Pergamon

Tetrahedron Letters 42 (2001) 8951–8954

TETRAHEDRON LETTERS

Homoallylic alcohols and trichloroacetamides as hydrogen bond donors for directed dihydroxylation

Timothy J. Donohoe,[a,*] Lee Mitchell,[a] Michael J. Waring,[a] Madeleine Helliwell,[a,†] Andrew Bell[b] and Nicholas J. Newcombe[c]

[a]*Department of Chemistry, The University of Manchester, Oxford Road, Manchester M13 9PL, UK*
[b]*Pfizer Limited, Sandwich, Kent CT13 9NJ, UK*
[c]*AstraZeneca Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG, UK*

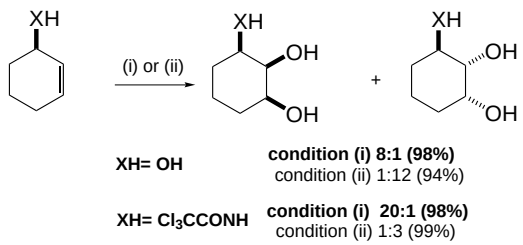
Received 19 September 2001; revised 20 October 2001; accepted 24 October 2001

Abstract—The synthesis and directed dihydroxylation of a series of homoallylic alcohols and trichloroacetamides is described. Using the combination of OsO_4 and TMEDA, moderate to high levels of stereoselectivity were obtained, depending upon the structure of the substrate. Proof of the structure of two osmate esters was obtained through X-ray crystallography.

The concept of using a substrate to direct a reaction with an external reagent is an extremely useful one in organic chemistry.[1] While many diverse Lewis acid/base interactions between reagent and substrate have been the origin of such a directing effect, perhaps the most common and useful type of association is based on hydrogen bonding.

It has been recently shown that combination of osmium tetroxide with TMEDA produces a reagent which accomplishes the directed dihydroxylation of allylic alcohols[2] and amides[3] (Scheme 1). We believe that TMEDA forms a bidentate, and reactive, complex with OsO_4 in situ. In each case, it was suggested that hydrogen bonding between the oxo-ligands of the oxidant (hydrogen bond acceptor) and the allylic group (hydrogen bond donor) was responsible for the high levels of *syn* selectivity that were observed. Importantly, such control during the oxidation event leads to a sense of stereoselectivity that cannot be obtained without the OsO_4/TMEDA reagent (see condition (i) versus condition (ii), Scheme 1).[4]

Positioning a hydrogen bond donor in the homoallylic position of substrates has also been investigated as a device for controlling stereoselective reactions and, with regard to peracid epoxidation, it was shown that effective hydrogen bonding can occur.[6] However, it is fair to



Scheme 1. *Reagents and conditions*: (i) OsO_4 (1 equiv.), TMEDA (1 equiv.), CH_2Cl_2, –78°C, then MeOH, H^+; (ii) OsO_4 (cat.), NMO, acetone/water, rt.[5]

* Corresponding author. Present address: Dyson Perrins Laboratory, South Parks Road, Oxford OX1 3QY, UK; e-mail: timothy.donohoe@chem.ox.ac.uk

† Author to whom correspondence regarding the X-ray crystal structure should be addressed. Crystal data: $C_{11}H_{24}N_2O_5Os$ *syn*-**2***M* = 454.52, orthorhombic, $a = 11.0606$ (17), $b = 14.287$ (3), $c = 9.0546$ (14) Å, $V = 1430.8$ (4) Å^3, $T = 296$ K, space group $P2_12_12_1$(no. 19), $Z = 4$, μ(Cu Kα) = 17.017 mm^{-1}, 1679 independent reflections which were used in all calculations. The final $\omega R(F^2)$ was 0.0937 (all data). $R(F)$ was 0.0350 using 1629 reflections with $I > 2\sigma(I)$. The structure was solved using the Patterson method, C-9 was disordered over two sites, A and B, whose occupancies were constrained to sum to 1.0. Full-matrix least-squares refinement was carried out on F^2.

