Pergamon

Tetrahedron Letters 42 (2001) 971–974

TETRAHEDRON LETTERS

Hydrogen bonding control in the oxidative cyclisation of 1,5-dienes

Timothy J. Donohoe,[a,*] Jonathan J. G. Winter,[a] Madeleine Helliwell[a,†] and Geoffrey Stemp[b]

[a]*Department of Chemistry, University of Manchester, Oxford Road, Manchester M13 9PL, UK*
[b]*SmithKlineBeecham Pharmaceuticals, New Frontiers Science Park, Harlow, Essex CM19 5AW, UK*

Received 14 October 2000; accepted 5 December 2000

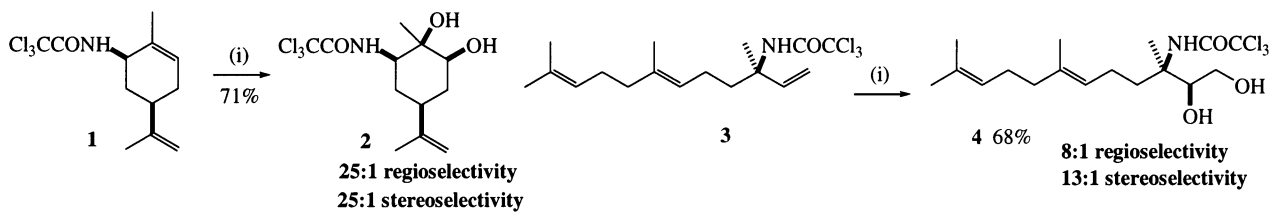
Abstract—The regioselective dihydroxylation of a series of functionalised polyenes is described. Under acidic conditions, the osmate ester derivatives obtained from oxidation with OsO_4/TMEDA undergo an intramolecular cyclisation reaction forming functionalised tetrahydrofurans with high stereoselectivity and in good yield. The generality of this method is illustrated with an application to the synthesis of a bis-tetrahydrofuran ring system.

Recently we reported that the combination of osmium tetroxide and TMEDA forms a reagent that is a willing hydrogen bond acceptor. Oxidation of a series of cyclic allylic alcohols[1] and amides[2] with this reagent gives a directed dihydroxylation reaction resulting in the formation of *syn* stereoisomers that are difficult to access by other means. We have also reported preliminary results on the oxidation of allylic alcohols containing more than one alkene unit and have shown that hydrogen bonding is a viable means of controlling regioselectivity.[1] As an extension of these studies we had cause to oxidise a series of allylic trichloroacetamides using the OsO_4/TMEDA combination (Scheme 1). As expected, the reactions were regioselective forming the diol products derived from attack at the proximal alkene. In each case the oxidation regime involved addition of the transition metal and TMEDA in dichloromethane at −78°C, followed by hydrolysis of the resulting osmate ester with acidic methanol.

In fact, the two oxidations illustrated below show that the directed dihydroxylation reaction is capable of controlling not only regioselectivity, but also gives (*syn*) stereoselectivity in both cyclic and acyclic[3] systems.

Dihydroxylation of alkenes **1** and **3** under more standard conditions (UpJohn- cat. OsO_4, NMO, acetone/water) did not show any comparable regio- or stereoselectivity. For example, the di-substituted alkene within compound **1** was oxidised exclusively (with no control of stereoselectivity) while the C-6,7 and C-10,11 alkenes within compound **3** were oxidised in approximately equal proportions (again with no control of stereoselectivity). The results shown in Scheme 1 illustrate that this method is particularly useful and unique for directing the oxidation of multifunctional compounds.

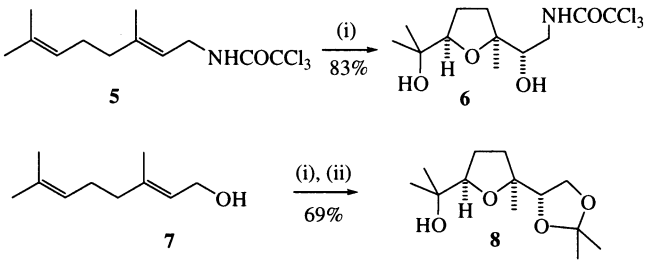
We then attempted the regioselective oxidation of alkenes **5** and **7**, fully expecting to achieve good yields of



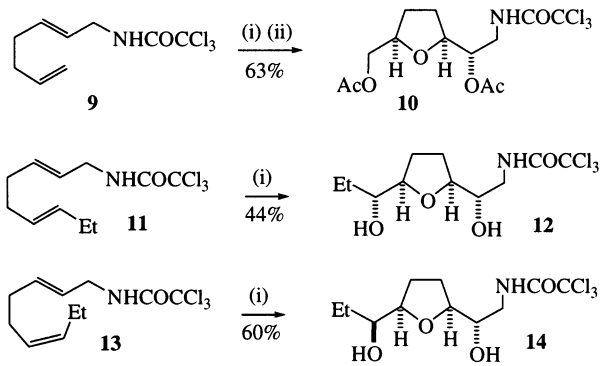
Scheme 1. *Reagents*: (i) OsO_4 (1 equiv.), TMEDA (1 equiv.), CH_2Cl_2, −78°C; then MeOH, HCl, rt.

