Stereochemical control of the intramolecular Diels–Alder reaction by remote allylic substituents on the diene

Michael J. Lilly and Michael S. Sherburn*

Department of Chemistry, Massey University, Private Bag 11222, Palmerston North, New Zealand

Intramolecular Diels–Alder reactions of substrates with stereocontrolling elements attached to the diene terminus provide *exo*-cycloadducts in good yields and high diastereofacial selectivity.

The Diels–Alder reaction is one of the most powerful and most commonly used reactions in synthetic organic chemistry. The stereochemical consequences of employing chiral precursors or catalysts have been actively studied for several years,[1] with much recent interest directed towards the application of chiral, acyclic dienes in intermolecular reactions,[2] particularly when a stereocentre is present at the allylic position of the diene.[2a] Reported methods for the stereochemical control of intramolecular Diels–Alder (IMDA) reactions[3] involve the placement of suitable substituents on the linking chain (tether) between the diene and dienophile,[4] by attaching auxiliaries to the dienophile[5] and the application of enantioselective catalysis.[6] We were intrigued by the possibility of controlling the diastereofacial selectivity of the IMDA reaction by constructing chiral substrates with a stereocontrolling element at the terminus of an acyclic diene, *i.e.* remote to the linking chain (Fig. 1). This approach offers new insights into the stereochemical preferences of the Diels–Alder reaction, since previous reports in this area employ either stereochemically-biased semicyclic dienes, or are complicated by the presence of tether substituents and dienophile auxiliaries.[7]

We chose to investigate a series of ester-tethered intramolecular cycloadditions with *Z*-alkene dienophiles bearing both internal and terminal ester activating groups, since a previous report indicated reasonably facile thermal reaction and high *exo*-selectivity.[8] The series of enantiopure compounds (**7a**–**d**) was prepared from inexpensive and readily available l-ascorbic acid as shown in Scheme 1. Thus, the α-hydroxy ester **1**[9] was silylated and reduced to afford the α-silyloxy aldehyde **2**. Wittig reaction with stabilised phosphorane **3** gave a mixture of stereoisomers from which the *E*,*E*-diene ester **4** was obtained upon isomerisation. After reduction, esterification of dienol **5** with maleic anhydride gave acid **6**, which was used for the preparation of the four precursors for IMDA reaction. Thus, treatment of **6** with diazomethane furnished the *tert*-butyldimethylsilyloxy methyl ester **7c**. Desilylation of **6** followed by methylation gave hydroxy methyl ester **7a**. The trimethylsilyl and triisopropylsilyl derivatives **7b** and **7d** were prepared by reacting alcohol **7a** with the requisite trialkylsilyl triflate.

Thermolysis of the IMDA precursors under identical conditions (Table 1) produced mixtures containing only two of the four possible cycloadducts in each case.† These products were characterised following derivatisation and extensive NMR studies including HETCOR, COSY and NOESY experiments. Coupling constants pointed to a *trans*-ring junction geometry‡ in each case, indicating that all products isolated were the result of the expected *exo*-cycloaddition mode. The alcohol substrate (**7a**) exhibited only a modest diastereofacial preference between the two *exo*-cycloadducts, but this improved considerably on replacement with silyloxy protecting groups. Furthermore, a progressive improvement in selectivity was observed as the size of the silyl group was increased. The triisopropylsilyl derivative **7d**, the most sterically demanding protecting group examined, provided a remarkably high level of stereocontrol. Interestingly, the major product for the alcohol substrate corresponded to the major product for the silyl ethers.§

It is noteworthy that the π-facial selectivity of these IMDA reactions is of the opposite sense to that witnessed for intermolecular Diels–Alder reactions between simple chiral dienols (and ether derivatives) and maleic anhydride.[2a] The reasons for this difference are not known but the absence of a