Crystal data: $C_{13}H_{24}Cl_3N_3O_5Os$ *syn*-**13***M* = 598.90, monoclinic, $a = 11.19$ (2), $b = 11.405$ (10), $c = 15.857$ (10) Å, $\beta = 102.57$ (4)°, $V = 1976$ (4) Å^3, $T = 296$ K, space group $P2_1/c$ (no. 14), $Z = 4$, μ(Mo Kα) = 6.888 mm^{-1}, 3844 independent reflections which were used in all calculations. The final $\omega R(F^2)$ was 0.0629 (all data). $R(F)$ was 0.0240 using 3605 reflections with $I > 2\sigma(I)$. The structure was solved using direct methods, and refined on F^2 using full-matrix least-squares.

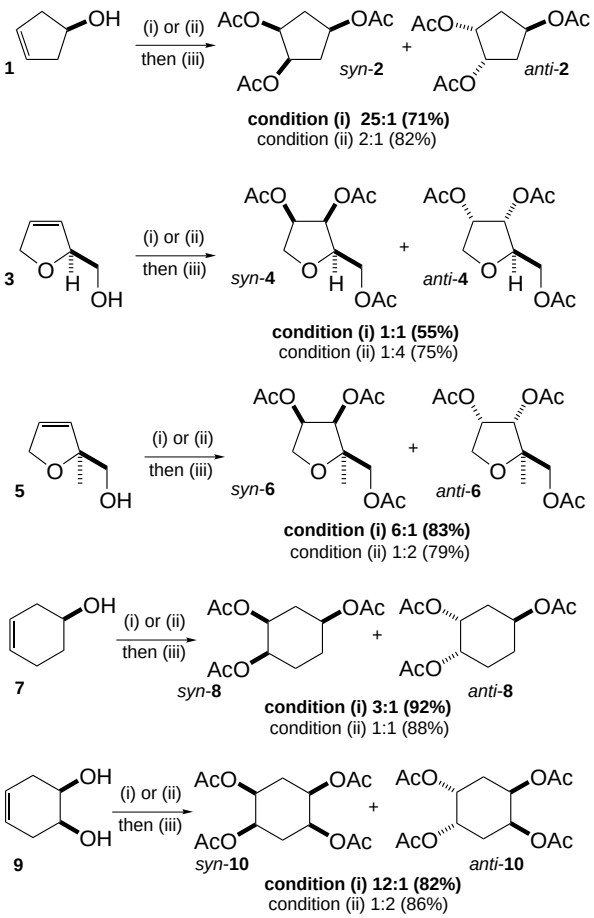
0040-4039/01/$ - see front matter
PII: S0040-4039(01)01999-2

say that the scope and nature of homoallylic directing groups has not been extensively developed in comparison to the corresponding allylic systems. Perhaps the main reason for this is the lack of readily available substrates on which to test out new reactions.

Therefore, we set out to synthesise and dihydroxylate a series of cyclic compounds with both alcohol and trichloroacetamide functionality in the homoallylic position. This type of remote stereocontrol should be a useful way to prepare stereochemically defined molecules suitable for use in synthesis.

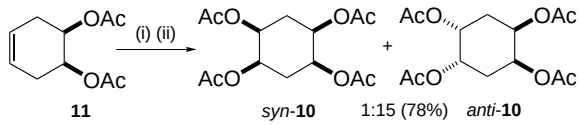
Scheme 2 shows the results obtained from oxidation of a series of five- and six-membered cyclic homoallylic alcohols.[7] The substrates were prepared using standard synthetic transformations including metathesis (**1** and **3**),[8] Birch reduction (**5**)[9] hydroboration and dihydroxylation (**9**).[10] The results show that, generally, oxidation under standard conditions (UpJohn[5]) gives low stereoselectivity for the *anti* diastereoisomer, while oxidation with OsO_4/TMEDA gives contra-steric selectivity for the *syn* diastereoisomer.

