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Trimethylsilyl Triflate Catalysed Diels-Alder Reaction of TMS Ethers of Conjugated Dienols with Cyclic Enones: Evidence for an Endo Transition State, and First Application to Synthesis of Enantiopure Octalins

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Abstract: The $AlCl_3$ catalysed 'ionic' Diels-Alder (DA) reaction of 6-methyl-2-cyclohexenones with 3,5-hexadien-1-ol in dichloromethane gives a trans-fused octalin hemiacetal with a β-equatorial methyl group and an axial hydroxyl. In contrast, trimethylsilyl triflate (TMSOTf, 5 mol%) at -20 °C in acetonitrile catalyses the DA reaction to give the trans-fused adduct acetal, whose controlled hydrolysis gives the hemiacetal with an α-axial methyl group. The adduct is thereby differentiated from the $AlCl_3$ DA adduct, and may be converted into the latter by treatment with *p*-toluenesulfonic acid in aqueous THF or by $AlCl_3$ in dichloromethane. In similar fashion, TMSOTf provides full acetal adducts from 2-cyclohexenone, 2-cycloheptenone and methyl vinyl ketone. The optically active enone acetal derived from (1*R*,2*R*)-1,2-diphenyl-1,2-ethanediol and 2-cyclohexenone gives a racemic acetal adduct derived from the TMS ether of hexadienol. The TMS ether of a mixture enriched in the 3*E*-isomer of (2*R*,5*E*)-2-methyl-3,5-heptadien-1-ol in acetonitrile containing TMSOTf (10 mol%) at -20 °C with 6-methyl-2-cyclohexenone gives the trans-fused acetal adduct, hydrolysis which provides the corresponding octalin hemiacetal as a single enantiomer. Similarly, the mixture enriched in the 3*E*-isomer of (2*S*,5*E*)-2-methyl-3,5-heptadienol TMS ether is converted by way of the octalin acetal into the octalin hemiacetal, enantiomeric with the foregoing product. The reactions are thereby shown to proceed via endo transition states. © 1998 Published by Elsevier Science Ltd. All rights reserved.

INTRODUCTION

Diels-Alder Reactions of Cyclohexenones

Although the Diels-Alder (DA) reaction of 2-cyclohexenones and 1,3-dienes is in principle offers a simple means of constructing decalin systems in complex polycyclic compounds,[1,2] its utility is considerably enhanced with the use of Lewis acid catalysts, which increase the rate, and improve yield, regio- and diastereoselectivity.[3,4,5] It is generally accepted that the concerted [4+2] cycloaddition mechanism still applies to the catalysed reaction, except in the case of the cycloaddition of 2-phenyl-2-cyclohexenone with 1,3-butadiene, for which a zwitterion intermediate is invoked to explain the formation of trans-fused cycloadducts.[7] For cyclohexenones, epimerization of the primary cis adducts at the α-carbon is sometimes observed under the influence of the catalyst, with the ultimate cis/trans ratio depending upon the solvent.[8,6] The presence of an alkyl group at C-2 lowers the reactivity of the enone, but excellent yields can still be obtained under catalytic conditions.[4] In contrast, 3-methyl-2-cyclohexenone does not undergo the reaction under thermal or catalytic conditions, but high pressure with catalysis overcomes the problem.[8] When a substituent renders the π-faces of

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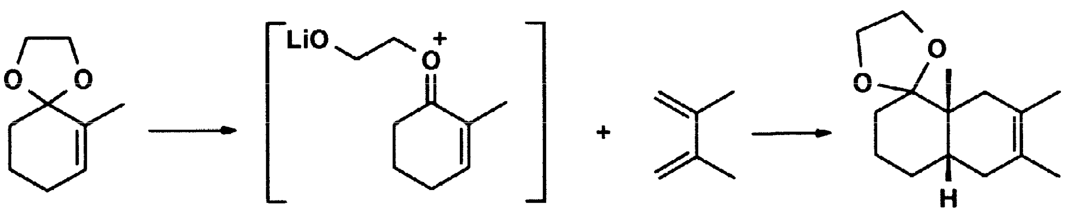
either reactant diastereotopic, diastereoisomers arising via addition syn or anti to the substituent are formed. For 4-alkyl cyclohexenones, anti-selectivity is slightly favoured for a methyl group, and increases as the alkyl group becomes larger. Anti selectivity is high for all 5-alkyl enones. On the other hand, syn selectivity is prevalent in 6-alkyl cyclohexenones.[9]

Electron-withdrawing groups on the enone and electron-donating groups on the diene increase the rate of the cycloaddition, and the use of catalysts and high pressure may be unnecessary.[10,11] The combination of catalysis, high pressure, and/or the use of activating substituents, permits the use of a wide variety of diene and enone dienophiles, and thus the potential of the methodology is apparent. Construction of bicyclic intermediates from simple 2-cycloalkenones and dienes as a result have been extensively applied in organic synthesis, especially of natural products.[12,13,14]

Ionic Diels-Alder Reactions

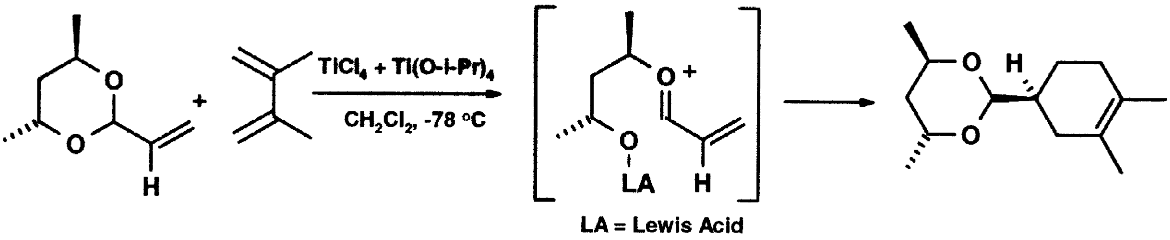
The discovery that cyclohexadiene underwent Diels-Alder dimerization with 70% yield at 0 °C in the presence of tris(*p*-bromophenyl)aminium hexachloroantimonate[15] caused Gassman and coworkers to investigate the reactions on the basis of *in situ* generation of allyl cations from the dienes. Both inter-[16] and intramolecular[17] cycloaddition reactions of allyl cations to 1,3-dienes were accomplished at low temperature with excellent stereoselectivities,[18,19] for which the authors proposed a stepwise process. It is important to point out here that the description 'Diels-Alder reaction' refers only to the formal outcome of these reactions and does not indicate whether they are stepwise or concerted.[18, 20]

Allylic alcohols, allylic ethers,[21] acrolein acetals[22] and vinyl and ethynyl ortho esters[23] are also used as sources of allyl cations. The reactions between enone acetals and dienes are catalysed by protic acid,[24] or proceed in $LiClO_4$-ether solutions in the presence of protic acid. An example relevant to our own work here is given in Scheme 1;[25] oxo-stabilized allyl (oxoalkenyl) cations are proposed as the reactive intermediates.[26]



Scheme 1

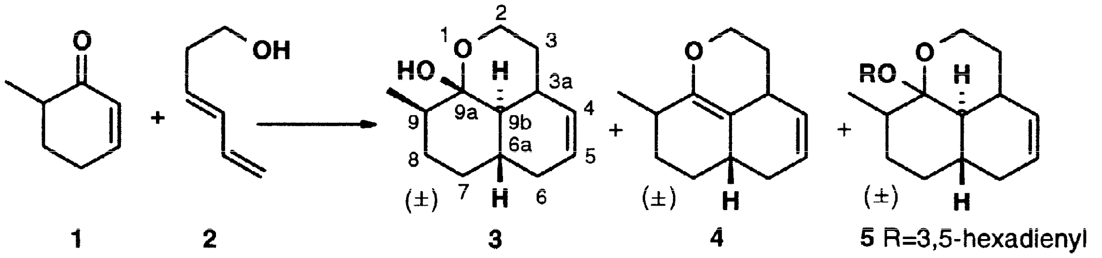
Substrate-controlled asymmetric "ionic" Diels-Alder reactions have been developed with dienophiles carrying a chiral auxiliary. Good diastereoselection was obtained using a chiral acetal and 1:1 $TiCl_4$-$Ti(O\text{-}i\text{-}Pr_4)$ (Scheme 2). Enantiomerically enriched cyclohexene carboxaldehyde derivatives were provided upon hydrolysis of the acetals. In an ingenious approach, chiral α,β-unsaturated ketones were converted *in situ* into cyclic oxo allyl cations, which reacted with the diene.[26]



Scheme 2

Diels Alder Reactions of Hexa-3,5-dienols

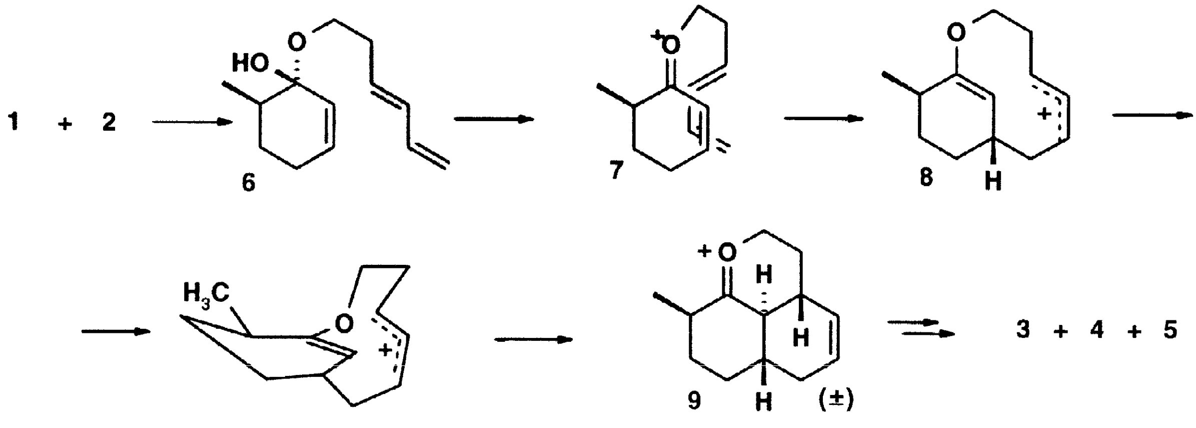
We reported that whereas (3*E*)-3,5-hexadienoic acid and its methyl ester failed to react with enone **1** under thermal or Lewis acid-catalysed conditions, (3*E*)-3,5-hexadien-1-ol **2** with enone **1** and an equivalent amount of $AlCl_3$ in dichloromethane below 0 °C gave racemic trans-fused hemiacetal adduct **3** as the major product, acetal **4** and enol diene **5** (Scheme 3).[27,28] Compound **4** was a 1:1 mixture, and compound **5** was a 4:1 mixture of diastereomers.



Scheme 3

Relative configuration of hemiacetal **3** was determined by NMR spectroscopy and by chemical correlation.[27] Nevertheless, configuration at C-9a could not be established. The β-methyl group at C-2 correlates with normal DA reactions involving 6-alkyl cyclohexenones, as pointed out above. Whether formation of the trans-ring junction in **3** was due to isomerization of an initial cis-adduct through reversible opening of the hemiacetal and enolization of the resulting ketone could not be established because of our inability to isolate the cis adduct. An alternative proposal was put forward that these cycloadditions proceeded through an oxy-allylic cation, especially as it is uniquely the dienyl alcohol, rather than the acid or ester, which is effective in the DA reactions. Thus, the Lewis acid mediates initial addition of the hydroxyl group of the dienyl alcohol to the enone to form hemiacetal **6**. This collapses to the oxy-allylic cation **7**, which then drives ring closure via the exocyclic allylic cation **8** to provide the trans-fused precursor cation **9** of the final products (Scheme 4).[27] In order to explain formation of the fully trans-fused product, it was assumed that the final C-C bond formation takes place through the β-face of the enol ether.

Formation of trans-fused products is a characteristic of "ionic" Diels-Alder reactions providing 6,5- and 6,6-fused ring systems. This reaction therefore is a new variant of the Gassman type "ionic" DA reaction, in which the cation is generated from a hemiacetal.[19,20,29] The highly stereoselective outcome of the reaction in the present case is particularly noteworthy.



Scheme 4

It is our purpose now to examine this reaction in more detail. Previously, we converted the adduct **3** into (±)-6,9-desdimethylartemisinin, a derivative of the antimalarial drug artemisinin. The synthesis, however, suffers both from the low yield, and the unfavourable stereochemistry at C-2 in **3**;[27] further details will be given in a future paper. As our eventual aim is to prepare enantiomerically pure artemisinin derivatives, we need to focus on enantioselective variants of the DA reaction by using either enantiopure acetals in place of the enones, and/or chiral Lewis acid catalysts for the reaction.

We have not yet uncovered successful working versions of the reaction employing these modifications. However, we have both obtained full structural details on adduct **3** by X-ray crystallography, and have dramatically improved the yields of adducts by using a different catalyst. Further we have discovered an enantioselective version, albeit low-yielding, which commences with chiral dienyl alcohols. We now describe in full the results of this work. A preliminary communication describing the catalyst modification has appeared,[30] and this has been highlighted in the review literature.[31]

DISCUSSION

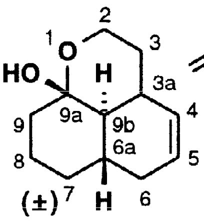
Structural Characterization of Compound 3

An equivalent amount of $AlCl_3$ was first mixed with 6-methyl-2-cyclohexenone in dichloromethane to form a red complex. This was then treated with (3*E*)-3,5-hexadien-1-ol at -20 °C to give racemic hemiacetal **3**. Spectroscopic data were consistent with those reported.[27] The NMR data did not permit disclosure of stereochemistry at the acetal carbon atom C-9a.. The compound was obtained after crystallization from light petroleum (b.p. 30-60 °C) as a single crystal, in the shape of a thin needle. The X-ray data, which have been presented previously, and deposited with CCDC,[30] indicate that the hydroxyl group at C-9a is axial, and the C-9 methyl is equatorial (Figure 1, below). The significance of the β-axial hydroxyl group is discussed below.

Brønsted Acid Catalysed Diels-Alder Reaction

The rationalization of intermediacy of the hemiacetals and collapse to cationic intermediates caused us to focus on catalysts which promote acetal formation between ketones and alcohols. The reaction involves oxo-stabilized cationic intermediates.[32] If the cation is conjugated with a double bond, then according to the mechanistic formulation of Scheme 4, closure should take place. Whilst trifluoroacetic acid (0.5 equiv.) gave no reaction, triflic acid with 2-cyclohexenone and dienol **2** in dichloromethane at -20 °C provided hemiacetal **10** (22%) and acetal **11** (3%). In the ^1H NMR spectrum of **10**, H-9b appeared as a doublet of doublets at 1.11 ppm with J = 10.3 and 10.7 Hz; thus H-9b is trans both to H-3a and H-6a. The stereochemistry is therefore the same as that in the adduct **3** obtained from the $AlCl_3$-catalysed reaction.