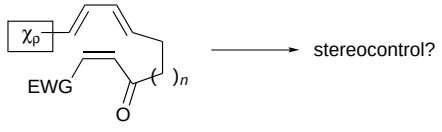
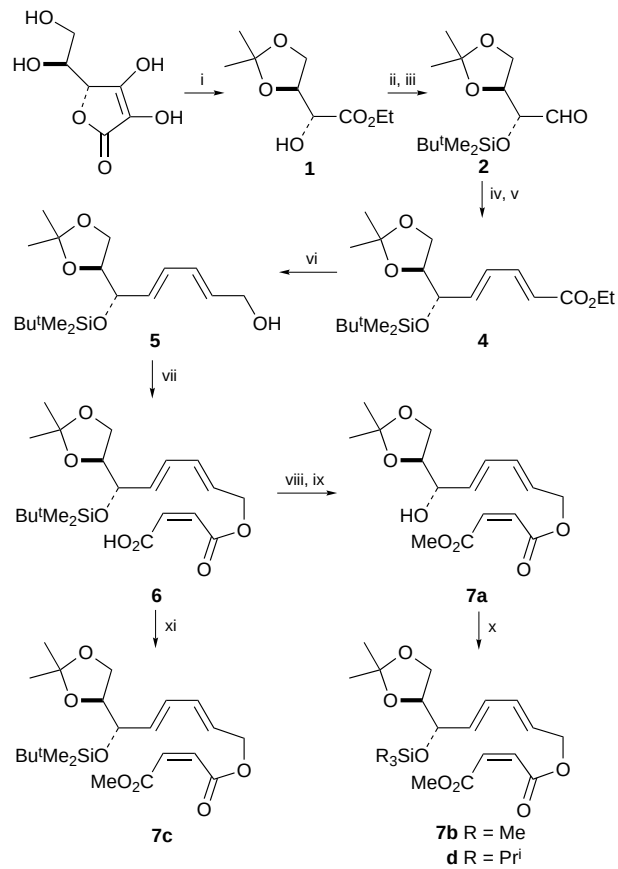
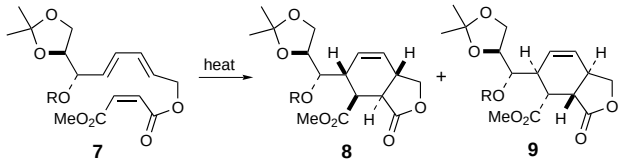


Fig. 1



Scheme 1 *Reagents and conditions*: i, see ref. 9 (63% over 3 steps); ii, Bu^tMe_2SiCl, imidazole, DMF, 20 °C, 68%; iii, DIBAL-H, CH_2Cl_2, −90 °C, 89%; iv, $Ph_3P{=}CHCH{=}CHCO_2Et$ **3**, CH_2Cl_2, reflux; v, PhSH, AlBN, PhH, *hν*, reflux; vi, DIBAL-H, CH_2Cl_2, −78 to 0 °C, 53% for 3 steps; vii, maleic anhydride, Et_3N, DMAP, CH_2Cl_2, 20 °C, 100%; viii, Bu_4NF, THF, 20 °C, 85%; ix, CH_2N_2, Et_2O, 20 °C, 74%; x, $R_3SiOSO_2CF_3$, pyridine, CH_2Cl_2, 20 °C, 51% for R = Me, 58% for R = Pr^i; xi, CH_2N_2, Et_2O, 20 °C, 80%

Table 1 Thermal IMDA reactions of **7**[a]



7 **8** **9**

Substrate **7**	R	*t*/h[b]	Yield (%)[c]	**8**:**9**[d]
a	H	5	86	66:34
b	Me_3Si	12	67	82:18
c	Bu^tMe_2Si	15	80	91:9
d	Pr^i_3Si	18	68	96:4

[a] Reactions were carried out in refluxing toluene at [**7**] = 0.05 m under Ar with BHT (0.20 equiv.); [b] Reactions were followed by TLC; [c] Isolated yield of **8** + **9**; [d] Ratio determined from ^{1}H NMR spectra of crude reaction mixtures.

cis-substituent on the diene and the presence of the dioxolane moiety in the precursors may be contributing factors.[2a] Moreover, recent NMR studies have shown that subtle factors affect the conformational preferences of chiral allylic secondary alcohols and derivatives.[10] Clearly, a complicated situation exists and a detailed explanation of these results must await further studies. The stereochemical outcome of the present series of reactions does, however, follow the same trend as silyl acetal-tethered IMDA reactions[11] in which the stereocontrolling element is part of the tether.¶

In summary, this work demonstrates that the stereochemical outcome of the intramolecular Diels–Alder reaction can be controlled by the incorporation of stereochemical information on the diene remote to the diene–dienophile tether. Remarkably high levels of stereoselectivity can be obtained for thermal (uncatalysed) reactions by judicious selection of the alcohol protecting group in the precursor. The products obtained from these reactions are enantiomerically pure and rich in functionality, offering the prospect of further elaboration into a multitude of useful chiral building blocks.

The authors would like to thank Dr Pat Edwards for assistance with NMR, Massey University for a Graduate Assistant Scholarship (to M. J. L.) and The New Zealand Lotteries Board for funding.

Footnotes

* E-mail: m.sherburn@massey.ac.nz

† In these experiments we observed small amounts of other compounds which may be the products of *endo*-mode cycloaddition. Thus far we have not been able to isolate sufficient quantities of pure compounds to allow characterisation of these very minor products.

