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A NOVEL STRATEGY FOR REGIO- AND STEREOCONTROL IN [4 + 2] CYCLOADDITIONS.

INTRAMOLECULAR DIELS-ALDER REACTION OF A SILYL ACETAL TRIENE

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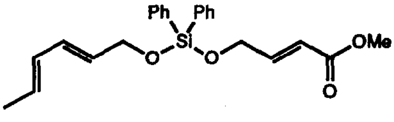
Summary: *The synthesis of the novel silyl acetal-containing triene 1 is described. Triene 1 underwent regiospecific and highly stereoselective intramolecular Diels-Alder reaction to give bicycle 5. Acidic methanolysis of 5 gave hydroxylactone 2, whose structure was established by X-ray crystallography.*

Intramolecular Diels-Alder (IMDA) reactions[1] are different from their intermolecular counterparts in that they are frequently highly stereoselective and almost invariably regiospecific. Stereoselectivity arises because of the steric constraints imposed by a bicyclic rather than a monocyclic transition state. Regiospecificity is a consequence of the prohibitively high transition state energy associated with formation of a bridged rather than a fused ring system.[2] Regioselectivity in the intermolecular reactions of substantially polarized dienes/dienophiles may be observed,[3] and reflects the most favourable match of $\mathrm{HOMO}_{\mathrm{diene}}$ and $\mathrm{LUMO}_{\mathrm{dienophile}}$ coefficients of the bonding atoms.[4] We have embarked on a research programme which seeks to exploit the desirable features of IMDA reactions for the synthesis of *inter*molecular reaction products. If the diene and dienophile cycloaddition partners could be tethered together, the subsequent Diels-Alder reaction would be intramolecular, with the attendant advantages described above. Removal of the tether would then give monocyclic material, ostensibly the product of a regio- and potentially stereocontrolled intermolecular cyclization process. Selection of a substrate on which to test this novel strategy must be governed by several factors. Firstly, the triene must be readily accessible by straightforward synthetic procedures. In particular, facile introduction of a readily available tethering group is a desirable feature. Secondly, the tether must be easy to remove after the cycloaddition. Finally, the nature of the tether must not be so as to hinder cycloaddition: ideally, it should accelerate the cyclization process. In this Letter we describe our initial studies on the cycloaddition behaviour of the novel silyl acetal-containing[5] triene 1, and the realization of the above strategy for the synthesis of hydroxylactone 2.



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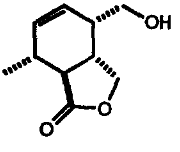

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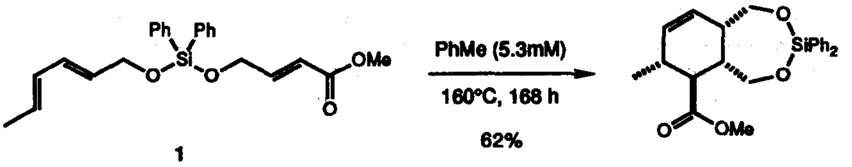
Silyl acetal 1 was prepared in a straightforward fashion as follows. Addition of a dichloromethane solution of 1 eq. each of (2*E*, 4*E*)-2,4-hexadien-1-ol 3[6] and methyl (2*E*)-4-hydroxy-2-butenoate 4[7] to a cooled (0°C) dichloromethane solution of dichlorodiphenylsilane (1 eq.; final concentration *ca.* 1M with respect to 3, 4 and Ph_2SiCl_2) and triethylamine (2.2 eq.) under argon caused immediate precipitation of triethylammonium chloride. Addition of petrol, filtration, and concentration of the filtrate under reduced pressure gave an oil. This was chromatographed (gradient elution: 1% - 25% ether-petrol) on Florisil® (200 mesh) to give 1 in 32% yield.[8]