However, yields of adduct from 6-methyl-2-cyclohexenone **1** with triflic acid were far too low for synthetic purposes, and use of Lewis acids that catalyze acetal formation was thus next examined.



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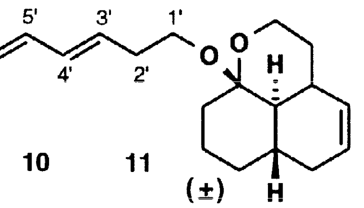
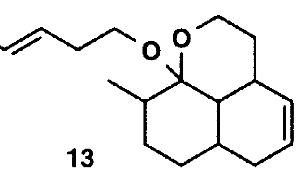


11

12

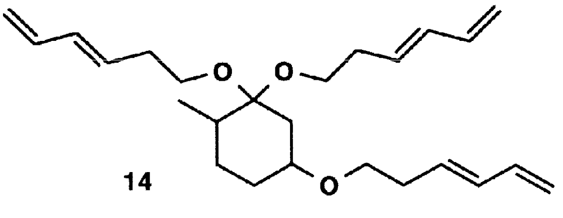


13

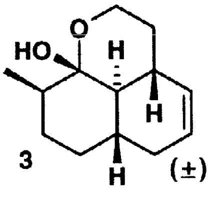
Trimethylsilyl Triflate Catalysed Diels-Alder Reaction

Lewis acids normally effective in promoting acetal formation – $ZnCl_2$, $TiCl_4$, BF_3-etherate, $FeCl_3$ *etc.*- all failed to induce reaction between 6-methylcyclohexenone **1** and dienol **2**. Whilst 1:1 $TiCl_4$-Ti(O-*i*-Pr_4) failed to induce a reaction with enone **2**, 2-cyclohexenone with dienol **2** did give the adduct, albeit in impractically low yield.

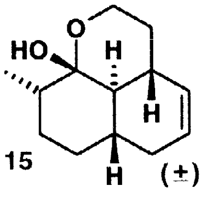
Noyori and coworkers developed an extremely useful method for the preparation of acetals from ketones and conjugated enones involving trimethylsilyl triflate (TMSOTf) as catalyst and the TMS ether of the alcohol in dichloromethane at -78 °C.[33] In adapting this method for the DA reaction, we treated a dichloromethane solution containing 2 mol% of TMSOTf at -78 °C with enone **1** under nitrogen. The TMS dienyl ether **12** was then added to the mixture. After 20 h, the mixture was quenched by addition of dry pyridine to give the racemic cycloadduct as full acetal **13** (46%), and a diastereomeric mixture of conjugate addition products **14**.[34] The constitution of racemic acetal **13** was unambiguously identified by its ^1H NMR spectrum, although the relative configuration could not be confirmed as the signal due to H-9b was overlapped with other signals. However, a clean doublet at 1.01 ppm due to a single methyl group in the ^1H NMR spectrum, and a unique set of signals in the ^{13}C NMR spectrum implied that the reaction was diastereoselective. However, *the data clearly differentiated it from the acetal* **5** (Scheme 3) *isolated from the $AlCl_3$ reaction.*



14



3



15

The acetal **13** was hydrolyzed to the hemiacetal **15** (85%) in aqueous THF (1:3 H_2O:THF) containing *p*-TsOH. The ^1H NMR spectrum again revealed that it had a structure different to that of hemiacetal **3** obtained from the $AlCl_3$-catalysed reaction. *Thus, the published*[30] *assumption that the stereochemistry of the product from the TMSOTf catalyzed reaction was the same as that of the* $AlCl_3$*-catalysed reaction product is incorrect.* H-2β and H-3α with J = 12.7 Hz are antiperiplanar. The methyl signal at δ 1.05 ppm has J = 7.3 Hz. H-9b appears as a doublet of doublets with J = 10.7 and 10.7 Hz with each of H-3a and H-6a respectively. H-9b is therefore antiperiplanar with these protons. Clearly, the trans-fused tricyclic structure of the adduct is intact. The most interesting signal is due to H-8β at δ 1.98. This contains two large (13.7 Hz) and two small (4.4 Hz) coupling constants. The small coupling with H-9 indicates an axial-equatorial interaction. Therefore, *the methyl group is axial.*

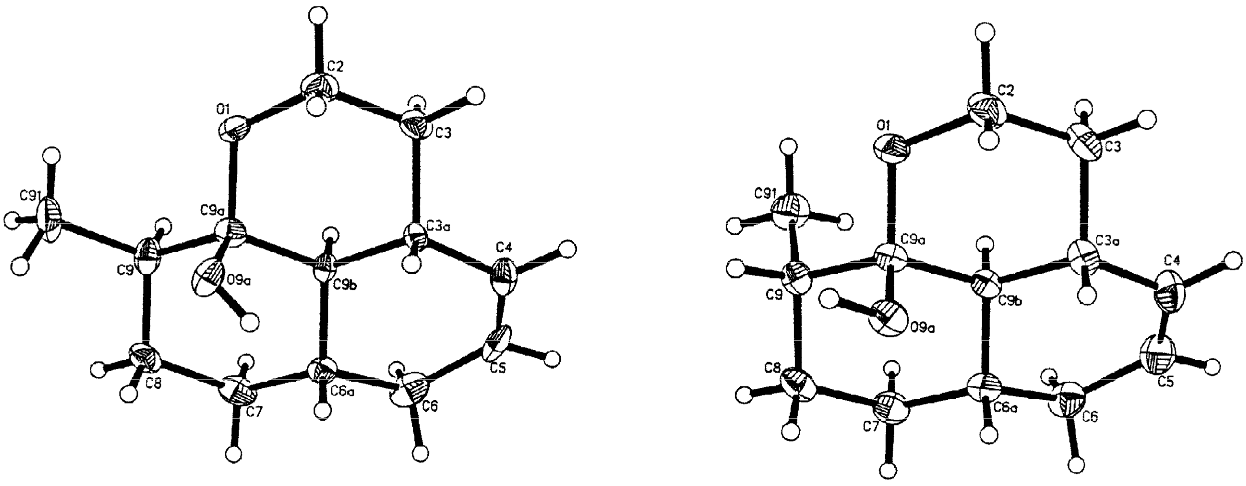
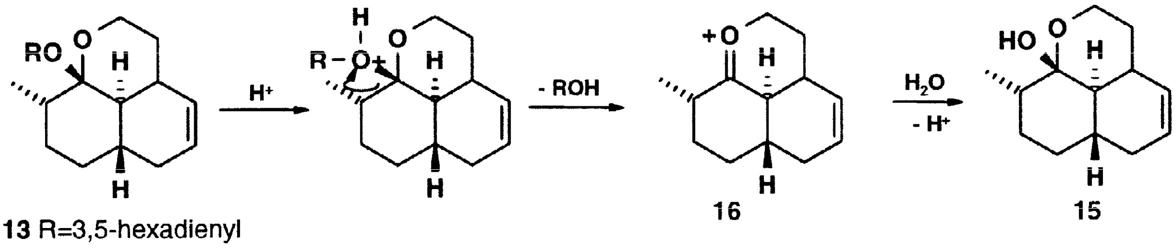


Figure 1: Structures of racemic hemiacetals (±)-**3** and (±)-**15** as determined by X-ray crystallography. (±)-**3**: $C_{13}H_{20}O_2$.0.5 H_2O: ($C_{26}H_{42}O_5$), Mr = 436.6, orthorhombic, Pna2_1, *a* = 24.971(6), *b* = 6.316(2), *c* = 14.733(3)Å, V = 2378Å^3, T = 198K, D_c = 1.21 gcm^{-3}, μ (Mo-Kα) = 0.82cm^{-1}, $F_{(000)}$ = 952. R = 0.067, Rw = 0.063, GOF = 1.46 for 1855 data to 2Θ =50°, [F≥3σ(F)], Δρ ≤ ±0.38eÅ^{-3}. (±)-**15**: $C_{13}H_{20}O_2$, Mr = 208.3, triclinic, P-1, *a* = 7.247(2), *b* = 8.772)2), *c* = 9.608(2)Å, α = 102.98(2), β = 97.65(2), γ = 105.20(2)°, V = 562.2Å^3, T = 235K, D_c = 1.23 gcm^{-3}, μ (Mo-Kα) = 0.81cm^{-1}, $F_{(000)}$ = 228. R = 0.060, Rw = 0.076, GOF = 2.14 for 2492 data to 2Θ = 60°, [F≥4σ(F)], Δρ ≤±0.47eÅ^{-3}

The conclusion was confirmed by the X-ray crystal structure determination which shows the hydroxyl group at C-9a is axial and trans to the methyl in **15**, in contrast to their cis relationship in hemiacetal **3**. The X-ray structures of racemic hemiacetals **3** and **15** are shown in Figure 1. Compounds **3** and **15** crystallize in Pna2_1 and P-1bar respectively, indicating an enantiomeric mixture within the crystal. The asymmetric unit of **3** contains two molecules, which are enantiomers of each other, plus a water of crystallization. Geometric parameters for the two compounds, and for compound **31** (see below) are sensible; the terminal hydroxy C(9a)-

O(9a) lengths vary from 1.413-1.421Å, slightly shorter than the bonds involving the ring oxygen O(1) (1.435-1.444Å). The C-C bonds have single bond lengths, except for the C(4)=C(5) double bond which ranges from 1.305-1.325Å in the three compounds. The cyclohexene rings containing this functionality are 'half-chairs' with C(6a) and C(9b) typically ±0.4Å out of the plane of the other four carbons. The other rings are chair cyclohexanes, and the anti-arrangement of OH and methyl groups at C(9a) and C(9) in **15** is shown by the torsion angles 170.7 and 169.9(ave), whereas for **3** the syn-arrangement of these groups is shown by torsion angles of 59.1 and -65.7 for its two crystallographically independent molecules.

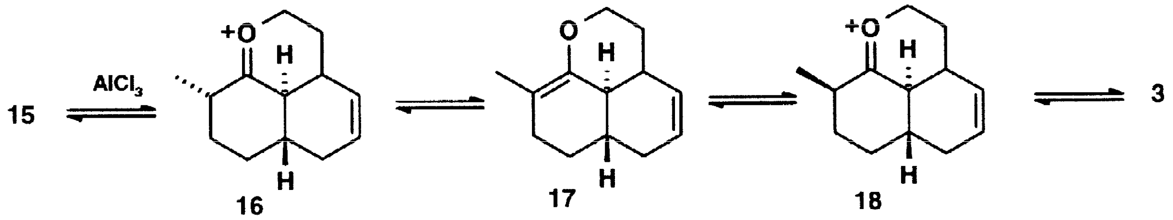
Although it cannot be proved that the configuration of the methyl group does not change during hydrolysis of the acetal **13**, the hydrolysis itself is likely to proceed as in Scheme 5. Protonation of the acetal oxygen and detachment of the dienyl alcohol leads to cation **16**. The axial methyl blocks approach of water from the α-face. Addition through the β-face leads to the trans relationship between hydroxyl and methyl groups.



Scheme 5

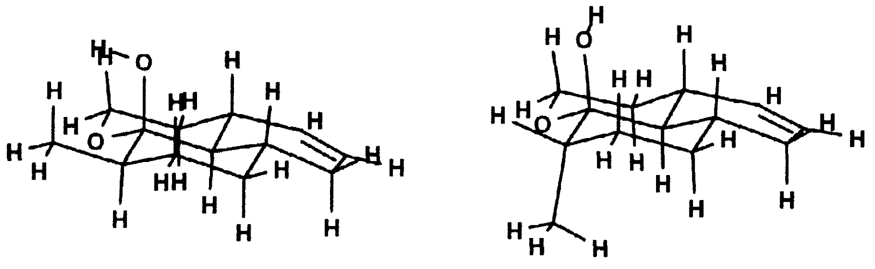
Conversion of Hemiacetal 15 into Hemiacetal 3

Treatment of hemiacetal **15** in THF at room temperature with catalytic anhydrous *p*-TsOH or in dichloromethane at 0 °C with $AlCl_3$ under nitrogen converted it into hemiacetal **3**. The isomerization very likely involves cation **16** which converts into enol ether **17** via removal of a proton; equilibrating protonation provides cation **18** and thence the more stable hemiacetal **3** (Scheme 6).



Scheme 6

Calculation of the relatively stabilities of the hemiacetals with MM+ (Hyperchem 5, Hypercube Inc., Gainesville FA) indicates that the hemiacetal **3** with an equatorial methyl group is more stable by 1.3 kcal mol^{-1} than **15** with the axial methyl group (Figure 2).

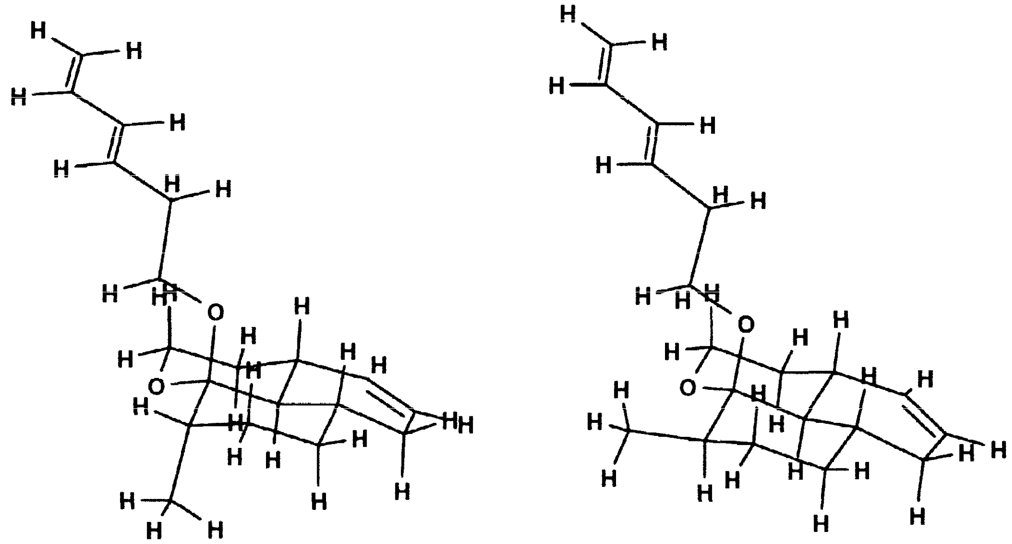


3
Energy = 16.974 kcal/mol

15
Energy = 18.371 kcal/mol

Fig. 2: Hemiacetals **15** and **3** with axial and equatorial methyl groups; minimum energy conformers calculated by MM+ (Hyperchem 5, Hypercube Inc., Gainesville, FA).

