

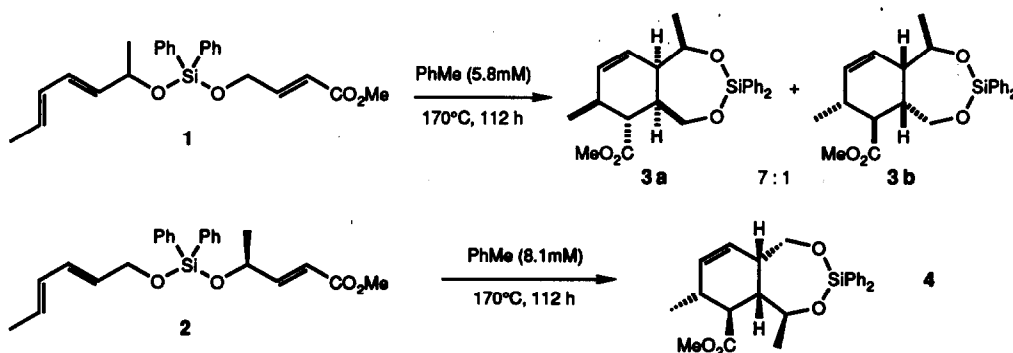
Intramolecular Diels-Alder Reactions of Silyl Acetal Trienes. Dienophile-controlled Cycloadditions of 'Matched' and 'Unmatched' Dimethylated Substrates

Donald Craig* and John C. Reader

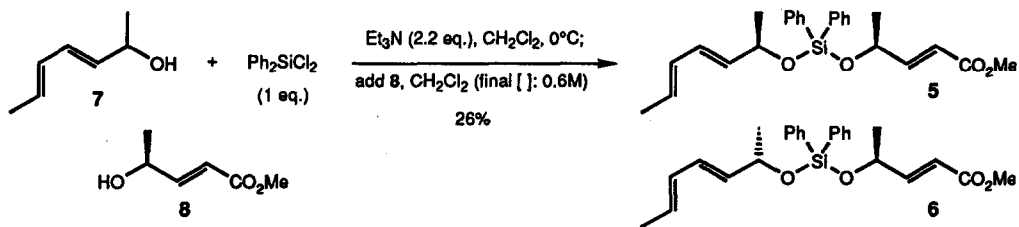
Department of Chemistry, Imperial College of Science, Technology and Medicine, London SW7 2AY, U.K.

Abstract: Thermal intramolecular Diels-Alder reaction of a mixture of silyl acetal trienes **5** and **6** followed by HF-mediated removal of the silicon tether gives in high overall yield the cyclic diol-esters **9** and **10**. Compound **10** is converted selectively under acid catalysis into hydroxylactone **11**. The structures of **9** and **11** are established by X-ray crystallography. The highly stereoselective nature of the IMDA reactions of **5** and **6** implied by the formation of **9** and **11** is interpreted in terms of transition-states whose geometry is constrained predominantly by the dienophile stereocentre.

The intramolecular Diels-Alder (IMDA) reactions¹ of triene substrates possessing a diene and dienophile connected *via* a removable linking group deliver the products of highly regio- and stereoselective overall *intermolecular* Diels-Alder processes upon cleavage of the temporary tether post-cycloaddition. This strategy is attracting increasing attention because it solves some of the selectivity problems frequently associated with bimolecular [4+2] cycloaddition reactions.² We recently reported³ that silyl acetal trienes⁴ **1** and **2** possessing stereocentres in the tether undergo highly stereoselective thermal IMDA reactions to give respectively the [5.4.0]bicyclic silyl acetals **3a** and **4** as the major products (Scheme 1). We became interested in looking at the cyclization behaviour of *dimethylated* trienes **5** and **6**: our earlier observations³ suggested that **5** should be an 'unmatched', and **6** a 'matched' substrate, since the directing effects of the stereocentres in **5** would be mutually opposing, and those in **6** complementary. This Letter presents the results of these investigations.

