnO_4$: (a) Klein, E.; Rojahn, W. *Tetrahedron* **1979**, *21*, 2353–2358; (b) Baldwin, J. E.; Crossley, M. J.; Lehtonen, E.-M. M. *J. Chem. Soc., Chem. Commun.* **1979**, 918–919; (c) Walba, D. M.; Wand, M. D.; Wilkes, M. C. *J. Am. Chem. Soc.* **1979**, *101*, 4396–4397; (d) Walba, D. M.; Edwards, P. D. *Tetrahedron Lett.* **1980**, *21*, 3531–3534; (e) Spino, C.; Weiler, L. *Tetrahedron Lett.* **1987**, *28*, 731–734; (f) Walba, D. M.; Przybyla, C. A.; Walker, C. B. *J. Am. Chem. Soc.* **1990**, *112*, 5624–5625; (g) Kocienski, P. J.; Brown, R. C. D.; Pommier, A.; Procter, M.; Schmidt, B. *J. Chem. Soc., Perkin Trans. 1* **1998**, 9–40; (h) Brown, R. C. D.; Hughes, R. M.; Keily, J.; Kenney, A. *Chem. Commun.* **2000**, 1735–1736; (i) Brown, R. C. D.; Bataille, C. J.; Hughes, R. M.; Kenney, A.; Luker, T. J. *J. Org. Chem.* **2002**, *67*, 8079–8085; (j) Cecil, A. R. L.; Hu, Y.; Vicent, M. J.; Duncan, R.; Brown, R. C. D. *J. Org. Chem.* **2004**, *69*, 3368–3374.
4. Oxidative cyclisation of 1,5-dienes using other metal-oxo species: (a) Ruthenium: Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938; (b) Piccialli, V.; Cavallo, N. *Tetrahedron Lett.* **2001**, *42*, 4695–4699; (c) Albarella, L.; Musumeci, D.; Sica, D. *Eur. J. Org. Chem.* **2001**, 997–1003; (d) Bifulco, G.; Caserta, V.; Gomez-Paloma, L.; Piccialli, V. *Tetrahedron Lett.* **2003**, *44*, 3429–3429; (e) Osmium: Donohoe, T. J.; Winter, J. J. G.; Helliwell, M.; Stemp, G. *Tetrahedron Lett.* **2001**, *42*, 971; (f) de Champdore, M.; Lasalvia, M.; Piccialli, V. *Tetrahedron Lett.* **1998**, *39*, 9781; (g) Donohoe, T. J.; Butterworth, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 978–981.
5. Brown, R. C. D.; Keily, J. F. *Angew. Chem., Int. Ed.* **2001**, *40*, 4496–4498.
6. Piccialli, V. *Tetrahedron Lett.* **2000**, *41*, 3731–3733.
7. Mancuso, A.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482.
8. Oare, D. A.; Henderson, M. A.; Sanner, M. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 132–157.
9. Oppolzer, W.; Dupuis, D.; Poli, G.; Raynham, T. M.; Bernardinelli, G. *Tetrahedron Lett.* **1988**, *29*, 5885–5888.
10. Procedure for oxidative cyclisation of dienone **8** to THP diol **13**: At −15 °C under N_2, powdered $KMnO_4$ (51.4 mg, 0.33 mmol) was added in one batch to a rapidly stirring solution of diene **8** (60 mg, 0.23 mmol) in AcOH/acetone (2:3, 2 mL). After 35 min, the reaction was quenched with satd $Na_2S_2O_{5(aq)}$ (5 mL) and H_2O (3 mL). EtOAc (10 mL) was added and the organic phase separated. The aqueous phase was extracted with EtOAc (2 × 10 mL) and the combined organic phase was dried ($MgSO_4$) and concentrated in vacuo. Purification by silica gel column chromatography (EtOAc/hexane, 2:3 to 1:1) gave the THP-diol **13** as a colourless oil (21 mg, 0.1 mmol, 30%). IR ν_{max} (neat) 3465 (br), 2937 (s), 1675 (s), 1600 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.92 (2H, d, $J = 8.8$ Hz), 6.97 (2H, d, $J = 8.8$ Hz), 4.99 (1H, d, $J = 2.8$ Hz), 3.89 (3H, s), 3.77 (1H, dt, $J = 11.1$, 2.8 Hz), 3.40 (1H, dt, $J = 4.3$, 8.3 Hz), 3.11 (1H, ddd, $J = 2.3$, 4.3, 11.2 Hz), 1.97–1.17 (8H, m), 0.87 (3H, t, $J = 7.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 164.2, 131.1, 127.7, 114.0, 80.5, 79.4, 75.2, 74.9, 55.7, 26.6, 24.8, 24.5, 22.8, 10.2; LRMS (ES^+) *m/z* 639 (100%, $[2M+Na]^+$), 331 (80%, $[M+Na]^+$); Elemental calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 66.33; H, 7.71.
11. Dr. M. E. Light and Professor M. B. Hursthouse are thanked for X-ray crystallographic analysis. Crystallographic data (excluding structure factors) for THP diol **14** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 241371. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].



12. Wolfe, S.; Ingold, C. F. *J. Am. Chem. Soc.* **1981**, *103*, 940–941.