With the energetically more-favoured hemiacetal **3** being isolated from the AlCl$_3$-catalysed DA reaction, it was necessary to establish which of the full acetals, **13** with axial methyl, and **19** with equatorial methyl, had the lower energy. Geometry optimization was performed with MM+. The results are unexpected (Figure 3). Acetal **13** possesses a lower calculated potential energy than acetal **19** by 1.55 kcal/mol. This may due to the gauche interaction between the equatorial methyl group and the hexadienylic side chain of the acetal. Although acetal **13** is the favoured product, it is not possible to establish if **13** is a kinetic or thermodynamic product of the TMSOTf-catalysed DA reaction.



13
Energy = 21.893 kcal/mol

19
Energy = 23.444 kcal/mol

Figure 3: Energy minimized structures and calculated energies of acetals **13** and **19**

Optimization of Reaction Conditions and Examples of the Reaction

From reactions with 2-cyclohexenone performed in diethyl ether or acetonitrile at -78 °C with 10 mol% TMSOTf, the cycloadduct **11**, but no conjugate addition product, was formed. However, with toluene as solvent, the yield of cycloadduct was depressed, and the conjugate addition product was also formed. Thus, it appears that the conjugate addition reaction can be suppressed by the use of a Lewis-basic solvent. Use of the *tert*-butyldimethylsilyl (TBDMS) dienyl ether rather than the TMS ether in acetonitrile gave adduct **11** in 64% yield. However, use of TBDMSOTf as catalyst with the TBDMS ether gave a poorer yield of the adduct.

The optimum procedure involved the addition of 1.2 equivalents of the enone to a solution of acetonitrile containing 5-10 mol% of the trialkylsilyl triflate catalyst at -20 °C under nitrogen. The mixture was stirred for 2 minutes and then 2 equivalents of the trialkylsilyl dienyl ether was added. The mixture was quenched with pyridine. The products were purified by column chromatography to yield the acetal adduct.

In Table 1 are listed the various conditions and enones tested in their reaction with TMS dienyl ether **12** and the corresponding TBDMS dienyl ether.

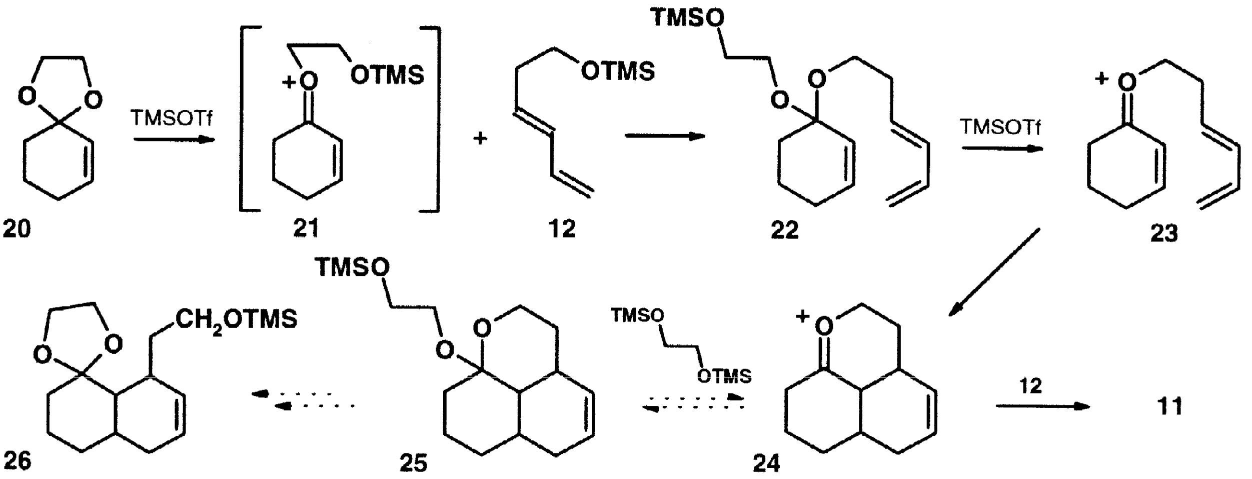
Enone	TMSOTf (mol%)	Reaction conditions	DA adduct, %	Conj. Adduct, %
6-Methylcyclohex-2-enone	2	CH_2Cl_2, -78 °C, 20 h	46	2
6-Methylcyclohex-2-enone	5	CH_3CN, -20 °C, 16 h	60	-
Cyclohex-2-enone	5	CH_3CN, -20 °C, 5 h	59	-
Cyclohex-2-enone	5	CH_3CN, 0 °C, 24 h	45	-
Cyclohex-2-enone	10	Et_2O, -78 °C, 16 h	45	-
Cyclohex-2-enone	10	Et_2O, -20 °C, 12 h	57	-
Cyclohex-2-enone	3	Toluene, - 78 °C, 14 h	24	8
Cyclohept-2-enone	10	Et_2O, -78 °C, 10 h; +20 °C, 10 h	32	-
Cyclohept-2-enone	5	CH_3CN, -30 °C, 10 h	55	8
Cyclohept-2-enone	6	Toluene, - 78 °C, 14 h; - 20 °C, 10 h	31	-
Methyl vinyl ketone	10	CH_3CN, -20 °C, 36 h	26	-
Cyclohex-2-enone	5 (with TBDMS dienyl ether)	CH_3CN, -20 °C, 19 h	64	-

Table 1: Yields of adducts from enones and dienol TMS ether **12** and dienol TBDMS ether.

As can be seen from Table 1, cycloheptenone also worked well for the reaction. In contrast, the acyclic methyl vinyl ketone, which was expected to react readily, gave a low yield of the acetal (26%); polymerization was seen to be a competing reaction.

Reaction with Enone Acetals

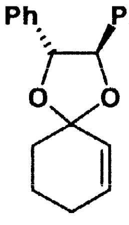
Although use of the TMSOTf catalyst represents a key development of the reaction, the necessity of using two equivalents of the silyl dienyl ether is not economical. It has been noted above that enone acetals serve as precursors of oxo allyl cations in the ionic DA reaction. The acetal reforms after the Diels-Alder reaction (*cf.* Schemes 1 and 2). In the present case involving the ethylene acetal **20** of 2-cyclohexenone, two possible outcomes, in which only one equivalent of the dienol TMS ether are required, were anticipated – generation of cation **21** is followed by formation of acetal **22** with **12**, generation of the new cation **23**, intramolecular cycloaddition to **24**, and recapture by the glycol TMS ether to generate the 6-membered acetal adduct **25** or the ethylene acetal adduct **26** (Scheme 7).



Scheme 7

However, treatment of ethylene acetal **20** under the optimum conditions with one equivalent of the dienol TMS ether **12** and 10 mol% TMSOTf resulted in consumption of the ethylene acetal within 3 h to give solely the dienyl acetal DA adduct **11** in 32% yield. Thus, equilibration involving **24** with the silyl dienyl ether **12** leading to **11** successfully, albeit surprisingly, competes with that of the ethylene glycol bis-TMS ether (formed upon ring opening induced by TMSOTf) leading to **25** (Scheme 7).[35] Although neither of the anticipated compounds was formed from the ethylene acetal **20**, the reaction was much faster than that involving the enone itself.

That the acetal is completely exchanged prior to the cycloaddition was supported by the results of the following experiment. Treatment of diphenylethylene acetal **27**, obtained from the bis-TMS ether of (1*R*,2*R*)-1,2-diphenyl-1,2-ethanediol[36] and 2-cyclohexenone, with the dienol TMS ether **12** and 5-10 mol% TMSOTf under the optimum conditions again gave the dienyl acetal DA adduct **11**. The product, as determined by GC with a Chiraldex β-TA column was racemic. As the chiral acetal failed to induce asymmetry in the product, this supports the idea that cation **23** is the intermediate. That is, prior to adduct formation, the chiral acetal group is completely removed.



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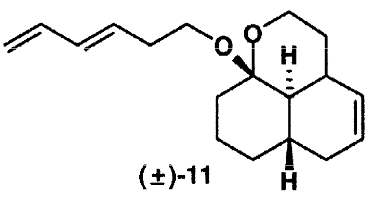


(±)-11

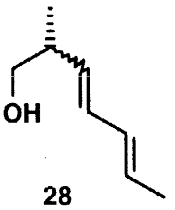
The recent modification of the Noyori acetalization wherein the TMS ether of the alcohol is generated *in situ* from the alcohol by exchange with a *sec*- or *tert*-alkoxysilane in the presence of catalyst was also tried here.[37] Thus, the TMS ether of cyclohexanol was mixed with 2-cyclohexenone and (3*E*)-3,5-hexadienol **2** under the optimum conditions. However, acetal **11** was again the only product obtained.

Reactions of the TMS Ether of 2-Methyl-3,5-heptadien-1-ol

The reactants used thus far do not have the constitutions to define whether the reactions proceed via an endo transition state, as indeed we have assumed (*cf.* Scheme 4). A diene bearing a methyl group attached to C-6 at least must be used for this purpose. For a reaction of (3*E*,5*E*)-heptadienyl alcohol proceeding via an endo transition state, the methyl group should acquire a trans relationship with the proton at the ring junction in the product (Scheme 8 below). If an exo transition state is involved, then this methyl group will become cis to the proton at the ring junction in the product. As we are also intent upon using these reactions to prepare analogues of qinghaosu, we need to use optically active heptadienols bearing a methyl group at C-2.

Commercially available (*S*)- and (*R*)-3-bromo-2-methylpropan-1-ols were converted into the phosphonium salts, and each was treated at 0 °C in THF with lithium hexamethyldisilazide[38] to generate the corresponding ylides. Treatment with crotonaldehyde at room temperature provided the dienyl alcohols **28** and **32** as 4:1 mixtures of 3*E*:3*Z* isomers, in accord with the expectation that nonstabilized γ-oxido ylides exhibit *E*-selectivity.[39] In each case, an unidentified non-polar product, possibly an ether, whose proton NMR spectrum was very similar to that of the alcohol, but with the signals shifted downfield, was also formed.. This could be hydrolyzed to the desired alcohol in aqueous THF in the presence of acid.

It was not possible to separate the dienyl stereoisomers, and therefore the mixtures were used in the Diels-Alder reactions. The TMS ether mixture **29** of the 4:1 mixture of (2*R*,3*E*,5*E*)- and (2*R*,3*Z*,5*E*)-dienols **28** was reacted with enone **1** in the presence of 10 mol% TMSOTf in acetonitrile at -20 °C during 1 day to give a product mixture in 24% yield. As it was anticipated that the chiral centre at C-2 of the dienyl silyl ether would not control facial selectivity of the reaction with the racemic enone **1**, it was expected that two diastereomers would be obtained. The proton NMR spectrum of the product was difficult to interpret, although it did indicate that a mixture of acetals **30**, arising from incorporation of the 3*E*,5*E*- and 3*Z*,5*E*-dienylic units into the side chain in the acetal adduct, was obtained.



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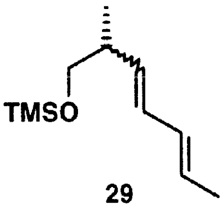

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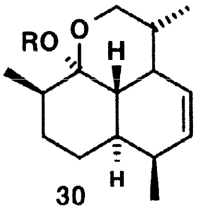
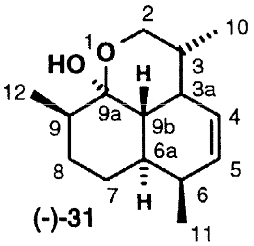


30

R = 2-methyl-3,5-heptadienyl



(-)-31

The acetal mixture **30** was hydrolyzed to give a single product identified as hemiacetal **31** which crystallized after isolation by column chromatography. *Both ^1H and ^{13}C NMR spectroscopy revealed it was a single compound.* The crystal structure determination of compound **15** (Figure 1) indicates the torsion angle of H5-C5-C6-H6β is +50.8° while the torsion angle of H5-C5-C6-H6α is -67.4°. Since the torsion angle of H5.....H6α is closer to 90°, the coupling constant $J_{5,6\alpha}$ (2.0 Hz) is smaller than $J_{5,6\beta}$ (4.9 Hz). In the case of compound **31**, which turns out to have an enantiomeric relationship with the structure depicted for racemic **15** (see above), the presence of the C-6 methyl group simplifies the splitting of H-5, which appears at δ 5.61 ppm as a double double doublet with coupling constants of 2.9 Hz, 4.4 Hz, and 10.3 Hz respectively. In contrast to H-5 in **15**, the coupling constant of less than 2 Hz is lacking in the signal due to H5 in compound **31**. This indicates that the methyl group in **31** has the same relative orientation as H6α in **15**; that is, this group is α in the enantiomer of **31**. According to convention, this group therefore projects from the β face in compound **31**.

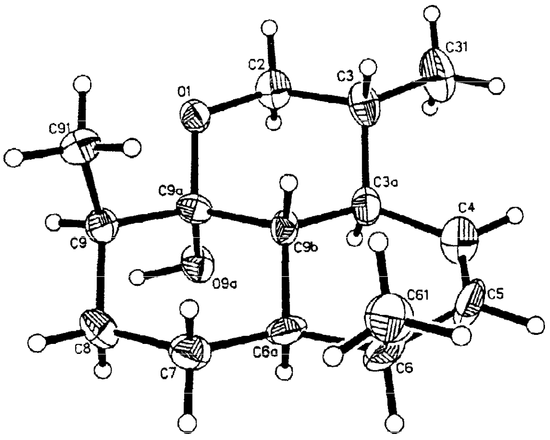
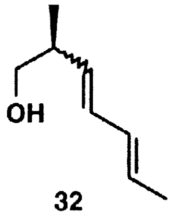


Figure 4: Structure of hemiacetal (-)-**31** as determined by X-ray crystallography.
(-)-**31**: $C_{15}H_{24}O_2$, Mr = 236.3, orthorhombic, $P2_1$, a = 14.388(3), b = 6.446(2), c = 15.309(5)Å, V = 1348Å^3, T = 228K, D_c = 1.16 gcm^{-3}, (Mo-Kα) = 0.75cm^{-1}, $F_{(000)}$ = 520. R = 0.059, Rw = 0.047, GOF = 1.23 for 1689 data to 2Θ = 47°, [F≥2σ(F)], Δρ ≤±0.22eÅ^{-3}.

An X-ray structural determination disclosed that the hemiacetal has indeed the structure as depicted in **31** (Figure 4). Compound **31** crystallizes in $P2_1$, a chiral space group. As in the case of compounds **3** and **15**, this has two molecules per asymmetric unit. However unlike compounds **3** and **15**, these have the same stereochemistry, thus supporting the enantiomeric purity of this compound. Geometric parameters for compound **31** are as for compound **15** described above. The absolute configuration was determined from the absolute configuration (2*R*) of the chiral dienyl alcohol used. The compound has a tricyclic fused pyran, cyclohexene and cyclohexane rings. Both the hydroxyl group at C-9a and the C-9 methyl are axial. The configuration of the chiral centres at C-3, C-6, C-9 are all (*R*)-. The *relative* configuration of the chiral centres at C-3a, C-6a, C-9, C-9a and C-9b are the same in both **15** and **31**.