Heating a thoroughly degassed[9] toluene solution of 1 in a base-washed[10] sealed tube gave a pale yellow oil after removal of the solvent under reduced pressure. ^{1}H nmr analysis (500 MHz) of the crude product revealed the presence of unreacted 1 (13%) together with the cyclization product (87%) *as a single stereoisomer*.[11] Since it was impossible at this stage to assign unequivocally the structure of the cycloadduct, it was decided to remove the silicon tether in order to generate material more predisposed towards crystallization. This would also test the feasibility of the final stage of our strategy. In the event, exposure of the purified[12] cycloadduct to HCl-methanol[13] gave in moderate yield hydroxylactone 2, mp 78-81°C (ether-petrol).[14] The structure of 2 was unambiguously determined by X-ray crystallography (Figure),[15] which enabled the assignment of the structure of the cycloadduct as 5[16] (Scheme 1).



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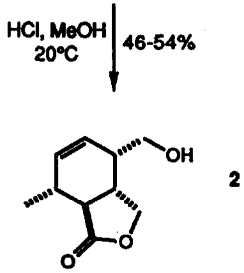

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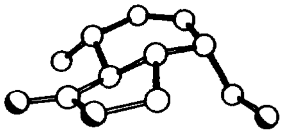
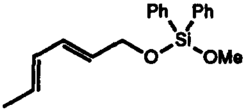
Scheme 1



Figure

In view of the highly regio- and stereoselective nature of the IMDA reaction of 1, it was decided to investigate a closely-related in*ter*molecular reaction in order to probe the regioselectivity and π-facial selectivity inherent in cycloadditions between diene/dienophile combinations such as 3 and 4. In order to model as closely as possible the IMDA reaction of 1, silyl acetals 6 and 7 were selected as substrates. Heating an equimolar mixture of 6 and 7 in degassed toluene (0.57M) at 150°C for 90 h generated four new components by tlc and ^{1}H nmr analysis. Attempted chromatographic purification gave disappointingly low yields of cycloadducts.[17] Also, substrate 6 was difficult to prepare in acceptably pure form.[18] Methyldiphenylsilyl ethers 8 and 9 were therefore chosen as being easier to synthesize[19] and less sensitive to hydrolysis than 6 and 7.



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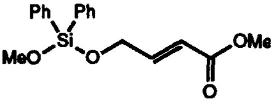

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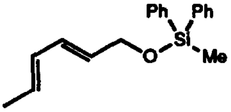

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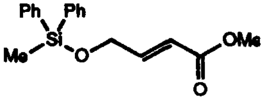
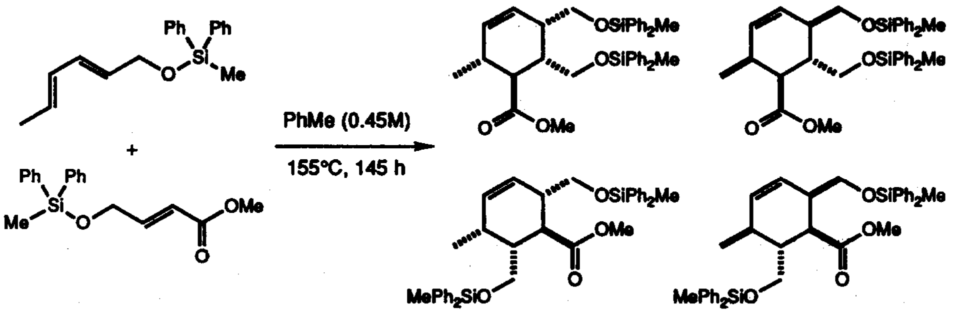


9

Heating a 1:1 mixture of silyl ethers **8** and **9** in degassed toluene gave material indicated by tlc to contain two new components. ^{1}H nmr (500 MHz) analysis of the crude reaction mixture showed the presence of four new methyl ester-containing compounds in the approximate ratio 3:2:2:1, in addition to unreacted **8** and **9** (*ca.* 35% conversion). Chromatography of the mixture (Florisil® 200 mesh, 2% - 6% ether-petrol) enabled separation of the two new components. The less polar of these was shown by ^{1}H nmr (500 MHz) to contain a single cycloadduct, with the more polar containing the remaining three isomeric products (Scheme 2).