‡ The coupling constants between protons at the ring junction (*J* 13.7 Hz) were consistent throughout this series and compared favourably with literature values for similar compounds (see ref. 8).

§ Silylation of a 1.9:1 mixture of **8a** and **9a** (Me_3SiCl, imidazole, DMF, 20 °C, 61%) furnished a 1.9:1 mixture of two compounds identical in all respects to **8b** and **9b**. The major isomer from this experiment corresponded with the major isomer from thermolysis of **7b**.

¶ We thank a referee for drawing our attention to this work.

References

1 For reviews on asymmetric Diels–Alder reactions, see W. Oppolzer, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 876; W. Oppolzer, in *Comprehensive Organic Synthesis*, ed. B. M. Trost, I. Fleming and L. A. Paquette, Pergamon, Oxford, 1991, vol. 5, p. 315; For reviews on enantioselective catalysis, see K. Narasaka, *Synthesis*, 1991, 1; H. B. Kagan and O. Riant, *Chem. Rev.*, 1992, **92**, 1007.

2 (*a*) Chiral 1-substituted 1,3-dienes: R. Tripathy, R. W. Franck and K. D. Onan, *J. Am. Chem. Soc.*, 1988, **110**, 3257; W. Adam, J. Glaser, K. Peters and M. Prein, *J. Am. Chem. Soc.*, 1995, **117**, 9190; G. T. Crisp and M. G. Gebauer, *J. Org. Chem.*, 1996, **61**, 8425; (*b*) Chiral 2-substituted 1,3-dienes: R. Bloch and N. Chaptal-Gradoz, *J. Org. Chem.*, 1994, **59**, 4162; J. Barluenga, M. Tomas, A. Suarez-Sobrino and L. A. Lopez, *J. Chem. Soc., Chem. Commun.*, 1995, 1785 and references cited therein.

3 For recent reviews, see D. Craig, *Chem. Soc. Rev.*, 1987, **16**, 187; W. R. Roush, in *Advances in Cyloaddition*, ed. D. P. Curran, JAI, Greenwich, CT, 1990, vol. 2, p. 91; W. R. Roush, in *Comprehensive Organic Synthesis*, ed. B. M. Trost, I. Fleming and L. A. Paquette, Pergamon, Oxford, 1991, vol. 5, p. 513.

4 For recent examples, see P. J. Ainsworth, D. Craig, A. J. P. White and D. J. Williams, *Tetrahedron*, 1996, **52**, 8937; W. R. Roush, J. A. Champoux and B. C. Peterson, *Tetrahedron Lett.*, 1996, **37**, 8989.

5 W. R. Roush, H. R. Gillis and A. I. Ko, *J. Am. Chem. Soc.*, 1982, **104**, 2269; D. A. Evans, K. T. Chapman and J. Bisaha, *Tetrahedron Lett.*, 1984, **25**, 4071; W. Oppolzer and D. Dupuis, *Tetrahedron Lett.*, 1985, **26**, 5437; D. A. Evans, K. T. Chapman and J. Bisaha, *J. Am. Chem. Soc.*, 1988, **110**, 1238.

6 K. Furuta, A. Kanematsu, H. Yamamoto and S. Takaoka, *Tetrahedron Lett.*, 1989, **30**, 7231; K. Narasaka, H. Kusama and Y. Hayashi, *Chem. Lett.*, 1991, 1413; K. Narasaka, M. Saitou and N. Iwasawa, *Tetrahedron: Asymmetry*, 1991, **2**, 1305; K. Ishihara, H. Kurihara and H. Yamamoto, *J. Am. Chem. Soc.*, 1996, **118**, 3049.

7 B. Fraser-Reid, Z. Benko, R. Guiliano, K. M. Sun and N. Taylor, *J. Chem. Soc., Chem. Commun.*, 1984, 1029; D. A. Evans and W. C. Black, *J. Am. Chem. Soc.*, 1993, **115**, 4497; D. J. Hart, W.-L. Wu and A. P. Kozikowski, *J. Am. Chem. Soc.*, 1996, **117**, 9369.

8 J. D. White and B. G. Sheldon, *J. Org. Chem.*, 1981, **46**, 2273.

9 E. Abushanab, P. Vemishetti, R. W. Leiby, H. K. Singh, A. B. Mikkilinelli, D. C.-J. Wu, R. Saibaba and R. P. Panzica, *J. Org. Chem.*, 1988, **53**, 2598.

10 B. W. Gung, J. P. Melnick, M. A. Wolf and A. King, *J. Org. Chem.*, 1995, **60**, 1947 and references cited therein.

11 D. Craig and J. C. Reader, *Tetrahedron Lett.*, 1992, **28**, 4073.

Received in Cambridge, UK, 18th February 1997; Com. 7/01125C