Thus configuration at C6 in compound **31** *corresponds to intercession of an endo transition state* (*cf.* Scheme 8).



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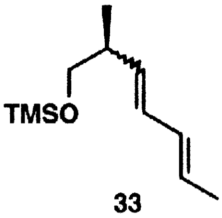

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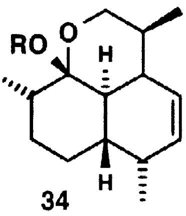

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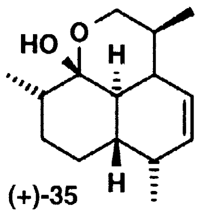


(+)-35

R = 2-methyl-3,5-heptadienyl

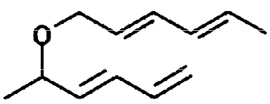
Next, the TMS ether **33** of a 4:1 mixture of (2*S*,3*E*,5*E*)- and (2*S*,3*Z*,5*E*)-dienols **32** was treated with enone **1** in the presence of TMSOTf. Once again, NMR spectra of the acetals **34** were difficult to interpret, although it was apparent that these were identical with the spectra of acetals **30**. The mixture was thus hydrolysed to the hemiacetal **35**. ^{1}H- and ^{13}C NMR spectra of the product also were identical with those of hemiacetal **31**. Molecular masses (MW = 236) and melting points (76.1 °C) were identical. The optical rotation for compound **31** ($[\alpha]_D^{21}$ = -100°, c = 0.60, $CHCl_3$) was opposite in sign to that of compound **35** ($[\alpha]_D^{21}$ = +102°, c= 0.61, $CHCl_3$). Therefore, compound **35** is the enantiomer of compound **31**.

Other Experiments

Diene substrates which cannot form an acetal with the enone were briefly examined as substrates for this reaction. With methyl (3*E*)-3,5-hexadienoate or methyl (3*E*)-3,5-hexadienyl ether and 2-cyclohexenone in the presence of TMSOTf, no reaction occurred during several days.

Treatment of the TMS ether **36** of (2*E*,4*E*)-2,4-hexadien-1-ol with 2-cyclohexenone under the optimum conditions resulted in rapid disappearance of the ether coupled with formation of a non-polar product, isolated in 30% yield. The ^{1}H NMR spectrum revealed that whilst the product contained no protons attributable to a cyclohexene ring, two different methyl signals at 1.26 and 1.75 ppm, and signals attributable to 9 dienylic protons, including two from a terminal double bond, indicated that the product was the dimeric ether **37**.

36

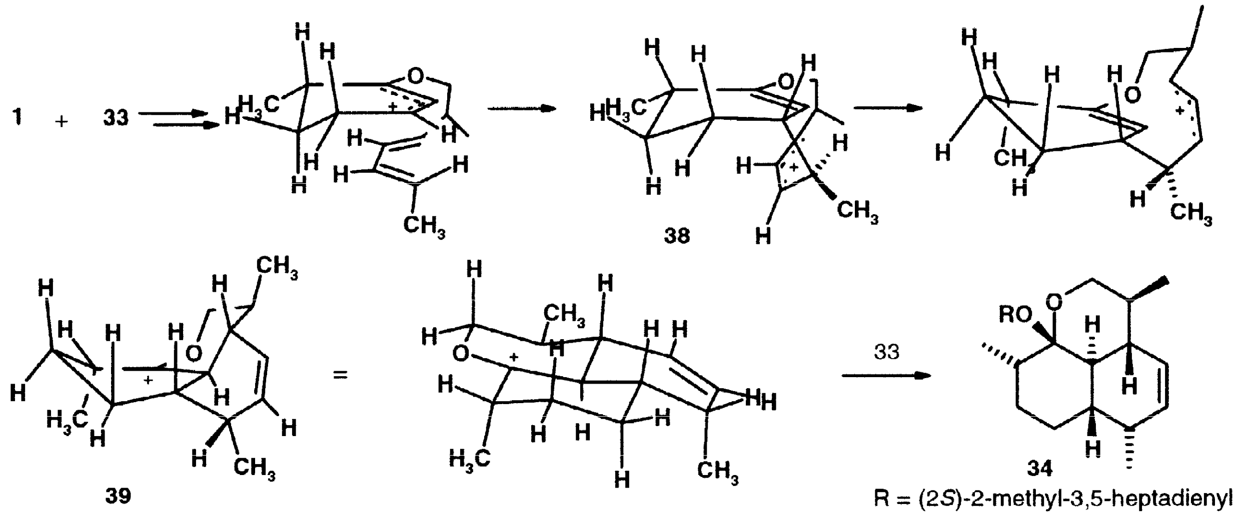


37

This product obviously arises by activation of the dienyl silyl ether by TMSOTf. Nucleophilic attack by the parent dienyl silyl ether on either the activated complex or on the derived cation at C-5 gives the product. Thus diene-allylic alcohols may not be suitable diene system for the DA reaction with enones under the current reaction conditions.[40]

Mechanistic Aspects

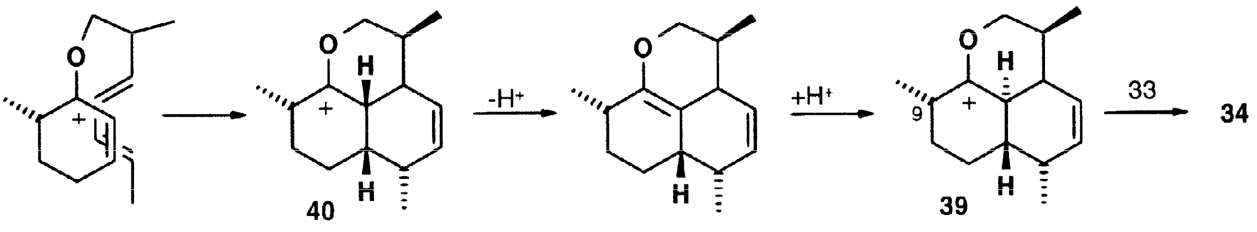
The fact that adduct **15** could be converted into the more stable adduct **3** by $AlCl_3$ suggests that adduct **15** probably was formed first in the $AlCl_3$ catalysed reaction, and was then transformed into the more stable isomer **3**. The original proposal that the diene adds anti to the C6-methyl (Scheme 4) is modified in light of the stereochemistry of adducts **15**, **34**, and **35** . That is, the pendant diene adds syn to the methyl group, as in other Diels-Alder reactions,[9] to form a 10-membered ring, as illustrated for TMS ether **33** (Scheme 8). The positive charge is thereby transferred to form allyl cation **38**. In order to furnish the trans ring junction, the exocyclic allyl cation has to be attacked from the *Re*-face; that is, the cation ensemble must have a lifetime long enough to flex to the upper face of the enone, as previously discussed for the original reaction. Collapse of the 10-membered ring gives the tricyclic cationic intermediate **39** with the positive charge at the carbon of the enone, according to the previous description.



R = (2*S*)-2-methyl-3,5-heptadienyl

Scheme 8

Nevertheless, it is possible that a cis-fused adduct is first formed, but this isomerizes rapidly to the trans-fused ring system, in accord with other Lewis acid catalysed Diels-Alder reactions.[4,6] The second C-C bond forming step takes place to give a cis-fused intermediate **40** (Scheme 9). This cis intermediate rapidly isomerizes to the more stable trans isomer **39**. The positive charge already at the carbonyl carbon next to the ring junction proton will obviously initiate the process. Deprotonation to form the enol ether and reprotonation to yield the more stable trans-product then follows. Clearly, formation of the trans-fused ring junction must already be complete prior to formation of the full acetal.

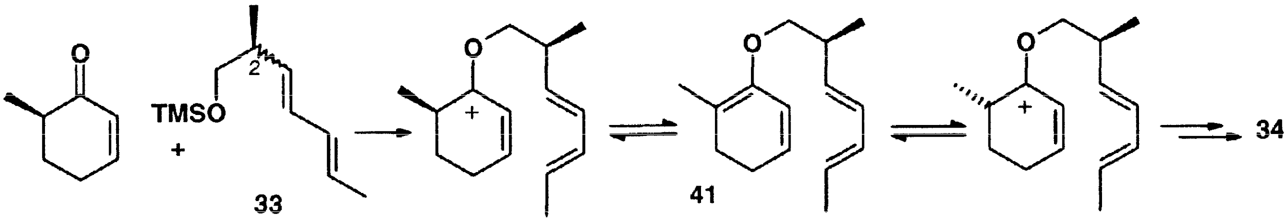


Scheme 9

It may be argued that if isomerization of cation **40** to **39** takes place, then equilibration of the C-9 axial to the equatorial methyl should also occur as a competing process (*cf.* Scheme 6). However, only the product with the 'unisomerised' axial methyl was obtained. Calculations show that the cation with the β-equatorial methyl group has lower energy than **39**. For the cation with the β-equatorial methyl group, approach of the silyl dienyl ether molecule at the upper face may become disfavoured with respect to the lower face. Nevertheless, the product with β-equatorial methyl and α-configured hexadienyl unit was never isolated from the reaction. As noted above (Figure 3), the full acetal which has a β-equatorial methyl with a β-3,5-hexadienyl unit is less stable than the α-axial methyl product.

Overall, the proposed stepwise mechanism is similar to that suggested for the "ionic" DA reactions investigated systematically by Gassman and co-workers as described in the Introduction. In the current case, however, cycloaddition occurs in an intramolecular mode; this provides a very special example of a 'tethered' DA reaction in which cycloaddition is greatly favoured.[41]

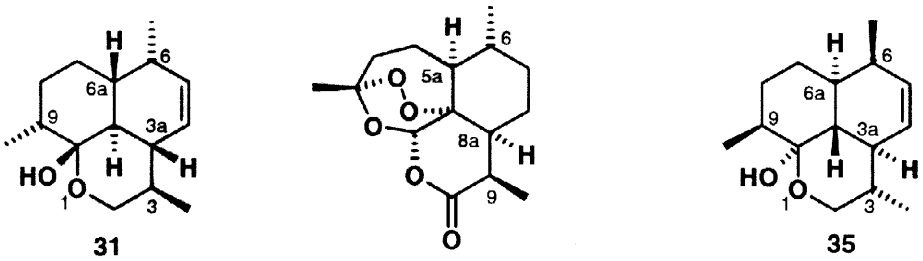
For the reactions involving the enantiomeric heptadienyl TMS ethers **29** and **33**, although the yields of the adducts are relatively low, there is the reasonable expectation that these may be enhanced through careful variation in the catalyst and solvent systems. The remarkable observation that the chiral centre at C-2 of the heptadienol controls *in an absolute sense* the stereochemistry in the tricyclic product obtained via the ionic Diels-Alder reaction appears to have no literature precedent. At this stage, it is uncertain if the chiral silyl dienyl ether reacts with one enantiomer of the enone, or whether the equilibration of the C-6 methyl in the so called "unreactive" enantiomer occurs via the oxyallylic cation formed prior to ring closure (Scheme 10). However, the second explanation is not yet supported as there is still no evidence that isomerization of the methyl group actually occurred in the TMSOTf-catalysed cases.



Scheme 10

Conclusion

It is clear that hemiacetals **31** and **35** cannot be used to prepare artemisinin or its enantiomer because of the wrong configurations at C3a and C6a, although the methyl groups at C-3 and C-6 do possess the correct configuration (Figure 5). The best approach is to target the C-6 epimer of compound **35** through use of (2*S*,3*E*,5*Z*)-2- methyl-3,5-heptadien-1-ol, and rely on inversion of configuration at C-3 in a later stage in the synthetic sequence. At this stage it is uncertain how (2*S*,3*Z*,5*E*)-or (2*S*,3*Z*,5*Z*)-2-methyl-3,5-heptadien-1-ol will



31 Artemisinin 35

Figure 5: Relationship between hemiacetal adducts and artemisinin

react in the ionic DA reaction. A 3*Z* configured double bond would render the endo transition state less accessible

EXPERIMENTAL SECTION

General Experimental

Diethyl ether, THF and toluene were dried over sodium and stored over sodium in the presence of benzophenone under nitrogen. The solvents were distilled immediately prior to use. Dichloromethane was dried over calcium hydride and distilled under nitrogen before use. Acetonitrile was dried over calcium hydride prior to distillation and stored over 4Å molecular sieves under nitrogen. ^{1}H and ^{13}C NMR spectra were recorded on CDCl$_3$ solutions on Bruker ARX 300 and JEOL JNM-EX-400 NMR spectrometers.. ^{1}H NMR spectra were referenced on CHCl$_3$ (δ 7.26 ppm), and ^{13}C NMR spectra on CDCl$_3$ (δ 77.0 ppm). Mass spectra and accurate mass measurements were recorded on a Finnegan TSQ-700 quadrupole mass spectrometer, and a Kratos MS-80 mass spectrometer, respectively. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Infra-red spectra were recorded on a Perkin-Elmer 16PC FT-IR spectrometer. Melting points were determined in capillary tubes on an Electrothermal melting point apparatus and are uncorrected. Merck Kieselgel 60 (230-400 mesh) was used for flash column chromatography under medium pressure. Analytical thin layer chromatography was carried out with pre-coated aluminium plates (Merck Kieselgel 60 F$_{254}$). Gas chromatographic analyses were conducted on a Hewlett Packard 5890 Series II instrument. Microanalyses were performed by MEDAC Ltd. at the Department of Chemistry, Brunel University.

Single crystal X-ray structure measurements were carried out on a Siemens P4-RA four-circle rotating anode diffractrometer. All computations in the structure determination and refinement were performed on a Silicon Graphics Indy computer using programs of the Siemens SHELXTL PLUS (Ver. 5) package. Single crystal structure determinations were carried out as follows; intensity measurements were collected using a Siemens P4-RA four-circle diffractometer operating at 10kW. All computations were carried out on a Silicon graphics Indy computer using the SHELXTL PLUS (version 4) suite of X-ray programs. All structures were solved by direct methods and refined by full-matrix least-squares. All non-hydrogen atoms were refined with anisotropic thermal parameters. All hydrogen atoms could be located in difference Fourier maps, but were inserted in geometrical positions $d_{(C\text{-}H)} = 0.96$Å, $d_{(O\text{-}H)} = 0.86$Å and refined with riding constraints and common isotropic thermal parameters.