Scheme 2

Thus an intermolecular reaction analogous to the IMDA reaction of **1** was shown to have given a mixture of all possible regio- and stereoisomers. Acidic methanolysis[13] of the cycloadduct mixture gave four isomeric hydroxylactones (*ca.* 75% combined yield) which were separated by chromatography on silica gel (50% ethyl acetate-petrol). One of these compounds had ^{1}H nmr properties[14] identical to those of hydroxylactone **2**.[20]

In summary, the experiments described above show that the regio- and stereochemical outcome of a Diels-Alder reaction may be profoundly affected by the simple expedient of tethering together the diene and dienophile components. Although the two extra synthetic operations required to introduce and remove the tether might be regarded as a drawback, these steps would be avoided if the tether could be incorporated *in situ* by exploiting ion-dipole or electrostatic interactions between suitably functionalized cycloaddition partners, with subsequent removal of the tether during work-up. The cyclization of triene **1** is one of an unusual class of thermal IMDA reaction giving rise to the bicyclo[5.4.0]undecene ring system,[21] and is to our knowledge the first case involving formation of a heterobicyclic system. We are currently investigating more efficient methods for the introduction and removal of the silyl acetal tether, and the effect on cyclization stereochemistry of asymmetric centres adjacent to the diene and dienophile π-systems. The results of these studies will be reported in due course.

Acknowledgements

We thank the SERC (Quota studentship to JCR) and ICI Pharmaceuticals for financial support of this research.

References and notes

1. For a review, and leading references, see: D. Craig, *Chem. Soc. Rev.*, **1987**, *16*, 187.
2. IMDA reactions giving a large ring in addition to the cyclohexene have been observed to give mixtures of regioisomers. For example, see: E. J. Corey and M. Petrzilka, *Tetrahedron Lett.*, **1975**, 2537.
3. For example, the regiospecific Lewis acid-mediated reaction of a silyl dienol ether with an aldehyde represents an extreme case of polarization of diene and dienophile substrates. See: M. Bednarski and S. Danishefsky, *J. Am. Chem. Soc.*, **1986**, *108*, 7060, and references cited therein.