* Corresponding author. E-mail: t.j.donohoe@man.ac.uk
† Author to whom correspondence regarding the crystal structures should be addressed.

0040-4039/01/$ - see front matter
PII: S0040-4039(00)02225-5



Scheme 2. *Reagents*: (i) OsO_4 (1 equiv.), TMEDA (1 equiv.), CH_2Cl_2, −78°C; then MeOH, HCl, rt; (ii) $(MeO)_2CMe_2$, TFA.



Scheme 3. *Reagents*: (i) OsO_4 (1 equiv.), TMEDA (1 equiv.), CH_2Cl_2, −78°C; then MeOH, HCl, rt; (ii) Ac_2O, Et_3N, CH_2Cl_2.

the corresponding dihydroxylated products (Scheme 2). While the initial osmylation proceeded as expected to give osmate esters, decomplexation of these esters gave not diol products, but high yields of the tetrahydrofurans **6** and **8** that had resulted from a further oxidative cyclisation of the intermediate osmate ester complexes.

The oxidative cyclisation of other 1-trichloroacetamide-2,6-dienes was investigated and we discovered that the cyclisation reaction was fairly general with yields ranging from 44 to 63% (Scheme 3).[4] The corresponding allylic alcohols also cyclised to tetrahydrofurans, but in yields that were 10–20% lower.[5]

The structures of compounds **8** and **14** were proven by X-ray crystallography on derivatives (Fig. 1).[6]

Finally, we also oxidised the farnesyl derivative **15** and isolated the cyclised product in good yield, 72% (Scheme 4). In order to manipulate the structure, and illustrate the utility of the methodology, we then protected the secondary alcohol (Ac_2O) and cleaved the alkene (Lemieux) to furnish a lactol.[7g] This compound was oxidised to the lactone **17** using Jones reagent. Given the widespread occurrence of tetrahydrofurans in nature, and that bis-tetrahydrofuran structures are the key constituents of a variety of acetogenin natural products, we expect that this methodology will prove to be of use in synthesis.

These types of oxidative cyclisation have been reported before, most notably with potassium permanganate[7] and chromium trioxide,[8] although a single recent report detailed the oxidative cyclisation of geranyl and neryl acetates with osmium tetroxide while this work was in progress.[9] It is fair to say that, generally, such cyclisations can give fairly low yields of tetrahydrofuran products, probably because of over oxidation of the substrate/reaction products.

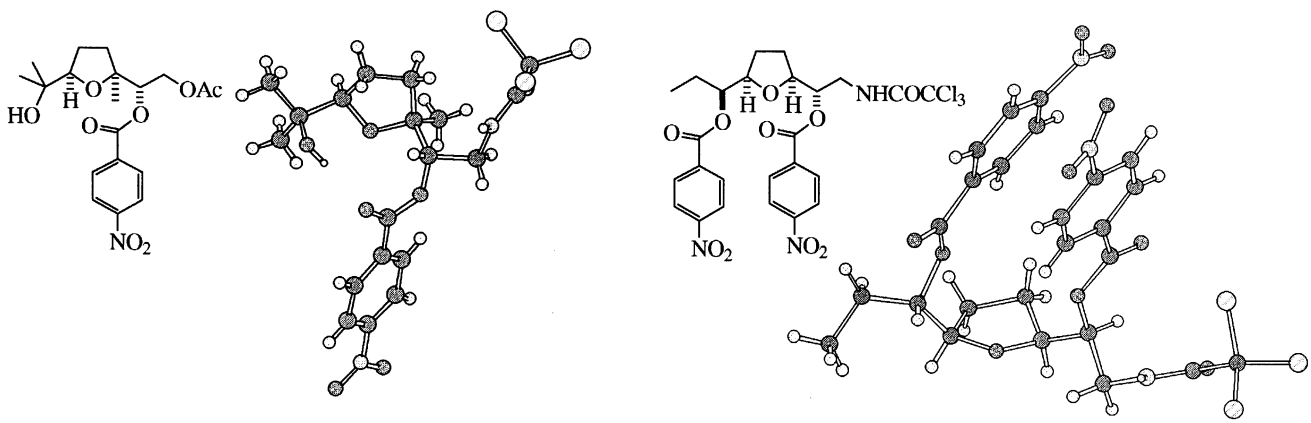
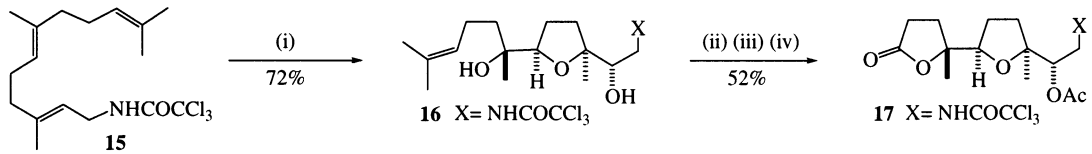