Preparation of Starting Compounds

(3*E*)-3,5-Hexadien-1-ol (2)

This was prepared from methyl sorbate via deconjugation and reduction according to literature procedures.[42-44] The final product was obtained by distillation as colourless liquid, b.p. 79-81 °C, 20 mm Hg (Kugelrohr, lit[44] 82 °C, 30 mm Hg); ^{1}H NMR (300 MHz) δ 1.55 (br., OH); 2.36 (2H, dt, $J_{1,2}$ = 6.9 Hz, $J_{2,3}$ = 6.9 Hz, H2); 3.69 (2H, t, $J_{1,2}$ = 6.3 Hz, H1); 5.01 (1H, d, $J_{5,6}$ = 10.4 Hz, H6); 5.14 (1H, d, $J_{5,6}$ = 16.4 Hz, H6); 5.68 (1H, dt, $J_{2,3}$ = 7.2 Hz, $J_{3,4}$ = 15.1 Hz, H3); 6.16 (1H, dd, $J_{3,4}$ = 15.0 Hz, $J_{4,5}$ = 10.4 Hz, H4); 6.32 (1H, ddd, $J_{4,5}$ = 10.2 Hz, $J_{5,6}$ = 10.2 Hz, $J_{5,6}$ = 16.9 Hz, H5).

(3*E*)-3,5-Hexadien-1-ol Trimethylsilyl Ether (12)

A solution of (3*E*)-3,5-hexadien-1-ol (2.71 g, 27.7 mmol) in dichloromethane (100 mL) at room temperature under nitrogen at 0 °C was treated with triethylamine (5.8 mL, 1.5 equiv.) and trimethylsilyl chloride (5.3 mL, 1.5 equiv.) at this temperature. The mixture was stirred for 50 min. before the addition of hexanes (100 mL). The mixture was then filtered and the filtrate was concentrated under reduced pressure. Another portion of hexanes (50 mL) was added to the residue which was filtered again. The hexanes was evaporated from the filtrate under reduced pressure and the crude product was purified by quickly passing through silica gel (3% ethyl acetate/ hexanes) to yield the product ether as colourless liquid (4.34 g, 92% yield) with a characteristic smell. ^{1}H NMR (400 MHz) δ 0.11 (9H, s, TMS); 2.32 (2H, dt, $J_{1,2}$ = 6.8 Hz, $J_{2,3}$ = 6.8 Hz, H2); 3.61 (2H, t, $J_{1,2}$ = 6.8 Hz, H1); 4.98 (1H, d, $J_{5,6}$ = 10.3 Hz, H6); 5.11 (1H, d, $J_{5,6}$ = 16.6 Hz, H6'); 5.7 (1H, dt, $J_{2,3}$ = 7.3 Hz, $J_{3,4}$ = 14.7 Hz, H3); 6.10 (1H, dd, $J_{3,4}$ = 15.1 Hz, $J_{4,5}$ = 10.3 Hz, H4); 6.31 (1H, ddd, $J_{4,5}$ = 10.3 Hz, $J_{5,6}$ = 10.3 Hz, $J_{5,6}$ = 17.1 Hz, H5); ^{13}C NMR (100 MHz) δ -0.42, SiCH$_3$; 36.02, C2; 62.22, C1; 115.35, C6; 131.21, C3; 132.80, C4; 137.13, C5; ν_{max} (film) 3087 w, 3011 w, 2956 m, 2863 m, 1654 w, 1603 w, 1415 w, 1381 w, 1251 s, 110 vs, 1003 m, 841 vs cm^{-1}; mass spectrum (CI): m/z 171 (M$^+$, 23%); 103 (100%).

(3*E*)-3,5-Hexadien-1-ol *tert*-Butyldimethylsilyl Ether

(3*E*)-3,5-Hexadien-1-ol (4.40 g, 44.9 mmol) in dichloromethane at room temperature under N$_2$ was treated with *tert*-butyldimethylsilyl chloride (8.82 g, 1.3 equiv.) and imidazole (4.70 g, 1.5 equiv.). The resulting solution was stirred overnight, and then treated with water (200 mL). The organic layer was separated, and the aqueous layer was extracted with hexanes (3 x 80 mL). The combined organic extracts were washed with water (100 mL), saturated sodium bicarbonate solution (100 mL) and dried (MgSO$_4$). Solvent was removed under reduced pressure and the crude product was filtered through silica gel to yield the ether as a colourless liquid (8.14 g, 86%). ^{1}H NMR (400 MHz) δ 0.05 (6H, s, methyl); 0.89 (9H, s, *t*-butyl); 2.30 (2H, dt, $J_{1,2}$ = 6.8 Hz, $J_{2,3}$ = 6.8 Hz, H2); 3.66 (2H, t, $J_{1,2}$ = 6.8 Hz, H1); 4.98 (1H, d, $J_{5,6}$ = 10.3 Hz, H6); 5.10 (1H, d, $J_{5,6}$ = 16.6 Hz, H6'); 5.70 (1H, dt, $J_{2,3}$ = 6.8 Hz, $J_{3,4}$ = 14.7 Hz, H3); 6.10 (1H, dd, $J_{3,4}$ = 15.1 Hz, $J_{4,5}$ = 10.3 Hz, H4); 6.3 (1H, ddd, $J_{4,5}$ = 10.3 Hz, $J_{5,6}$ = 10.3 Hz, $J_{5,6}$ = 17.1 Hz, H5); ^{13}C NMR (100 MHz) δ -5.28, SiCMe$_3$; 25.92, SiCH$_3$;

36.20, C1; 62.81, C2; 115.20, C6; 131.39, C3; 132.74, C4; 137.17, C5; ν_{max} (film) 3012 w, 2956 s, 2857 s, 1653 w, 1604 w, 1472 m, 1382 m, 1256 s, 1196 m, 1100 vs, 1079 s 1005 s, 908 vs cm^{-1}.

(3*E*)-3,5-Hexadienyl Methyl Ether

Sodium hydride (60%, 601.7 mg, 15.0 mmol) was washed with freshly distilled THF (3 x 6 mL) and then suspended in THF (6 mL). The suspension was cooled to 0 °C and treated with 3,5-hexadien-1-ol (981 mg, 10.0 mmol) and methyl iodide (2.0 mL, 32.1 mmol). The mixture was warmed slowly to room temperature and stirred for 1 day. The reaction mixture was then treated with aqueous sodium thiosulfate (15 mL) followed by water (25 mL). The mixture was extracted with diethyl ether (3 x 20 mL), and the combined extracts were washed with water (2 x 20 mL) and brine (20 mL), and then dried ($MgSO_4$). After removal of solvent, the crude product was purified by distillation to give the ether (850 mg, 76%) as colourless liquid (b.p. 125 °C, Kugelrohr).[45] ^{1}H NMR (400 MHz) δ 2.37 (2H, dt, $J_{1,2}$ = 6.8 Hz, $J_{2,3}$ = 6.8 Hz, H2); 3.34 (3H, s, OMe); 3.43 (2H, t, $J_{1,2}$ = 6.8 Hz, H1); 4.99 (1H, d, $J_{5,6}$ = 10.3 Hz, H6); 5.11 (1H, d, $J_{5,6}$ = 16.6 Hz, H6); 5.70 (1H, dt, $J_{2,3}$ = 7.3 Hz, $J_{3,4}$ = 14.7 Hz, H3); 6.12 (1H, dd, $J_{3,4}$ = 15.1 Hz, $J_{4,5}$ = 10.3 Hz, H4); 6.31 (1H, ddd, $J_{4,5}$ = 10.3 Hz, $J_{5,6}$ = 10.3 Hz, $J_{5,6}$ = 17.1 Hz, H5).

(2*R*,3*E*,5*E*)- and (2*R*,3*Z*,5*E*)-2-Methyl-3,5-heptadien-1-ol (28) and TMS Ether (29)

(2*S*)-3-Bromo-2-methylpropan-1-ol (1.408 g, 9.20 mmol) and triphenylphosphine (3.113 g, 11.9 mmol, 1.3 equiv.) in toluene (15 mL) was heated at 85 °C for 10 days under nitrogen. The mixture was cooled to room temperature and filtered. The salt was washed with hexanes and diethyl ether and dried under vacuum to yield [(2*S*)-3-hydroxy-2-methylpropyl]triphenylphosphonium bromide (2.10 g, 55%) as a white powder. ^{1}H NMR (300 MHz) δ 0.51 (3H, d, *J* = 6.7 Hz, Me); 2.11-2.23 (1H, m, H2); 2.63 (1H, ddd, *J* = 5.2 Hz, *J* = 16.1 Hz, *J* = 16.1 Hz, H1); 3.63-3.70 (2H, m, 2 x H3); 4.90 (1H, ddd, *J* = 1.6 Hz, *J* = 16.3 Hz, *J* = 16.3 Hz, H1); 4.18 (br. s., OH); 7.65-7.93 (15H, m, ArH). ^{13}C NMR (100 MHz) δ 17.34, Me; 26.11, *J* = 49.8 Hz, C1; 31.69, *J* = 12.9 Hz, C2; 66.35, *J* = 5.23 Hz, C3; 118.90, *J* = 84.5 Hz; 130.39, *J* = 12.8 Hz; 133.50, *J* = 9.2 Hz; 134.90.

n-Butyllithium (2.2 M, 17 mL) was added slowly to hexamethyldisilazane (4.45 g, 27.6 mmol) in THF (30 mL) at 0 °C. The solution was warmed to room temperature and stirred for 15 min. The lithium hexamethyldisilazide solution was then added to a suspension of the phosphonium bromide (5.73 g, 13.8 mmol) in THF (30 mL) at room temperature. The resulting solution was stirred for 15 min to give an orange-coloured solution. Crotonaldehyde (986 mg, 14.1 mmol) was added then dropwise, and the mixture was stirred for 70 min before the addition of water (60 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 x 60 mL). The combined organic extracts were washed with water (2 x 60 mL), brine (60 mL) and dried ($MgSO_4$). Solvent was removed under reduced pressure and hexanes (20 mL) was added to the residue to precipitate the triphenylphosphine oxide. Diethyl ether was added and the mixture was then filtered. Solvent was removed under reduced pressure and the crude product was purified by flash chromatography (10-20% ethyl acetate/hexanes). The first fraction (326 mg) was followed by a second of (2*R*,3*E*,5*E*)-2-methyl-3,5-heptadien-1-ol and (2*R*,3*Z*,5*E*)-2-methyl-3,5-heptadien-1-ol (991 mg, 57%). The first fraction in THF-water (10:1, 11 mL) containing a few crystals of *p*-toluenesulfonic acid was stirred overnight. The mixture was poured onto water (10 mL) and triethylamine (5 drops) was added. The product was extracted with diethyl ether (3 x 10 mL). The combined organic layers was washed with water (2 x 10 mL), brine (10 mL) and dried ($MgSO_4$). Solvent was removed under reduced pressure and the crude product was submitted to flash chromatography (20% ethyl acetate/hexanes) to give a 4:1 mixture (2*R*,3*E*,5*E*)-2-methyl-3,5-heptadien-1-ol and (2*R*,3*Z*,5*E*)-2-methyl-3,5-heptadien-1-ol (110 mg, 63%). Major (3*E*,5*E*) isomer: ^{1}H NMR (400 MHz) δ 1.01 (3H, d, *J* = 6.8 Hz, 2-Me); 1.74 (3H, d, *J* = 6.3 Hz, 3H, H7); 2.34 (1H, dddq, *J* = 6.8 Hz, *J* = 6.8 Hz, *J* = 6.8 Hz, *J* = 6.8 Hz, H2); 3.37-3.43 (1H, m, H1); 3.5-3.5 (1H, m, H1); 5.4 (1H, dd, *J* = 6.4 Hz, *J* = 14.2 Hz, H3); 5.64 (1H, dq, *J* = 6.8 Hz, *J* = 14.2 Hz, H6); 5.99-6.13 (2H, m, H4 and H5); ^{13}C NMR (100 MHz) δ 16.41; 17.91; 39.6; 63.31; 128.28; 131.24; 131.39; 133.29; mass spectrum (EI): m/z 126 (M^+, 40%); minor (3*Z*,5*E*) isomer: ^{1}H NMR (400 MHz) δ 0.97 (3H, d, *J* = 6.8 Hz, 2-Me); 1.77 (3H, d, *J* = 6.8 Hz, H-7); 2.85 (1H, m); 5.04 (1H, dd, *J* = 10.3 Hz, *J* = 10.3 Hz); 5.71 (1H, dq, *J* = 6.8 Hz, *J* = 14.7 Hz); 6.34 (1H, dd, *J* = 12.7 Hz, *J* = 13.2 Hz); ^{13}C NMR (100 MHz) δ 16.96; 18.24; 35.16; 67.64; 126.84; 130.57; 130.68; 131.33.

A dichloromethane solution (20 mL) of the 4:1 mixture of dienols (991 mg, 7.87 mmol) under N_2 at 0 °C was treated successively with triethylamine (1.5 mL, 1.5 equiv.) and trimethylsilyl chloride (1.3 mL, 1.5 equiv.). The mixture was stirred for 1 h before the addition of hexanes (20 mL). The mixture was then filtered and the filtrate was concentrated under reduced pressure. Another portion of hexanes (10 mL) was added to the residue, and the resulting mixture was filtered again. The filtrate of hexanes was evaporated under reduced pressure and the crude product was purified by quickly passing through silica gel (2% ethyl acetate/hexanes) to yield a 4:1 mixture of (2*R*,3*E*,5*E*)- and (2*R*,3*Z*,5*E*)-2-methyl-3,5-heptadien-1-ol trimethylsilyl ether as a colourless liquid (742 mg, 48%) with a characteristic smell. Major (3*E*,5*E*) isomer: ^{1}H NMR (300 MHz) δ 0.10 (9H, s, TMS); 1.00 (3H, d, *J* = 6.8 Hz, Me); 1.73 (3H, d, *J* = 6.2 Hz, $CH\underline{H}_3$); 2.34 (1H, dddq, *J* = 6.8 Hz, *J* = 6.8 Hz, *J* = 6.8 Hz, *J* = 6.8 Hz, H2); 3.35 (1H, dd, *J* = 7.32 Hz, *J* = 9.8 Hz, H1); 3.48 (1H, dd, *J* = 6.2 Hz, *J* = 6.9 Hz, H1); 5.48 (1H, dd, *J* = 7.1 Hz, *J* = 14.2 Hz, H2); 5.56-5.70 (1H, m, H6); 5.93-6.07 (2H, m, H4 and H5); ^{13}C NMR (75 MHz) δ -0.47; 16.61; 18.00; 39.10; 67.64; 127.46; 129.93; 131.72; 134.06.