4. K. N. Houk, M. N. Paddon-Row, N. G. Rondan, Y. Wu, F. K. Brown, D. C. Spellmeyer, J. T. Metz, Y. Li, and R. J. Loncharich, *Science*, 1986, *231*, 1108, and relevant references cited therein.
5. The term 'silyl acetal' has been used to describe functional groups containing contiguous oxygen, silicon and oxygen atoms: Y. Guindon, R. Fortin, C. Yoakim, and J. W. Gillard, *Tetrahedron Lett.*, 1984, *25*, 4717, and references cited therein.
6. Prepared by $LiAlH_4$ reduction of methyl (2*E*, 4*E*)-2,4-hexadienoate (91%); contaminated with *ca.* 15% of the 2*Z*, 4*E*-isomer (by ^1H nmr).
7. Prepared by Wittig reaction (0.17M in benzene, 80°C, 5 h) of $Ph_3P{=}CHCO_2Me$ with 2,5-dihydroxy-1,4-dioxane (91%).
8. The major by-products of this reaction were bis[(2*E*)-3-methoxycarbonyl-2-propenyloxy]diphenylsilane (*ca.* 5%) and bis[(2*E*, 4*E*)-2,4-hexadienyloxy]diphenylsilane (*ca.* 10%). Spectral data for *[(2E, 4E)-2,4-hexadienyloxy][(2E)-3-methoxycarbonyl-2-propenyloxy]diphenylsilane*, 1: υ_{max} (film) 3026, 2919, 1727, 1666, 1593, 1431, 1381, 1301, 1281, 1127, 990, 966, 836, 720, 701, 625 cm^{-1}; δ (500 MHz) 7.72-7.64 (4H, m, *o*-C_6H_5), 7.50-7.32 (6H, m, *m*- and *p*-C_6H_5), 7.05 (1H, dt, J 15, 3.5 Hz, H-2'), 6.25 (1H, dt, J 15, 2 Hz, H-3'), 6.25-5.95 (2H, m, H-3, H-4), 5.75-5.60 (2H, m, H-2, H-5), 4.49 (2H, dd, J 3, 2 Hz, H-1'), 4.33 (2H, br. d, J 5.5 Hz, H-1), 3.75 (3H, s, OCH_3), 1.75 (3H, br. d, J 6.5 Hz, H-6); *m/z* (EI) 394 (M^+), 297 (M^+ - $CH_3CH{=}CHCH{=}CHCH_2O$), 199 (Ph_2SiOH) (Found: C, 70.04; H, 6.51. $C_{23}H_{26}O_4Si$ requires C, 70.02; H, 6.64%).
9. Degassing of solutions was carried out by alternate ultrasonication and purging with argon (three cycles).
10. Carried out by heating the sealed tube under reflux with bis(trimethylsilyl)amine for 12 h.
11. Only one new methyl ester singlet and one new methyl doublet were visible in the ^1H nmr spectrum of the crude product.
12. Carried out to remove polar impurities by chromatography on Florisil® (200 mesh) (6% ether-petrol). We were unable to separate pure 5 from unreacted 1. The yields cited in Scheme 1 for formation of 5 and 2 take into account the contamination of 5 with 1. The yield of 5 is based on unreacted 1.
13. Methanolysis reactions were carried out by adding concentrated hydrochloric acid (2.5 μl) to a methanolic solution (0.05M) of 5 (70 mg), followed by addition of solid sodium hydrogencarbonate, filtration, concentration under reduced pressure, and chromatography on silica gel (50% - 75% ether-petrol). Methanolysis of intermolecular products was carried out similarly.
14. Spectral data for *[4R*, 5R*, 8S*, 9R*]-5-(hydroxymethyl)-8-methyl-1-oxo-2-oxabicyclo[4.3.0]-6-nonene*, 2: υ_{max} (Nujol) 3453 (sharp), 2913, 1742, 1461, 1378, 1062, 997, 722 cm^{-1}; δ (500 MHz) 5.68 (1H, dt, J 10, 2 Hz, H-7), 5.58 (1H, ddd, J 10, 4.5, 2.5 Hz, H-6), 4.41 (1H, dd, J 9, 7 Hz, H-3), 4.32 (1H, dd, J 12, 9 Hz, H-3), 3.73 (1H, br. dt, J 11.5, 4 Hz, CH_2OH), 3.65 (1H, m, CH_2OH), 2.58 (1H, m, H-5), 2.54-2.46 (1H, m, H-4), 2.39 (1H, m, H-8), 2.10 (1H, dd, J 14, 10 Hz, H-9), 1.43 (1H, br. t, J 4 Hz, OH), 1.28 (3H, d, J 7 Hz, CH_3); *m/z* (EI) 182 (M^+), 164 (M^+ - H_2O), 151 (M^+ - CH_2OH) (Found: C, 66.05; H, 7.44. $C_{10}H_{14}O_3$ requires C, 65.92; H, 7.74%).