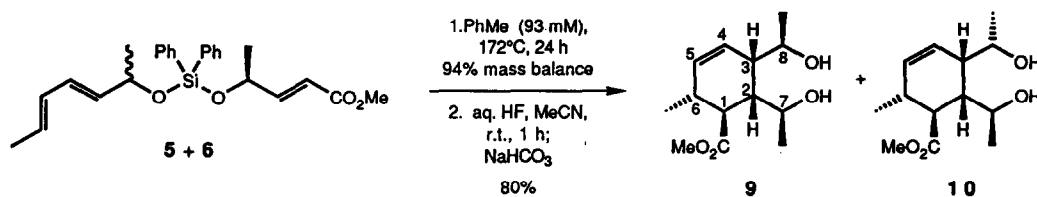


Scheme 1



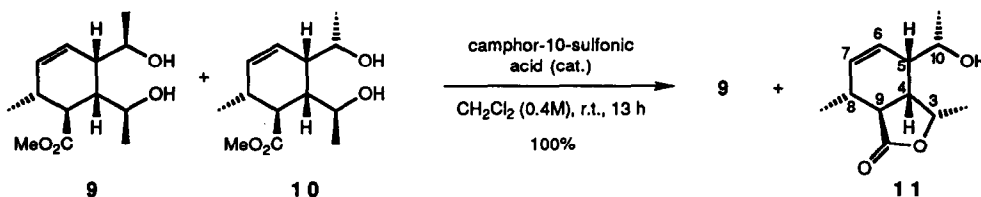
Scheme 2

Trienes **5** and **6** were prepared as an inseparable mixture of enantiomerically pure diastereomers⁵ from alcohols **7** and **8**³ according to the route depicted in Scheme 2.⁶ Lower reaction temperatures, and variation of the order of addition of the diene and dienophile components failed to give any reproducible improvement in the yield of trienes. Thermolysis of a toluene solution of the mixture of **5** and **6** as described previously^{3,4(c)} gave in excellent yield a *ca.* 1:1 mixture of two major cycloadducts, together with a small (*ca.* 5%) amount of a third bicyclic product.⁷ The IMDA reaction of **5** and **6** was noticeably more rapid than those of the less substituted analogues.^{3,4(c)} Desilylation of the cycloadduct mixture gave the diol-esters **9** and **10** (Scheme 3).



Scheme 3

The formation of **9** and **10** from the parent IMDA cycloadducts was appreciably more sluggish than acetal cleavage from the less substituted analogues **3** and **4** reported previously.³ Varying amounts of a *single*, separable hydroxylactone were obtained according to the duration of the deprotection reaction. Difficulties encountered in the separation of **9** from **10** led us to look at ways of maximizing the extent of formation of this substance. Treatment of the *ca.* 1:1 mixture of **9** and **10** with catalytic acid effected clean conversion to a separable mixture of the diol-ester **9** and the hydroxylactone **11** (Scheme 4). The structures of both these materials were unambiguously established by X-ray crystallography (Figure).^{8,9}