(2*S*,3*E*,5*E*)- and (2*S*,3*Z*,5*E*)-2-Methyl-3,5-heptadien-1-ol (32) and TMS Ether (33)

2(*R*)-3-Bromo-2-methylpropan-1-ol (962 mg, 6.29 mmol) and triphenylphosphine (2.146 g, 11.9 mmol, 1.3 equiv.) in toluene (10 mL) were heated at 80 °C for 8 days under nitrogen. The mixture was cooled to room temperature and filtered. The salt was washed with hexane and diethyl ether, and dried under vacuum to yield [(2*R*)-3-hydroxy-2-methylpropyl]triphenylphosphonium bromide (1.466 g, 56%) as a white powder; ^{1}H NMR (400 MHz) δ 0.51 (3H, d, *J* = 6.8 Hz, Me); 2.15-2.20 (1H, m, H2); 2.61 (1H, ddd, *J* = 5.4 Hz, *J* = 16.1 Hz, *J* = 16.1 Hz, H1); 3.64-3.68 (2H, m, 2 x H3); 4.90 (1H, dd, *J* = 15.13 Hz, *J* = 16.12 Hz, H1); 7.66-7.93 (15H, m, ArH).

The phosphonium bromide (2.00 g, 4.82 mmol) was deprotonated with lithium hexamethyldisilazide, and then treated with crotonaldehyde (345 mg, 4.93 mmol) according to the foregoing conditions to give a 4:1 mixture of (2*S*,3*E*,5*E*)-2-methyl-3,5-heptadienol and (2*S*,3*Z*,5*E*)-2-methyl-3,5-heptadienol (312 mg, 51%) as a colourless liquid. Major (3*E*,5*E*) isomer: ^{1}H NMR (400 MHz) δ 1.01 (3H, d, J = 6.8 Hz, 2-Me); 1.74 (3H, d, J = 6.34 Hz, H7); 2.34 (1H, dddq, J = 6.8 Hz, J = 6.8 Hz, J = 6.8 Hz, J = 6.8 Hz, H2); 3.37-3.43 (1H, m, H1); 3.46-3.52 (1H, m, H1); 5.40 (1H, dd, J = 6.4 Hz, J = 14.2 Hz, H3); 5.64 (1H, dq, J = 6.8 Hz, J = 14.2 Hz, H6); 5.99-6.13 (2H, m, H4 and H5); ^{13}C NMR (100 MHz) δ 16.41; 17.91; 39.6; 63.31; 128.28; 131.24; 131.39; 133.29; mass spectrum (EI): m/z 126 (M$^+$, 36%); minor isomer: ^{1}H NMR (400 MHz) δ 0.97 (3H, d, J = 6.84 Hz, 2-Me); 1.77 (3H, d, J = 6.84 Hz, H7); 2.85 (1H, m); 5.04 (1H, dd, J = 10.3 Hz, J = 10.3 Hz); 5.71 (1H, dq, J = 6.8 Hz, J = 14.7 Hz); 6.34 (1H, dd, J = 12.7 Hz, J = 13.2 Hz); ^{13}C NMR (100 MHz) δ 16.96; 18.24; 35.16; 67.64; 126.84; 130.57; 130.68; 131.33.

The TMS ether mixture **33** was prepared from the 4:1 mixture of (2*S*,3*E*,5*E*)- and (2*S*,3*Z*,5*E*)-2-methyl-3,5-heptadienol (777 mg, 6.17 mmol) and trimethylsilyl chloride (1.0 mL, 1.5 equiv.) as described above for the 2*R*-mixture. The crude product was purified by quickly passing it through silica gel (2% ethyl acetate/ hexanes) to yield the TMS ether mixture as a colourless liquid (928 mg, 76%) with characteristic smell. Data for the major (3*E*,5*E*) isomer: ^{1}H NMR (300 MHz) δ 0.10 (9H, s, TMS); 1.00 (3H, d, J = 6.8 Hz, 2-Me); 1.73 (3H, d, J = 6.2 Hz, H7); 2.34 (1H, dddq, J = 6.8 Hz, J = 6.8 Hz, J = 6.8 Hz, J = 6.8 Hz, H2); 3.35 (1H, dd, J = 7.3 Hz, J = 9.8 Hz, H1); 3.48 (1H, dd, J = 6.2 Hz, J = 6.9 Hz, H1); 5.48 (1H, dd, J = 7.1 Hz, J = 14.2 Hz, H2); 5.56-5.70 (1H, m, H6); 5.93-6.07 (2H, m, H4 and H5); ^{13}C NMR (75 MHz) δ -0.47; 16.61; 18.00; 39.10; 67.64; 127.46; 129.93; 131.72; 134.06.

6-Methylcyclohexenone (1)

This was prepared according to the literature procedure from 2-methylcyclohexanone by way of 2-bromo-6-methylcyclohexanone.[46] 6-Methyl-2-cyclohexenone was obtained as colourless liquid with b.p. 68-72 °C, 20 mm Hg (lit.[46] 66-68 °C, 18 mm Hg); ^{1}H NMR (400 MHz) δ 1.12 (3H, J = 6.4 Hz, methyl); 1.7-1.8 (1H, m); 2.0-2.1 (1H, m); 2.3-2.4 (3H, m); 5.96 (1H, dt, $J_{2,4}$ = 2.0 Hz, $J_{2,3}$ = 9.8 Hz, H2); 6.91 (1H, m, H3).

2-Cyclohexenone Ethylene Acetal (20)

2-Cyclohexenone (1.70 g, 17.71 mmol) was treated with 1,2-ethanediol bis-TMS ether (3.70 g, 17.96 mmol) in dichloromethane (1.5 mL) containing TMSOTf (1 mol%) at -78 °C according to the literature procedure.[33] The crude product was purified by flash chromatography (1% ethyl acetate/hexanes) to yield the cyclic acetal (1.27 g, 51%) as colourless oil; ^{1}H NMR (400 MHz) δ 1.70-1.90 (4H, m, 2 x H6, 2 x H5); 2.02-2.04 (2H, m, 2 x H4); 3.92-4.00 (4H, m, 2 x H4', 2 x H5'); 5.58 (1H, ddd, $J_{2,3}$ = 10.3 Hz, $J_{2,4}$= 2.0 Hz, $J_{2,4}$= 2.5 Hz, H2); 5.96 (1H, ddd, $J_{2,3}$=10.3 Hz, $J_{3,4}$=3.9 Hz, $J_{3,4}$= 2.4 Hz, H3); Mass spectrum (EI): m/z 292 (M$^+$, 1%); 186 (100%).

2-Cyclohexenone (1*R*,2*R*)-1,2-Diphenylethylene Acetal (27)

(1*R*,2*R*)-1,2-Diphenyl-1,2-ethandiol was prepared according to the literature procedure[36] and converted into the bis-TMS ether as follows. A stirred solution of the diol (102.7 mg, 0.479 mmol) in dichloromethane (5 mL) at room temperature under N_2 was treated successively with triethylamine (0.15 mL, 2.3 equiv.) and trimethylsilyl chloride (0.15 mL, 2.5 equiv.). After 3 h, hexanes (15 mL) and ethyl acetate (5 mL) were added and the resulting mixture was filtered. The filtrate was concentrated under reduced pressure. Hexanes (20 mL) and a small amount of ethyl acetate were added to the residual material, and the mixture filtered again. Solvent was removed from the filtrate under reduced pressure. The crude product was purified by flash chromatography (10% ethyl acetate/hexanes). The diol bis-TMS ether (138.4 mg, 80%) solidified under high vacuum; ^{1}H NMR (400 MHz) δ 0.01 (18H, s, TMS); 4.72 (2H, s, H1 and H2); 7.14-7.24 (10H, m, ArH); ^{13}C NMR (100 MHz) δ -0.03 $SiMe_3$; 79.80 OCH; 127.16; 127.35; 128.13; 141.81.

The bis-TMS ether (357.4 mg, 0.997 mmol) in dichloromethane (1 mL) was added to a dichloromethane solution (0.1 mL) containing 2-cyclohexenone (96 mg, 1.00 mmol) and TMSOTf (5 mol%) at -78 °C. The mixture was stirred at this temperature overnight. The reaction was quenched by addition of pyridine (30 μL). Solvent was removed under reduced pressure and the crude residue was submitted to flash chromatography (5% ethyl acetate/hexanes). The product (214.8 mg, 74%) solidified under high vacuum, to give needles, m.p. 73.5-73.8 °C (lit.[47] 77-79 °C), from hexane; ^{1}H NMR (400 MHz) δ 1.90-1.95 (2H, m, 2 x H5'); 2.10-2.15 (4H, m, 2 x H4' and 2 x H6'); 4.72 (1H, d, J = 8.8 Hz); 4.82 (1H, d, J = 8.3 Hz); 5.91 (1H, $J_{1,2}$ = 10.3 Hz, H2'); 6.08 (1H, ddd, $J_{1,2}$ = 10.25 Hz, $J_{2,3}$ = 3.4 Hz, $J_{2,3}$ = 3.9 Hz, H3'); 7.20-7.35 (10H, m, ArH); ^{13}C NMR (100 MHz) δ 20.71; 24.93; 35.01; 84.99; 85.38; 106.48; 126.63; 126.91; 128.35; 128.41; 133.05; 136.66; 136.84; mass spectrum (EI): m/z 292 (M^+, 1%); 264 (4%); 186 (100%); 157 (29%); 105 (20%); 79 (32%).

Diels-Alder Reactions

Aluminium Chloride Catalysed Reaction: 3,5-Hexadienol (2) and 6-Methyl-2-cyclohexenone (1).

6-Methyl-2-cyclohexenone (113 mg, 1.0 mmol) was added dropwise to a stirred suspension of $AlCl_3$ (137 mg, 1.0 mmol) in dichloromethane (1 mL) at 10 °C under nitrogen. After stirring at room temperature for 15 min the solution became yellow in colour. The mixture was cooled to -20 °C and 3,5-hexadien-1-ol (150 mg, 1.5 mmol) in dichloromethane (0.5 mL) was added dropwise. Stirring was continued at 0 °C for 2 h, during which time the solution became deep red in colour. The mixture was poured onto saturated ammonium chloride solution (11 mL) and extracted with diethyl ether (3 x 5 mL). The combined extracts were washed with water (2 x 10 mL) and saturated chloride solution (2 x 5 mL), and then dried ($MgSO_4$). Removal of solvent under reduced pressure left a brown oil which was submitted to flash chromatography (5% ethyl acetate/hexanes). The major product was a colourless oil which crystallised under high vacuum. The solid was washed with light petroleum to give (3a*RS*,6a*SR*,-9*RS*,9a*SR*,9b*RS*)-9a-hydroxy-9-methyl-2,3,3a,6,6a,7,8,9,9a,9b-decahydro-1-oxa-1*H*-phenalene **3** (20.2 mg, 10%) as colourless fine needles, m.p. 66.9-67.0 °C (lit[27] 73-74 °C); ^{1}H NMR (400 MHz) δ 0.91 (3H, d, J = 6.8 Hz, methyl); 1.0-1.1 (2H, m); 1.3-1.8 (7H, m); 1.82 (1H, s, OH); 2.1-2.1 (2H, m); 2.4-2.5 (1H, m); 3.70 (1H, ddd, $J_{2\alpha,3\beta}$ = 1.5 Hz, $J_{2\alpha,3\alpha}$ = 4.9 Hz, J_{gem} = 11.2 Hz, H2α); 4.05 (1H, ddd, $J_{2\beta,3\beta}$ = 2.9 Hz, J_{gem} = 11.2 Hz, $J_{2\beta,3\alpha}$ = 14.2 Hz, H2β); 5.5 (1H, ddd, $J_{3a,4}$ = 2.0 Hz, $J_{4,6}$ = 2.0 Hz, $J_{4,5}$ = 9.8 Hz, H4); 5.57 (1H, dddd, $J_{5,6\alpha}$ = 2.0 Hz, $J_{3a,5}$ = 2.4 Hz, $J_{5,6\beta}$ = 4.9 Hz, $J_{4,5}$ = 9.8 Hz, H5); ^{13}C NMR (100 MHz) δ 12.77, 30.71, 31.26, 32.09, 33.07, 33.29, 33.48, 50.63, 61.38, 96.66, 125.76, 130.69.

Brønsted Acid Catalysed Reaction: 3,5-Hexadienol (2) and 2-Cyclohexenone.

To acetonitrile (0.1 mL) containing triflic acid (20 mol%) under nitrogen at -20 °C was added 2-cyclohexenone (98.4 mg, 1.03 mmol) in acetonitrile (2 mL). The mixture was stirred for 2 min before the addition of (3*E*)-3,5-hexadien-1-ol (131.8 mg, 1.34 mmol, 1.3 equiv.) in acetonitrile (2 mL). Stirring was continued at -20 °C for 90 h. Triethylamine (0.1 mL) was added, and then the mixture was poured onto water (5 mL), and extracted with diethyl ether (3 x 5 mL). The combined organic extracts were washed with water (2 x 5 mL) and dried ($MgSO_4$). Solvent was removed under reduced pressure and the residue was submitted to flash chromatography (5% ethyl acetate/hexanes) to yield (3a*RS*,6aSR,9a*SR*,9b*RS*)-9a-hydroxy-2,3,3a,6,6a,7,8,9,9a,9b-decahydro-1-oxa-1*H*-phenalene **10** (44.2 mg, 22%) as white cubes, m.p. 115.8-116.0 °C; ^{1}H NMR (400 MHz) δ 0.97 (1H, m); 1.11 (1H, dd, $J_{3a,9b}$ = 10.3 Hz, $J_{6a,9b}$ = 10.7 Hz, H9b); 1.44 (1H, dddd, J = 4.9 Hz, J = 12.7 Hz, J = 12.7 Hz, J = 12.7 Hz); 1.56-1.73 (7H, m); 1.77-1.82 (1H, m,); 2.15-2.20 (1H, m); 2.40-2.46 (1H, m, H3a); 3.71 (1H, ddd, $J_{2\alpha,3\beta}$ = 1.5 Hz, $J_{2\alpha,3\alpha}$ = 4.9 Hz, J_{gem} = 11.2 Hz, H2α); 4.11 (1H, ddd, $J_{2\beta,3\beta}$ = 2.9 Hz, $J_{2\beta,3\alpha}$ = 14.2 Hz, J_{gem}= 11.2 Hz, H2β); 5.46 (1H, dd, $J_{3a,4}$= 2.0 Hz, $J_{4,5}$= 9.8 Hz, H4); 5.57 (1H, dddd, $J_{5,6\beta}$= 2.0 Hz, $J_{3a,5}$= 2.4 Hz, $J_{5,6\beta}$= 4.9 Hz, $J_{4,5}$= 9.8 Hz, H5); ^{13}C NMR (100 MHz) δ 21.12; 31.15; 31.94; 33.09; 33.15; 33.62; 38.89; 50.03; 61.44; 95.89; 125.83; 130.60; ν_{max} (CCl_4) 3380 br s; 3017,s; 2935 s; 2882 s; 1650 w; 1464 w; 1440 m; 1398 w; 1342 m; 1231 m; 1191 s; 1144 m; 1067 s cm^{-1}; mass spectrum (EI): m/z 194 (M^+, 3%); 176 (100%); Anal. calcd for $C_{12}H_{18}O_2$ C 74.18, H 9.34; found C 74.13, H 9.25.