Figure 1.



Scheme 4. *Reagents*: (i) OsO_4 (1 equiv.), TMEDA (1 equiv.), CH_2Cl_2, −78°C; then MeOH, HCl, rt; (ii) Ac_2O; (iii) OsO_4 (cat.) quinuclidine, $NaIO_4$; (iv) CrO_3, H_2SO_4, acetone.

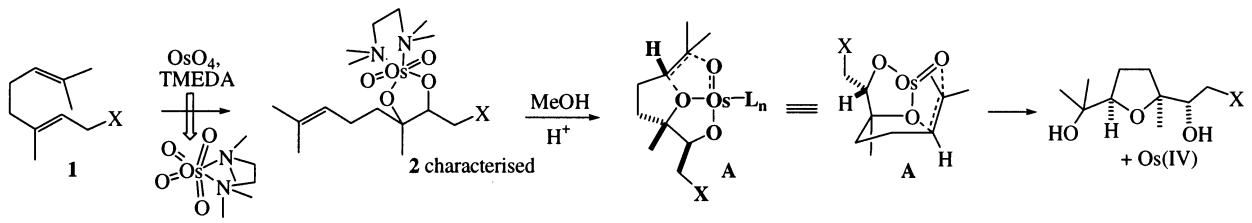


Figure 2.

In terms of mechanism we are confident that the reaction initiates with a regioselective dihydroxylation of the polyene, controlled by hydrogen bonding (in some cases we have been able to fully characterise the resulting osmate esters). For the cyclisation process we invoke addition of the O–Os=O fragment across the remote alkene bond as originally proposed by Baldwin for $KMnO_4$.[10] This process would involve reduction of Os(VI) to Os(IV), and the cyclisation is possible because the reacting partners are intramolecular. Subsequent hydrolysis of the osmate ester in situ would produce the diol product. At this time, we do not have any evidence to indicate the nature of the other ligands on osmium as it undergoes the oxidative cyclisation and it could be the case that acid serves to promote whatever ligand exchange is necessary to allow cyclisation to occur. Alternatively, acid could protonate the oxo ligands thus making the metal a better electrophile and more reactive in the cyclisation. If this addition mechanism is correct then we would expect the cyclisation to be stereospecific with respect to addition across the alkene (and this is certainly borne out by the oxidation of **11** and **13**). It is also worth noting that there is a clear stereoselectivity for formation of a *cis*-tetrahydrofuran (Fig. 2). The preference for production of *cis*-tetrahydrofurans is explained via reaction through transition structure **A**; the intact glycol osmium bonds help to enforce the *cis* stereochemistry across the incipient five-membered ring.

This method of cyclisation should prove relatively easy to study because we know that osmium(VI) is the active oxidising agent and we also know which alkene is oxidised first. Indeed, this ability to separate the initial osmylation reaction from the cyclisation event should prove invaluable in developing and understanding the method further, particularly with regard to catalytic variants. The good yields recorded in this paper bode well for the introduction of an efficient and stereoselective oxidation protocol based on the use of osmium and using hydrogen bonding as a controlling element.

Acknowledgements

We thank the EPSRC and SmithKline Beecham for funding this work. AstraZeneca, Pfizer and GlaxoWellcome are thanked for unrestricted support which aided the project. We also thank R. C. D. Brown for useful discussions.