The stereochemistry of the products was determined by a number of methods. For example, X-ray crystallography was used to solve the structure of derivatives of *syn*-**2** and both compounds *anti*-**4** and *anti*-**10** are known in the literature. The *syn* and *anti* stereochemistry of both *syn*-**6** and *syn*-**8** was assigned by analogy.



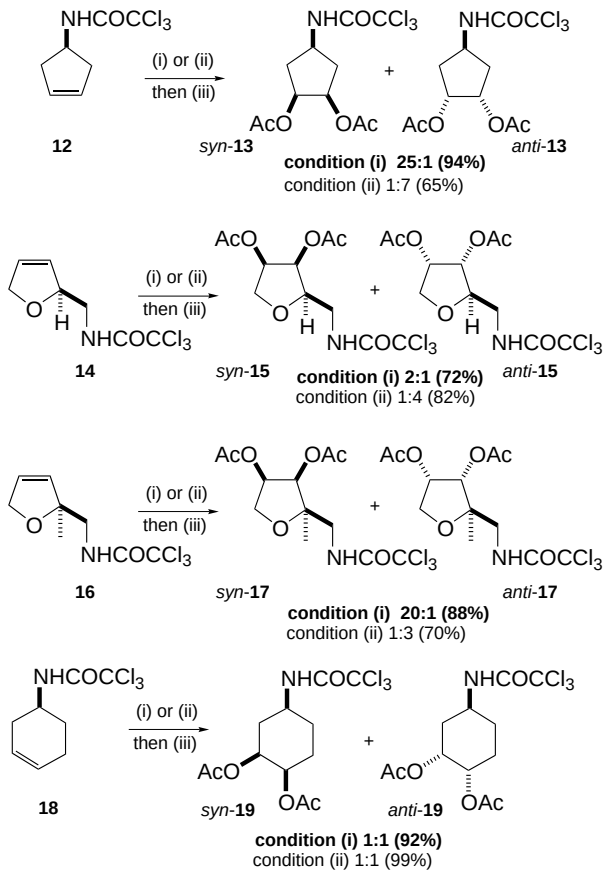
Scheme 2. *Reagents and conditions*: (i) OsO_4 (1 equiv.), TMEDA (1 equiv.), CH_2Cl_2, −78°C, then MeOH, H^+; (ii) OsO_4 (cat.), NMO, acetone/water, rt; (iii) Ac_2O, py.

Proof of the involvement of hydrogen bonding during oxidation was sought in the preparation and dihydroxylation of **11**, which is without a hydrogen bond donor (Scheme 3). In this case, the bulky OsO_4/TMEDA oxidant approaches the alkene from the face opposite to the two acetoxy groups, thus confirming our hypothesis.



Scheme 3. *Reagents and conditions*: (i) OsO_4 (1 equiv.), TMEDA (1 equiv.), CH_2Cl_2, −78°C, then MeOH, H^+; (ii) Ac_2O, py.

We then prepared a set of homoallylic trichloroacetamides and studied directed dihydroxylation reactions under OsO_4/TMEDA conditions (Scheme 4). The substrates were prepared by a variety of synthetic routes including metathesis (**12** and **14**), Birch reduction chemistry (**16**)[9] and Curtius rearrangement (**18**).



Scheme 4. *Reagents and conditions*: (i) OsO_4 (1 equiv.), TMEDA (1 equiv.), CH_2Cl_2, −78°C, then MeOH, H^+; (ii) OsO_4 (cat.), NMO, acetone/water, rt; (iii) Ac_2O, py.

Again, it can be seen that choice of the conditions enables the synthesis of predominantly the *syn* or the *anti* diastereoisomer.