A less polar, minor product (3a*RS*,6a*SR*,9a*RS*,9b*RS*)-9a-[(3*E*)-3',5'-hexadienoxy]-2,3,3a,6,6a,7,8,9,9a,-9b-decahydro-1-oxa-1*H*-phenalene **11** (9.2 mg, 3%) was also obtained as colourless liquid. Its characterization is described below.

Trimethylsilyl Triflate Catalysed Reaction: i. 3,5-Hexadienol TMS Ether (12) and 6-Methyl-2-cyclohexen-1-one (1).

6-Methyl-2-cyclohexenone (102.3 mg, 0.930 mmol) was added slowly to acetonitrile (0.3 mL) containing TMSOTf (5 mol%) at -20 °C under nitrogen,. The mixture was stirred for 2 min before the addition of 3,5-hexadien-1-ol trimethylsilyl ether (263.8 mg, 1.552 mmol). The mixture gradually turned red. Stirring was continued at -20 °C for 16 h before dry pyridine was added to quench the reaction. Solvent was removed under reduced pressure to leave a residue which was submitted to flash chromatography (1% ethyl acetate/ hexanes) to give (3a*RS*,6a*SR*,9*SR*,9a*RS*,9b*RS*)-9a-[(3*E*)-3',5'-hexadienoxy]-9-methyl-2,3,3a,6,6a,7,8,9,9a,9b-decahydro-1-oxa-1*H*-phenalene **13** (133.9 mg, 60%) as a colourless liquid; ^{1}H NMR (400 MHz) δ 1.00 (3H, d, J = 7.3 Hz, methyl); 1.13-1.39 (4H, m); 1.48-1.78 (5H, m); 2.08-2.19 (2H, m); 2.36 (2H, dt, $J_{1',2'}$ = 6.8 Hz, $J_{2',3'}$ = 6.8 Hz, 2 x H2'); 2.49-2.55 (1H, m, H3a); 3.36-3.46 (2H, m, H1'); 3.64 (1H, ddd, $J_{2\alpha,3\beta}$ = 1.5 Hz, $J_{2\alpha,3\alpha}$ = 4.9 Hz, J_{gem} = 10.7 Hz, H2α); 372 (1H, ddd, $J_{2\beta,3\beta}$ = 2.9 Hz, $J_{2\beta,3}$ = 12.7 Hz, J_{gem} = 10.7 Hz, H2β); 4.98 (1H, d, $J_{5',6'}$ = 9.8 Hz, H6'); 5.11 (1H, d, $J_{5',6'}$ = 17.1 Hz, H6'); 5.46 (1H, dd, $J_{3a,4}$ = 2.0 Hz, $J_{4,5}$ = 10.3 Hz, H4); 5.56 (1H, dddd, $J_{5,6\alpha}$ = 2.0 Hz, $J_{3a,5}$ = 2.4 Hz, $J_{5,6\beta}$ = 4.9 Hz, $J_{4,5}$ = 9.8 Hz, H5); 5.79 (1H, dt, $J_{2',3'}$ = 7.3 Hz, $J_{3',4'}$ = 14.7 Hz, H3'); 6.13 (1H, dd, $J_{3',4'}$ = 15.1 Hz, $J_{4',5'}$ = 10.3 Hz, H4'); 6.3 (1H, ddd, $J_{4',5'}$ = 10.26 Hz, $J_{5',6'}$ = 10.3 Hz, $J_{5',6'}$ = 16.6 Hz, H5'); ^{13}C NMR (75 MHz) δ 13.60, Me; 27.34, CH_2; 27.68, CH_2; 30.73, CH; 31.83, CH; 31.91, CH; 32.84, CH_2, 33.29, CH_2; 33.43, CH_2; 44.48, CH; 57.53, CH_2; 61.58, CH_2; 99.94, C9a; 115.17, C6'; 125.65, C5, 131.32, C5; 131.97, C3'; 132.51, C4'; 137.12, C5'; ν_{max} (film) 3087 w; 3014 s; 2926 vs; 2869 s; 1696 w; 1650 m; 1604 m; 1456 s; 1438 s; 1379 m; 1267 s; 1237 m; 1149 s; 1084 s; 1043 s cm^{-1}; mass spectrum (EI): m/z 288 (M, 2%); 191 (100%).

The acetal adduct (933 mg, 3.24 mmol) in THF-water (3:1, 20 mL) containing *p*-toluenesulfonic acid (64.4 mg, 10 mol%) was stirred overnight at room temperature. The mixture was poured onto water (30 mL) and triethylamine (10 drops) and then extracted with diethyl ether (3 x 30 mL). The combined organic layer was washed with water (2 x 30 mL), brine (50 mL) and dried ($MgSO_4$). After evaporation of the solvent, the residue was submitted to flash chromatography (5% ethyl acetate/hexanes) to provide (3a*RS*,6a*SR*,-9*SR*,9a*SR*,9b*RS*)-9a-hydroxy-9-methyl-2,3,3a,6,6a,7,8,-9,9a,9b-decahydro-1-oxa-1*H*-phenalene **15** (574 mg, 85%) as colourless needles, m.p. 109.2-109.6 °C; ^{1}H NMR (400 MHz) δ 1.05 (3H, d, J = 7.3 Hz, methyl); 1.21 (1H, dddd, $J_{7\alpha,8\alpha}$ = 3.9 Hz, $J_{6a,7\alpha}$ = 13.7 Hz, $J_{7\alpha,8\beta}$ = 13.7 Hz, J_{gem} = 13.7 Hz, H7α); 1.27 (1H, dd, $J_{3a,9b}$ = 10.7 Hz, $J_{6a,9b}$ = 10.7 Hz., H9b); 1.33-1.45 (2H, m, H3α and H8α); 1.52-1.59 (2H, m, H7β and OH); 1.60-1.78 (4H, m, H3β, H6a, H6β and H9); 1.98 (1H, dddd, $J_{7\beta,8\beta}$ = 4.4 Hz, $J_{8\beta,9\beta}$ = 4.4 Hz, $J_{7\alpha,8\beta}$ = 13.7 Hz, J_{gem} = 13.7 Hz, H8β); 2.15-2.19 (1H, m, H6α); 2.43-2.49 (1H, m, H3a); 3.70 (1H, ddd, $J_{2\alpha,3\beta}$ = 1.0 Hz, $J_{2\alpha,3\alpha}$ = 4.9 Hz, J_{gem} = 11.2 Hz, H2α); 4.08 (1H, ddd, $J_{2\beta,3\beta}$ = 2.9 Hz, $J_{2\beta,3\alpha}$ = 9.8 Hz, J_{gem} = 12.7 Hz, H2α); 5.48 (1H, ddd, J = 2.0 Hz, J = 2.0 Hz, J = 9.8 Hz, H4); 5.57 (1H, dddd, J = 2.0 Hz, J = 2.4 Hz, J = 4.9 Hz, J = 9.8 Hz, H5); ^{13}C NMR (300 MHz) δ 13.85, Me; 27.66, C8; 28.56, C7; 31.23, C3a; 32.30, C6a; 32.96, C3; 33.29, C6; 40.56, C9; 44.10, C9b; 61.35, C2; 97.74, C9a; 125.83, C5; 131.0, C4; ν_{max} (CCl_4) 3433 br s, 3000 m, 2934 s, 2862 m, 1646 w, 1436 w, 1415 m, 1148 s, 1077 s, 980 s cm^{-1}; mass spectrum (EI): m/z 208 (M^+, 8%); 190, (41%); 151 (100%). Anal.: calculated for $C_{13}H_{20}O_2$ C 74.95, H 9.68; found C 74.92, H 9.94.

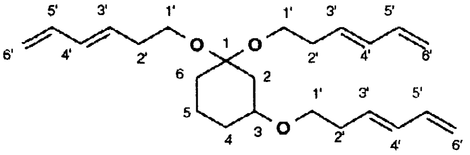
ii. 3,5-Hexadien-1-ol TMS Ether (12) and 2-Cyclohexen-1-one

2-Cyclohexenone (132.9 mg, 1.38 mmol) in acetonitrile (0.2 mL) was treated with (3*E*)-3,5-hexadien-1-ol trimethylsilyl ether (410.2 mg, 2.41 mmol) in the presence of 5 mol% catalyst for 5 h according to the above conditions to give (3a*RS*,6a*SR*,9a*RS*,9b*RS*)-9a-[(3*E*)-3',5'-hexadienoxy]-2,3,3a,6,6a,7,8,9,9a,9b-decahydro-1-oxa-1*H*-phenalene **11** (194.7 mg, 59% yield) as a colourless oil; ^{1}H NMR (400 MHz) δ 0.95 (1H, dddd, J = 4.4 Hz, J = 10.7 Hz, J = 13.2 Hz, H7); 1.08 (1H, dd, $J_{3a,9b}$ = 10.7 Hz, $J_{6a,9b}$ = 10.8 Hz, H9b); 1.26 (1H, ddd, $J_{8\alpha,9\alpha}$ = 3.9 Hz, $J_{8\alpha,9\beta}$ = 13.7 Hz, J_{gem} = 13.7 Hz, H9α); 1.35-1.78 (7H, m); 1.98-2.02 (1H, m, H9β); 2.14 (1H, dddd, $J_{4,6\alpha}$

= 2.0 Hz, $J_{5,6\alpha}$ = 2.0 Hz, $J_{6\alpha,6a}$ = 7.3 Hz, J_{gem} = 9.8 Hz, H6α); 2.36 (2H, dt, $J_{1',2'}$ = 6.8 Hz, $J_{2',3'}$ = 6.8 Hz, 2 x H2'); 2.49-2.54 (1H, m, H3a); 3.36 (1H, dt, $J_{1',2'}$ = 6.8 Hz, J_{gem} = 8.8 Hz, H1'); 3.46 (1H, dt, $J_{1',2'}$ = 6.8 Hz, J_{gem} = 8.8 Hz, H1'); 3.6 (1H, ddd, $J_{2\alpha,3\beta}$ = 1.5 Hz, $J_{2\alpha,3\alpha}$ = 4.9 Hz, J_{gem} = 10.7 Hz, H2α); 3.77 (1H, ddd, $J_{2\beta,3\beta}$ = 2.9 Hz, J_{gem} = 11.2 Hz, $J_{2\beta,3\alpha}$ = 12.7 Hz, H2β); 4.98 (1H, d, $J_{5',6'}$ = 10.3 Hz, H6'); 5.11 (1H, d, $J_{5',6'}$ = 17.1 Hz, H6'); 5.45 (1H, dd, $J_{3a,4}$ = 1.5 Hz, $J_{4,5}$ = 9.8 Hz, H4); 5.55 (1H, dddd, $J_{5,6\alpha}$ = 2.0 Hz, $J_{3a,5}$ = 2.4 Hz, $J_{5,6\beta}$ = 4.9 Hz, $J_{4,5}$ = 9.76 Hz, H5); 5.79 (1H, dt, $J_{2',3'}$ = 7.3 Hz, $J_{3',4'}$ = 14.6 Hz, H3'); 6.13 (1H, dd, $J_{3',4'}$ = 10.3 Hz, $J_{4',5'}$ = 15.1 Hz, H4'); 6.33 (1H, ddd, $J_{4',5'}$ = 10.3 Hz, $J_{5',6'}$ = 10.3 Hz, $J_{5',6'}$ = 17.1 Hz, H5'); ^{13}C NMR (100 MHz) δ 21.53, CH_2; 30.57, C3a; 31.63, C6a; 32.19 CH_2; 33.02, CH_2; 33.18, CH_2,; 33.22, CH_2; 33.68, CH_2; 51.18, C9b; 58.22, C1'; 61.53, C2; 97.89, C9a; 115.22, C6'; 125.63, C5; 130.90, C4; 131.90, C3'; 132.56, C4'; 137.11, C5'; ν_{max} (film) 3016 m, 2926 s, 2876 m, 1650 w, 1603 w, 1460 m, 1440 m, 1269 m, 1145 m, 1087 s, 1042 s, 1006 s, 901 vs cm^{-1}; mass spectrum: m/z 274 (M, 2%); 231 (2%); 193 (2%); 177 (100%); found M$^+$ 274.1917. $C_{18}H_{26}O_2$ requires M$^+$ 274.1933.

The acetal (458 mg, 1.67 mmol) in THF-water (10:3, 13 mL) containing *p*-toluenesulfonic acid (30.1 mg) was stirred overnight at room temperature. The mixture was then poured onto water (20 mL) and triethylamine (5 drops), and then extracted with diethyl ether (3 x 15 mL). The combined organic layer was washed with water (2 x 15 mL), brine (20 mL) and dried ($MgSO_4$). After evaporation of the solvent under reduced pressure, the residue was submitted to flash chromatography (5% ethyl acetate/hexanes) to provide (3a*RS*,6aSR,9a*SR*,9b*RS*)-9a-hydroxy-2,3,3a,6,6a,7,8,9,9a,9b-decahydro-1-oxa-1*H*-phenalene **10** (269 mg, 83%) as white solid.

The conjugate addition product **i** was also isolated from DA reactions conducted in acetonitrile or toluene. ^{1}H NMR (300 MHz) δ 1.14-1.32 (4H, m, 2 x H4 and 2 x H5); 1.60-1.64 (1H, m, 1 x H6); 1.97- 2.06 (2H, m, 1 x H2, 1 x H6); 2.30-2.39 (7H, m, 6 x H2', 1 x H2); 3.35-3.54 (7H, m, 6 x H1', H3); 5.00 (3H, d, $J_{6',5'}$ = 10.1 Hz, 3 x H6'); 5.12 (3H, d, $J_{6',5'}$ = 17.0 Hz, 3 x H6'); 5.66-5.75 (3H, m, 3 x H3'); 6.11-6.26 (3H, m, 3 x H4'); 6.25-6.35 (3H, m, 3 x H5'); mass spectrum (EI): m/z 372 (M, 2%); 275 (51%); 177 (39%); 161 (83%); 133 (48%); 119 (36%); 97 (100%); this compound was too unstable for elemental analysis. The compound (190.1 mg, 0.511 mmol) in acetonitrile (1 mL) containing TMSOTf (10 mol%) was stirred for 36 h. The solvent was then removed under reduced pressure and the crude mixture was submitted to flash chromatography (1% ethyl acetate/hexanes) to yield the acetal **11** (56.6 mg, 40%).



i

iii. 3,5-Hexadien-1-ol *tert*-Butyldimethylsilyl Ether and 2-Cyclohexen-1-one

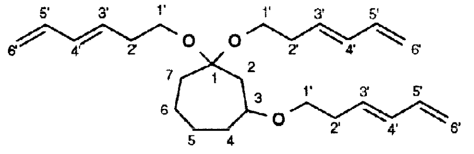
Cyclohexenone (162.1 mg, 1.69 mmol) in acetonitrile (0.2 mL) containing TMSOTf (5 mol%) at -20 °C under nitrogen was treated with (3*E*)-3,5-hexadien-1-ol *tert*-butyldimethylsilyl ether (585.3 mg, 2.76 mmol). The

mixture was stirred at -20 °C for **18 h. Dry pyridine** was added to quench the reaction. Solvent was **removed** under reduced pressure and the residue was submitted to flash chromatography (1% ethyl acetate/hexanes) to give the acetal adduct **11** (242.8 mg, 64%) as a colourless liquid.

iv. 3,5-Hexadien-1-ol TMS Ether (12) and Cyclohept-2-enone.