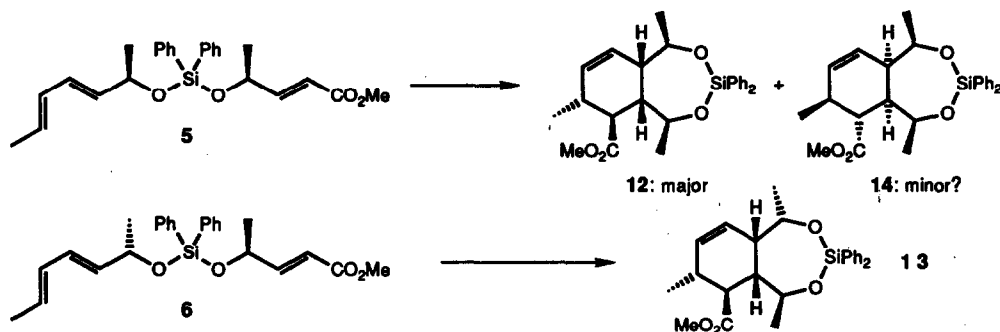


Scheme 4



Figure. X-Ray structures of 9 and 11

The isolation of compounds 9 and 11 implies predominant formation of bicyclic products 12 (from 5) and 13 (from 6) in the IMDA reaction (Scheme 5). Both 12 and 13 are formed in cyclization processes in which the diene approaches the *si*-face of the *S*-configured dienophile. This corresponds to *like*-attack, and is as observed for the substrate 2 having a single stereocentre α - to the dienophile double bond. Silyl acetal 12 is formed *via* approach of the dienophile to the *re*-face of a diene possessing an *R*-stereocentre, *i.e.* *like*-attack also. This is the 'unmatched' case, since the cyclization behaviour of 1 indicates that *unlike*-attack is preferred for a substrate having an α -methylated diene unit. Isomer 13 corresponds to the 'matched' case, since it arises through a *like*_{dienophile}-*unlike*_{diene} interaction. The apparently greater influence of the dienophile stereocentre in determining product stereochemistry³ leads us to speculate that the unidentified diastereomer formed in the IMDA reaction of the mixture of 5 and 6 is 14, corresponding to the minor *unlike*_{dienophile}-*unlike*_{diene} cyclization mode of the 'unmatched' substrate 5.¹⁰



Scheme 5

In summary, we have shown that the stereochemical course of IMDA reactions of silyl acetal trienes methylated α - to both diene and dienophile is controlled largely by the configuration of the dienophile stereocentre. This effect is such that even 'unmatched' substrates such as 5 undergo highly stereoselective intramolecular cycloaddition reactions. We are currently exploring the synthesis and IMDA reactivity of carbon analogues^{2(a)} of the silyl compounds 1, 2, 5 and 6. The results of these studies will be reported in due course.

Acknowledgements

We thank the SERC (Quota Studentship to J. C. R.) and ICI Pharmaceuticals for financial support.