Examination of the results illustrated in Schemes 2 and 4 leads us to conclude that the directing effect is strongest when the hydrogen bond donor is positioned directly on the ring (compare the oxidation of **1** with **3** and **12** with **14**); presumably this is a steric effect whereby the exocyclic methylene chain prevents directed dihydroxylation. We can also see that five-membered rings tend to yield higher stereoselectivities than their six-membered counterparts (compare **1** with **7** and **12** with **18**).

Furthermore, one can conclude that, generally, homoallylic trichloroacetamides give superior levels of *syn* selectivity in the dihydroxylation, presumably because of their increased hydrogen bond donor ability when compared to the corresponding homoallylic alcohols. However, in this regard, the non-selective oxidation of **18** was surprising (especially when compared to the alcohol **7**) and we assume that this is because the hydrogen bond acceptor group must adopt an axial position in order to deliver the oxidant. Evidently, the bulky amide group resists reaction through this conformation. This requirement for an axial directing group would also explain why **9** (which must have one axial hydroxyl group) is oxidised more selectively than **7**.

The stereochemistry of a derivative of *syn*-**13** was proven by X-ray crystallography and that of *syn*-**15** and *syn*-**17** by NOE experiments.

In fact, we were able to obtain crystal structures of osmate esters derived from the two five-membered ring compounds *syn*-**2** and *syn*-**13** (Fig. 1); both structures show the chelated nature of the TMEDA ligand and the osmium metal.

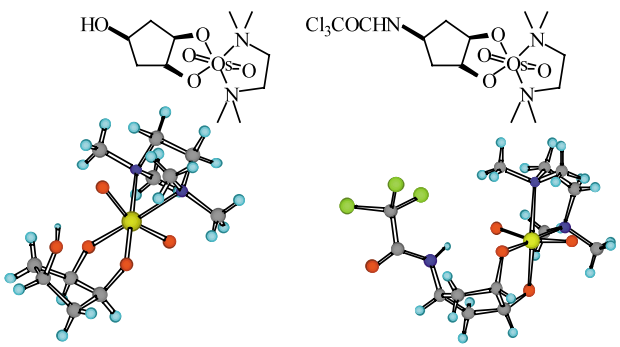


Figure 1. X-Ray crystal structures of osmate esters from *syn*-**2** and *syn*-**3**.

To conclude, we have shown that a range of homoallylic alcohols and trichloroacetamides are potentially useful hydrogen bond donors for the directed dihydroxylation reaction. Access to both triols and amino diol derivatives with defined stereochemistry is now possible and we aim to use this methodology in synthesis.

Acknowledgements

We are grateful to the EPSRC, Pfizer and AstraZeneca Pharmaceuticals for financial support of this project.