15. We thank Dr. D. J. Williams of this department for this determination.
16. ^1H nmr data for *[6R*, 9S*, 10R*, 11R*]-10-methoxycarbonyl-9-methyl-3,3-diphenyl-2,4,3-dioxasilabicyclo[5.4.0]-7-undecene*, 5: δ (500 MHz) 7.75 (2H, m, *o*-C_6H_5), 7.68 (2H, m, *o*-C_6H_5), 7.49-7.36 (6H, m, *m*- and *p*-C_6H_5), 5.57-5.50 (2H, m, H-7, H-8), 4.12 (1H, dd, J 12.5, 2 Hz, CH_2O), 3.93 (1H, dd, J 12.5, 4 Hz, CH_2O), 3.83 (3H, s, OCH_3) 3.77-3.73 (2H, m, CH_2O), 2.68 (1H, m), 2.53 (2H, m), 2.22 (1H, m) (H-6, H-9, H-10, H-11), 1.00 (3H, br. d, J 6.5 Hz, C-9 CH_3).
17. The low mass balance for this reaction was apparently due to hydrolysis of 6 and 7, as evidenced by tlc.
18. Preparation of silyl acetals 6 and 7 was carried out as for triene 1, substituting methanol for methyl (2*E*)-4-hydroxy-2-butenoate (for 6) and for (2*E*, 4*E*)-2,4-hexadien-1-ol (for 7). Acetal 6 was difficult to separate in practical quantities (≥ 2 mmol) from bis[(2*E*, 4*E*)-2,4-hexadienyloxy]diphenylsilane formed as a by-product. Acetal 7 was obtained pure.
19. Ethers 8 and 9 were prepared in high yield from 3 and 4 respectively ($Ph_2MeSiCl$, Et_3N, CH_2Cl_2).
20. ^1H nmr data for the three hydroxylactones isomeric with 2: least polar (higher R_f than 2): δ (500 MHz) 5.82 (1H, ddd, J 9.5, 4.5, 2.5 Hz), 5.48 (1H, dt, J 9.5, 1.5 Hz), 4.46 (1H, dd, J 8, 6.5 Hz), 4.18 (1H, dd, J 11.5, 8 Hz), 3.84 (1H, ddd, J 10.5, 8, 3 Hz), 3.70-3.63 (2H, m), 2.64-2.53 (3H, m), 2.33 (1H, dd, J 14, 10 Hz), 1.11 (3H, d, J 6.5 Hz); more polar (lower R_f than 2): δ (500 MHz) 5.86 (1H, ddd, J 9, 4.5, 2.5 Hz), 5.45 (1H, dt, J 10, 1.5 Hz), 4.66 (1H, dd, J 9, 6.5 Hz), 4.01 (1H, dd, J 10.5, 9 Hz), 3.80-3.75 (1H, m), 3.53-3.47 (2H, m), 2.76-2.71 (1H, m), 2.46 (1H, dd, J 14, 5 Hz; overlapping with 1H, m), 2.30-2.25 (1H, m), 1.07 (3H, d, J 6.5 Hz); most polar: δ (500 MHz) 5.77 (1H, ddd, J 9.5, 3, 2 Hz), 5.55 (1H, ddd, J 9.5, 3, 2.5 Hz), 4.44 (1H, dd, J 9, 7.5 Hz), 4.03 (1H, dd, J 8.5, 5 Hz), 3.88-3.83 (1H, m), 3.70-3.64 (1H, m), 3.10 (1H, m), 2.93 (1H, t, J 7.5 Hz), 2.21-2.14 (1H, m), 1.93-1.87 (1H, m), 1.83 (1H, br. t, J 6 Hz), 1.12 (3H, d, J 7.5 Hz). To date, we have not assigned the regio- or stereochemical nature of these products. It should be noted that the two regioisomers opposite to 2 may each form two isomeric hydroxylactones. Full structural assignments will be published at a later date. All ^1H nmr spectra were recorded on $CDCl_3$ solutions at ambient temperature.
21. For the previous examples, see: (i) W. Oppolzer and R. L. Snowden, *Helv. Chim. Acta*, 1981, *64*, 2592; (ii) D. A. Smith, K. Sakan, and K. N. Houk, *Tetrahedron Lett.*, 1986, *27*, 4877.

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