References

1. Donohoe, T. J.; Moore, P. R.; Waring, M. J.; Newcombe, N. J. *Tetrahedron Lett.* **1997**, *38*, 5027.
2. (a) Donohoe, T. J.; Blades, K.; Moore, P. R.; Winter, J. J. G.; Helliwell, M.; Stemp, G. *J. Org. Chem.* **1999**, *64*, 2980; (b) Donohoe, T. J.; Blades, K.; Winter, J. J. G.; Stemp, G. *Tetrahedron Lett.* **2000**, *41*, 4701.
3. Donohoe, T. J.; Waring, M. J.; Newcombe, N. J. *Tetrahedron Lett.* **1999**, *40*, 6881.
4. Diene **5** was prepared from commercially available geranyl amine. The remaining substrates were prepared from the transposed allylic alcohol via the Overman rearrangement (**1**, **3**, **11** and **13**) or from the structurally analogous allylic alcohol via the Mitsunobu reaction (using phthalimide nucleophile) followed by deprotection ($MeNH_2$) and acylation (Cl_3CCOCl) (**9** and **15**).
5. We hypothesise that the lower yields with allylic alcohols are a consequence of migration of the initially formed osmate esters and that these rearranged esters then hydrolyse rather than cyclise.
6. Compounds **8**, **10**, **14** and **16** showed similar NMR spectra and their structures are assigned by analogy. All new compounds displayed spectroscopic data consistent with their structures and were fully characterised ($^1H/^{13}C$ NMR, mass spectrometry, IR and HRMS or microanalysis).

   Representative procedure: Farnesyl trichloroacetamide **15** (61 mg, 0.17 mmol) was dissolved in CH_2Cl_2 (15 mL) and cooled to −78°C under an atmosphere of nitrogen. To this mixture was added TMEDA (19 mg, 0.17 mmol), then osmium tetroxide (42 mg, 0.17 mmol). The solution turned a dark brown and was allowed to warm to rt over 2 h, then concentrated to dryness in vacuo. The resulting brown oily solid was redissolved in methanol and conc. HCl (two drops) was added. This mixture was then stirred for 2 h until a yellow precipitate had formed, then the mixture was partially concentrated in vacuo to a brown liquid. This material was loaded onto a column of silica gel and purified by flash column chromatography to give **16** (50 mg, 72% yield). Compound **16** was protected as the mono-acetate under standard conditions (excess Et_3N and Ac_2O in CH_2Cl_2) producing a colourless oil (41 mg, 74% yield); ν_{max}(film)/cm^{-1} 3348, 2973, 1717 and 1522; δ_H (300 MHz; $CDCl_3$) 1.08 (3H, s), 1.30 (3H, s), 1.43–1.60 (2H, m), 1.60 (3H, s), 1.68 (3H, s), 1.80–2.10 (6H, m), 2.10 (3H, s), 2.22 (1H, br s), 3.54 (1H, dd, *J* 5.7 and 14.7), 3.82 (1H, ddd, *J* 1.8, 5.1 and 14.7), 3.92 (1H, t, *J* 6.5), 5.02 (1H, dd, *J* 1.8 and 5.6), 5.12 (1H, dd, *J* 5.9 and 7.0), and 7.38 (1H, br s); δ_C (75 MHz; $CDCl_3$) 17.6, 20.8, 21.6, 22.4, 23.7, 25.6, 25.8, 35.2, 40.3, 42.0, 72.8, 75.6, 83.5, 84.6, 124.4, 131.4, 162.2 and 170.9.

7. (a) Klein, E.; Rojahn, W. *Tetrahedron* **1965**, *21*, 2353; (b) Walba, D. M.; Wand, M. D.; Wilkes, M. C. *J. Am. Chem. Soc*. **1979**, *101*, 4396; (c) Walba, D. M.; Edwards, P. D. *Tetrahedron Lett*. **1980**, *21*, 3531; (d) Spino, C.; Weiler, L. *Tetrahedron Lett*. **1987**, *28*, 731; (e) Walba, D. M.; Przybyla, C. A.; Walker, C. B. *J. Am. Chem. Soc*. **1990**, *112*, 5624; (f) Kocienski, P. J.; Brown, R. C. D.; Pommier, A.; Procter, M.; Schmidt, B. *J. Chem. Soc*., *Perkin Trans. 1* **1998**, 9; (g) Brown, R. C. D.; Hughes, R. M.; Keily, J.; Kenney, A. *Chem. Commun*. **2000**, 1735.
8. Walba, D. M.; Stoudt, G. S. *Tetrahedron Lett*. **1982**, *23*, 727.
9. Piccialli, V. *Tetrahedron Lett*. **2000**, *41*, 3731. Oxidation of **5** using 5 mol% OsO_4 (Piccialli's conditions) gave compound **6** in 30% yield, illustrating the potential of this method to be used with catalytic OsO_4.
10. Baldwin, J. E.; Crossley, M. J.; Lehtonen, E.-M. M. *J. Chem. Soc*., *Chem. Commun*. **1979**, 918.