References and notes

- For a review of the IMDA reaction, and leading references, see: Craig, D. *Chem. Soc. Rev.* **1987**, 187.
- (a) IMDA Reaction of a triene tethered with a carbon acetal: Boeckman, Jr., R. K.; Estep, K. G.; Nelson, S. G. *Tetrahedron Lett.* **1991**, *32*, 4095; (b) IMDA reactions of trienes tethered with a phenylboronate ester group incorporated *in situ*: Narasaka, K.; Shimada, S.; Osoda, K.; Iwasawa, N. *Synthesis* **1991**, 1171; (c) use of metal atoms as tethers in IMDA reactions of complexes having vinylphosphine and phosphole ligands: Green, R. L.; Nelson, J. H.; Fischer, J. *Organometallics* **1987**, *6*, 2256; Solujic, L.; Milosavljevic, E. B.; Nelson, J. H.; Alcock, N. W.; Fischer, J. *Inorg. Chem.* **1989**, *28*, 3453; (d) type 2 'IMDA' reactions of trienes possessing hydrogen-bond 'tethers': Hatakeyama, S.; Sugawara, K.; Takano, S. *J. Chem. Soc., Chem. Commun.* **1992**, 953.
- Craig, D.; Reader, J. C. *Tetrahedron Lett.* **1992**, *33*, 4073.
- For examples of IMDA reactions of trienes tethered with a silyl acetal, see: (a) Shea, K. J.; Staab, A. J.; Zandi, K. S. *Tetrahedron Lett.* **1991**, *32*, 2715; Shea, K. J.; Zandi, K. S.; Staab, A. J.; Carr, R. *ibid.* **1990**, *31*, 5885; (b) Gillard, J. W.; Fortin, R.; Grimm, E. L.; Maillard, M.; Tjepkema, M.; Bernstein, M. A.; Glaser, R. M. *Tetrahedron Lett.* **1991**, *32*, 1145; (c) Craig, D.; Reader, J. C. *Tetrahedron Lett.* **1990**, *31*, 6585.
- Nmr data for the mixture of **5** (methyl (4*S*,8*R*)(2*E*,9*E*,11*E*)-4,8-dimethyl-6,6-diphenyl-5,7,6-dioxasila-2,9,11-tridecatrienoate) and **6** (methyl (4*S*,8*S*)(2*E*,9*E*,11*E*)-4,8-dimethyl-6,6-diphenyl-5,7,6-dioxasila-2,9,11-tridecatrienoate): δ_{H} (500 MHz, CDCl_3) 7.67-7.63 (4H, m, *ortho* C_6H_5), 7.44-7.33 (6H, m, *meta* and *para* C_6H_5), 6.932 and 6.929 (1H, dd, *J* 15.5, 4 Hz, H-2), 6.08 and 6.07 (1H, dd, *J* 15.5, 1.5 Hz, H-1), 6.03-5.94 (2H, m, H-10 and H-11), 5.65-5.54 (2H, m, H-9 and H-12), 4.66 (1H, m, H-4), 4.49 and 4.48 (1H, quintet, *J* 6.5 Hz, H-2), 3.74 and 3.73 (3H, s, OCH_3), 1.74 (3H, d, *J* 6.5 Hz, H-13), 1.27, 1.25, 1.24 and 1.23 (6H, d, *J* 6.5 Hz, C-4 CH_3 and C-8 CH_3).
- Yields cited herein (%) are for pure materials, isolated by flash chromatography on Florisil® (**5** and **6**) or silica gel, characterized by ^1H nmr, ir, ms and elemental combustion analysis.
- Determined by high-field (500 MHz) ^1H nmr analysis of crude reaction mixtures.
- We thank Dr D. J. Williams and Ms A. M. Z. Slawin (Imperial College) for these determinations.
- Methyl (1*S*,2*S*,3*S*,6*R*,7*S*,8*R*)-2,3-bis(1-hydroxyethyl)-6-methyl-4-cyclohexene-1-carboxylate **9**: mp 123-125°C (ether-petrol); $[\alpha]_{\text{D}}^{20} +25.5^\circ$ (*c* 0.2, CHCl_3); δ_{H} (500 MHz, CDCl_3) 5.64 (1H, ddd, *J* 9.9, 6, 2.5 Hz, H-4), 5.49 (1H, ddd, *J* 10, 2.5, 1 Hz, H-5), 3.85 (1H, dq, *J* 6.5, 3 Hz, H-7), 3.79 (3H, s, OCH_3), 3.70 (1H, dq, *J* 8.5, 6 Hz, H-8), 2.69-2.64 (1H, m, H-6), 2.58 (1H, dd, *J* 11.5, 10 Hz, H-1), 2.43-2.38 (1H, m, H-3), 1.97 (1H, dt, *J* 11.5, 3.5 Hz, H-2), 1.36 (3H, d, *J* 6.5 Hz, C-7 CH_3), 1.25 (3H, d, *J* 6 Hz, C-8 CH_3), 0.98 (3H, d, *J* 7 Hz, C-6 CH_3). (3*S*,4*S*,5*S*,8*R*,9*S*,10*S*)-5-(1-Hydroxyethyl)-3,8-dimethyl-1-oxo-2-oxabicyclo[3.4.0]-6-nonene **11**: mp 130.5-132°C (ether-petrol); $[\alpha]_{\text{D}}^{20} +30^\circ$ (*c* 0.78, CHCl_3); δ_{H} (500 MHz, CDCl_3) 5.86 (1H, br. d, *J* 10 Hz, H-6), 5.75 (1H, ddd, *J* 10, 5, 2.5 Hz, H-7), 4.79, (1H, quintet, *J* 7 Hz, H-3), 4.29 (1H, dq, *J* 6.5, 2 Hz, H-10), 2.92 (1H, dd, *J* 14.5, 10 Hz, H-9), 2.53 (1H, ddd, *J* 14.5, 7, 5.5 Hz, H-4), 2.46-2.43 (1H, m, H-5), 2.39 (1H, m, H-8), 1.55 (3H, d, *J* 7 Hz, C-3 CH_3), 1.30 (3H, d, *J* 7 Hz, C-8 CH_3), 1.28 (3H, d, *J* 6.5 Hz, C-10 CH_3).
- In intermolecular Diels-Alder reactions of dienes having an α -alkoxy-bearing stereocentre *like*-addition is frequently preferred. See: Franck, R. W.; Argade, S.; Subramaniam, C. S.; Frechet, D. M. *Tetrahedron Lett.* **1985**, *26*, 3187; Tripathy, R.; Franck, R. W.; Onan, K. D. *J. Am. Chem. Soc.* **1988**, *110*, 3257.