References

1. Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.
2. (a) Donohoe, T. J.; Moore, P. R.; Waring, M. J.; Newcombe, N. J. *Tetrahedron Lett.* **1997**, *38*, 5027; (b) Ling, R.; Mariano, P. S. *J. Org. Chem.* **1998**, *63*, 6072; (c) Harris, J. M.; Keranen, M. D.; O'Doherty, G. *J. Org. Chem.* **1999**, *64*, 2982.
3. (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.; Winter, J. J. G.; Stemp, G. *Tetrahedron Lett.* **2000**, *41*, 4701.
4. (a) Cha, J. K.; Christ, W.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943; (b) Cha, J. K.; Christ, W.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3947; (c) Cha, J. K.; Christ, W.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247; (d) Cha, J. K.; No-Soo, K. *Chem. Rev.* **1995**, *95*, 1761.
5. VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.
6. (a) Derby, A. C.; Henbest, H. B.; McClenaghan, I. *J. Chem. Ind.* **1962**, 462; (b) Bingham, K. D.; Meakins, J. D.; Wicha, J. *J. Chem. Soc. (C)* **1969**, 510; (c) Rotella, D. P. *Tetrahedron Lett.* **1989**, *30*, 1913; (d) de Sousa, S. E.; Kee, A.; O'Brien, P.; Watson, S. T. *Tetrahedron Lett.* **1999**, *40*, 387; (e) Barrett, S.; O'Brien, P.; Steffens, H. C.; Towers, T. D.; Voith, M. *Tetrahedron* **2000**, *56*, 9633; (f) See also Ref. 1.
7. Representative experimental procedure: To a solution of **9** (50 mg, 0.44 mmol) and TMEDA (56 mg, 0.48 mmol) in dichloromethane (10 mL) precooled to −78°C was added a solution of OsO_4 (114 mg, 0.45 mmol) in dichloromethane (~1 mL). The solution turned deep red then brown–black. The solution was stirred until complete (TLC analysis, ca. 1 h) before being allowed to warm to room temperature. The solution was then concentrated under reduced pressure and the resulting residue redissolved in methanol (10 mL). Hydrochloric acid (conc. three drops) was then added and the solution stirred for 2 h. The solution was then concentrated under reduced pressure and the product was redissolved in pyridine (5 mL) and acetic anhydride (5 mL) and *N*,*N*-dimethylaminopyridine (5 mg, cat.) was added. The mixture was then heated at 80°C for 12 h. It was then allowed to cool and was diluted with diethyl ether (100 mL). The solution was then filtered through Celite® and washed with dilute hydrochloric acid (100 mL, 2 M), potassium carbonate solution (saturated, 100 mL) and brine (100 mL). The ethereal layer was then dried ($MgSO_4$) and then concentrated under reduced pressure to yield the crude mixture of peracetylated products which were then purified by flash chromatography (EtOAc) to afford *syn*-**10** as a colourless solid (114 mg, 82%); mp 65–66°C; δ_H (300 MHz; $CDCl_3$) 5.11–5.03 (4H, m), 2.35 (2H, dt, $J=14$ and 7), 2.06 (12H, s), 1.84 (2H, dt, $J=14$ and 3); δ_C (75 MHz, $CDCl_3$) 170, 67.9, 28.0, 20.9.

Other representative data is as follows:
syn-**2**: δ_H (300 MHz; $CDCl_3$) 5.16–5.02 (3H, m), 2.35 (2H, dt, $J=14$ and 7), 2.08 (6H, s), 2.06 (3H, s), 1.95 (2H, dt, $J=14$ and 4); δ_C (75 MHz, $CDCl_3$) 171, 170, 72.1, 70.4, 35.5, 35.4, 20.8.
syn-**6**: δ_H (300 MHz; $CDCl_3$) 5.43 (1H, q, $J=5$), 5.17 (1H, d, $J=5$), 4.26–4.09 (3H, m), 3.89 (1H, dd, $J=10$, 5), 2.10 (6H, s), 2.08 (3H, s), 1.36 (3H, s); δ_C (75 MHz, $CDCl_3$) 171, 170 (2), 80.8, 76.2, 71.2, 68.9, 65.3, 22.3, 20.6, 20.4, 18.3.
syn-**8**: δ_H (300 MHz; $CDCl_3$) 5.17–5.11 (1H, m), 4.84–4.72 (2H, m), 2.04 (3H, s), 1.98 (3H, s), 1.86 (3H, s), 2.05–1.45 (6H, m); δ_C (75 MHz, $CDCl_3$) 170 (3), 69.5, 69.3, 67.9, 31.4, 25.3, 24.7, 21.1, 20.9, 20.8.

8. For a pertinent review, see: Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371.
9. (a) Birch, A. J.; Slobbe, J. *Tetrahedron Lett.* **1975**, 627; (b) For a review, see: Donohoe, T. J.; Guyo, P. M.; Raoof, A. *Target. Heterocyclic Syst.* **1999**, *3*, 117 (Italian Society of Chemistry).
10. Maras, A.; Secen, H.; Suetbeyaz, Y.; Balci, M. *J. Org. Chem.* **1998**, *63*, 2039.