2-Cycloheptenone (246.7 mg, 1.79 mmol) in acetonitrile (0.3 mL) was treated with the dienol TMS ether (562.3 mg, 3.31 mmol) in the presence of 5 mol% TMSOTf for 10 h to give 3,5-hexadien-1-ol (54.1 mg, 17%), and the DA acetal adduct (217.4 mg, 55%) as an oil; ^{1}H NMR (400 MHz) δ 1.14 (1H, dd, *J* = 10.3 Hz, *J* = 10.3 Hz, H10b); 1.25-1.43 (3H, m); 1.53-1.70 (7H, m); 1.80-1.88 (1H, m); 1.98-2.09 (2H, m); 2.36 (2H, dt, *J* = 6.8 Hz, *J* = 6.8 Hz, H2'); 2.44-2.49 (1H, m, H3a); 3.46 (1H, dt, *J* = 6.8 Hz, *J* = 9.3 Hz, H1'); 3.55 (1H, dt, *J* = 6.8 Hz, *J* = 8.8 Hz, H1'); 3.62-3.70 (2H, m, 2 x H2); 4.98 (1H, d, *J* = 9.8 Hz, H6'); 5.11 (1H, dd, *J* = 0.98 Hz, *J* = 16.6 Hz, H6'); 5.39 (1H, ddd, *J* = 2.0 Hz, *J* = 2.0 Hz, *J* = 9.8 Hz, H4); 5.58 (1H, dddd, *J* = 2.0 Hz, *J* = 2.4 Hz, *J* = 4.9 Hz, *J* = 9.8 Hz, H5); 5.78 (1H, dt, *J* = 7.3 Hz, *J* = 14.7 Hz, H3'); 6.13 (1H, dd, *J* = 10.3 Hz, *J* = 15.1 Hz, H4'); 6.3 (1H, ddd, *J* = 10.3 Hz, *J* = 10.3 Hz, *J* = 17.1 Hz, H5'). ^{13}C NMR (100 MHz) δ 22.94; 24.20; 32.69; 33.24; 33.40; 35.29; 35.74; 36.99; 53.94; 59.63; 61.33; 101.10; 115.20; 126.10; 131.77; 131.88; 132.50; 137.13 (two signals overlapped); ν_{max} (film) 3085 w; 3013 s; 2918 vs; 2848 s; 1694 w; 1649 m; 1603 w; 1458 s; 1442 s; 1381 m; 1334 s; 1268 s; 1202 m; 1146 s; 1089 s; 1043 s cm^{-1}; mass spectrum (EI): m/z 288 (M$^+$, 4%); 207 (4%); 191 (100%); found M$^+$ 288.2072. $C_{19}H_{28}O_2$ requires M$^+$ 288.2089.

A more polar product, identified on the basis of NMR spectra as the conjugate addition product **ii** (27.5 mg, 4%) was also obtained. ^{1}H NMR (300 MHz) δ 1.25-2.04 (9H, m, 2 x H4 and 2 x H5); 2.26-2.34 (7H, m, 6 x H2'and 1 x H2); 3.38-3.48 (7H, m, 6 x H1' and H3); 4.98 (3H, d, $J_{5',6'}$ = 10.1 Hz, 3 x H6'); 5.10 (3H, d, $J_{5',6'}$ = 16.8 Hz, 3 x H6'); 5.68-5.73 (3H, m, 3 x H3'); 6.11 (3H, dd, *J* = 10.6 Hz, *J* = 15.0 Hz 3 x H4'); 6.27-6.33 (3H, m, 3 x H5'). The compound was too unstable to obtain elemental analysis or high resolution mass spectrum.



ii

v. 3,5-Hexadien-1-ol TMS Ether 12 and Methyl Vinyl Ketone

Methyl vinyl ketone (73.5 mg, 1.05 mmol) in acetonitrile (0.2 mL) was treated with the dienyl silyl ether (252.1 mg, 1.48 mmol) and 10 mol% TMSOTf during 9 h according to the above method to give the acetal adduct (47.9 mg, 26%) as a colourless, unstable liquid; ^{1}H NMR (400 MHz) δ 1.24-1.57 (7H, m); 1.70-1.76 (1H, m); 2.09-2.13 (2H, m); 2.33 (2H, dt, *J* = 6.8 Hz, *J* = 6.8 Hz, H2'); 2.37 (1H, m, H3a); 3.42 (1H, dt, *J* = 6.8 Hz, *J* = 8.8 Hz, H1'); 3.51 (1H, dt, *J* = 6.8 Hz, *J* = 8.8 Hz, H1'); 3.61 (1H, ddd, *J* = 1.5 Hz, *J* = 4.9 Hz, *J* = 11.2, Hz, H2β); 3.70 (1H, ddd, *J* = 4.9 Hz, *J* = 11.2 Hz, *J* = 13.7 Hz, H2α); 4.98 (1H, d, *J* = 10.3 Hz, H6'); 5.11 (1H, d, *J* = 17.1 Hz, H6'); 5.44 (1H, ddd, *J* = 2.0 Hz, *J* = 2.0 Hz, *J* = 9.8 Hz, H4); 5.61 (1H, dddd, *J* = 2.9 Hz, *J* = 3.4 Hz, *J* = 6.4 Hz, *J* = 9.8 Hz, H5); 5.73 (1H, dt, *J* = 7.3 Hz, *J* = 15.1 Hz, H3'); 6.11 (1H, dd, *J* = 10.3 Hz, *J* =

15.1 Hz, H4'); 6.32 (1H, ddd, J = 10.3 Hz, J = 10.3 Hz, J = 17.1 Hz, H5'); ^{13}C NMR (100 MHz) δ 21.99; 23.16; 26.27; 32.62; 32.94; 33.26; 48.51; 59.41; 61.27; 99.49; 115.19; 126.41; 131.57; 131.88; 132.52; 137.15; ν_{max} 3017 m, 2935 s, 2879 s, 1651 w, 1604 w, 1436 m, 1381 m, 1266 s, 1157 s, 1058 s 1007 s cm^{-1}; mass spectrum (EI): m/z 248 (M$^+$, 1%); 151 (100%); found M$^+$ 248.1762. $C_{16}H_{24}O_2$ requires M$^+$ 248.1776.

vi. 3,5-Hexadien-1-ol TMS Ether (12) and 2-Cyclohexen-1-one Ethylene Acetal (20)

Cyclohexenone ethylene acetal (129.2 mg, 0.923 mmol) in acetonitrile (0.3 mL) was treated with (3*E*)-3,5-hexadien-1-ol trimethylsilyl ether (313.5 mg, 0.923 mmol) and the catalyst (10 mol%) for 2.5 h according to the above conditions to give the acetal **11** (87.3 mg, 32%) as the only detectable product.

vii. 3,5-Hexadien-1-ol TMS Ether (12) and 2-Cyclohexenone (1*R*,2*R*)-1,2-Diphenylethylene Acetal (27)

The acetal (107.9 mg, 0.37 mmol) in acetonitrile (0.5 mL) was treated with (3*E*)-3,5-hexadien-1-ol trimethylsilyl ether (128.9 mg, 0.76 mmol) and the catalyst (10 mol%) overnight at -20 °C according to the above conditions to give the acetal **11** as the only detectable product. Analysis by gas chromatography with a Chiraldex β-TA column (oven temp: 90 °C, injector temp: 200 °C, detector temp: 220 °C, retention time for the two enantiomers: 48.9 and 50.45 min) indicated no detectable enantiomeric excess of one enantiomer.

viii. (2*E*,4*E*)-2,4-Hexadien-1-ol Trimethylsilyl Ether 36 and 2-Cyclohexen-1-one

(2*E*,4*E*)-2,4-Hexadien-1-ol TMS ether (596.0 mg, 3.51 mmol), prepared from commercially available dienol, was added to acetonitrile containing 2-cyclohexenone and TMSOTf (5 mol%) at -20 °C under nitrogen. After 3 h, the only product, identified as 5-(2',4'-hexadienoxy)-1,3-hexadiene (92.4 mg, 30% yield) was isolated as colourless oil by flash column chromatography (1% ethyl acetate/hexanes); ^{1}H NMR (400 MHz) δ 1.26 (3H, d, $J_{5,6}$ = 6.4 Hz, H6); 1.75 (3H, d, $J_{5',6'}$ = 6.8 Hz, H6'); 3.83-4.04 (3H, m, H5 and 2 x H1'); 5.10 (1H, dd, J_{gem} = 11.7 Hz, $J_{1,2}$ = 10.3 Hz, H1); 5.21 (1H, dd, J_{gem} = 11.7 Hz, $J_{1,2}$ = 16.6 Hz, H1); 5.57-5.73 (3H, m, H4, H2' and H5'); 6.02-6.21 (3H, m, H3, H3' and H4'); 6.34 (1H, ddd, $J_{1,2}$ = 10.3 Hz, $J_{2,3}$ = 10.3 Hz,, $J_{1,2}$ = 16.6 Hz, H2).

ix. (2*R*,3*E*,5*E*)- and (2*R*,3*Z*,5*E*)-2-Methyl-3,5-heptadien-1-ol TMS Ether (29) with 6-Methyl-2-cyclohexen-1-one (1)

6-Methyl-2-cyclohexenone (76.3 mg, 0.694 mmol) in acetonitrile (0.1 mL) containing TMSOTf (10 mol%) at -20 °C under nitrogen was treated with the 4:1 3*E*:3*Z* mixture of the TMS ether **29** (257.1 mg, 1.298 mmol). After 20 h at -20 °C, the mixture was quenched by addition of dry pyridine, and then poured onto saturated $NaHCO_3$ solution. The mixture was extracted with diethyl ether (3 x 5 mL), and the combined extracts were dried ($MgSO_4$), and then evaporated under reduced pressure. The residue was submitted to flash chromatography (1% ethyl acetate/hexanes) to give (3*R*,3a*R*,6*R*,6a*R*,9*R*,9a*R*,9b*S*)-9a-[(*R*)-(5*E*)-2'-methyl-3',5'-heptadienoxy]-3,6,9-trimethyl-2,3,3a,6,6a,7,8,9,9a,9b-decahydro-1-oxa-1*H*-phenalene **30** (106.5 mg, 24%) as a mixture of diastereomers isomeric in the dienyl side chain, as a colourless liquid. The ^{1}H NMR spectrum was complicated by the presence of the two isomers. ^{13}C NMR (100 MHz) (major isomer) δ 13.36; 13.89; 16.76; 17.45; 18.02; 22.19; 27.29; 31.68; 32.82; 34.86; 35.93; 36.99; 37.66; 38.36; 62.74; 67.66; 100.03; 126.23; 127.48; 129.52; 131.77; 133.35; 134.79; mass spectrum (EI): m/z 344 (M$^+$, 5%); 219 (100%).

For characterization, the product mixture was hydrolysed to the hemiacetal **31**. The acetal mixture (98.1 mg, 0.285 mmol) in THF-water (4:1, 5 mL) containing *p*-toluenesulfonic acid (a few crystals) was stirred overnight at room temperature. The mixture was then poured onto water (5 mL) containing triethylamine (3 drops), and then extracted with diethyl ether (3 x 5 mL). The combined extracts were washed with water (10 mL), brine (5 mL) and dried (MgSO$_4$). After evaporation of the solvent, the crude mixture was submitted to flash chromatography (5% ethyl acetate/hexanes) to provide (3*R*,3a*R*,6*R*,6a*R*,9*R*,9a*R*,9b*S*)-9a-hydroxy-3,6,9-trimethyl-2,3,3a,6,6a,7,8,-9,9a,9b-decahydro-1-oxa-1*H*-phenalene **31** (32.8 mg, 49%) as colourless needles, m.p. 76.1 °C, $[\alpha]_D^{21}$ -100° (c 0.60, CHCl$_3$); ^{1}H NMR (400 MHz) δ 0.86 (3H, d, J = 6.8 Hz, Me); 0.88 (3H, d, J = 7.3 Hz, Me); 1.04 (3H, d, J = 6.8 Hz, Me); 1.25-1.32 (1H, m, H7); 1.40 (1H, dd, J = 10.8 Hz, J = 10.8 Hz,, H9b); 1.43-1.53 (3H, m, H3, H7 and H8); 1.55 (s, OH); 1.73-1.78 (2H, m, H6a and H9); 1.98 (1H, dddd, J = 4.4 Hz, J = 4.4 Hz, J = 13.2 Hz, J = 13.2 Hz, H8); 2.08-2.14 (1H, ddd, J = 2.0 Hz, J = 10.7 Hz, J = 10.7 Hz, H3a); 2.16-2.20 (1H, m, H6); 3.56 (1H, dd, J = 4.9 Hz, J = 11.2 Hz, H2); 3.65 (1H, dd, J = 11.2 Hz, J = 11.2 Hz, H2); 5.61 (1H, ddd, J = 2.9 Hz, J = 4.4 Hz, J = 10.3 Hz, H5); 5.70 (1H, dd, J = 1.5 Hz, J = 9.8 Hz, H4); ^{13}C NMR (100 MHz) δ 13.25, Me; 13.45, Me; 16.36, Me; 22.19, C7; 28.06, C8; 32.34, C6; 34.86, C6a; 35.91, C3; 37.52, C9b; 37.83, C3a; 40.30, C9; 67.22, C2; 97.72, C9a; 125.46, C4; 133.13, C5; ν_{max} (CCl$_4$) 3441 s; 3017 s; 2940 vs; 2866 s; 1652 w; 1463 m; 1404 m; 1381 w; 1224 w; 1167 s; 1125 s; 1079 m; 1037 s cm^{-1}; mass spectrum (EI): m/z 236 (M$^+$, 4%); 218 (98%); 179 (100%); found M$^+$ 236.1771. $C_{15}H_{24}O_2$ requires M$^+$ 236.1776; calcd. for $C_{15}H_{24}O_2$ C 76.23, H 10.23; found C 76.35, H 10.18.

x. (2*S*,3*E*,5*E*)- and (2*S*,3*Z*,5*E*)- 2-Methyl-3,5-heptadien-1-ol TMS Ether (33) with 6-Methyl-2-cyclohexen-1-one (1).

6-Methyl-2-cyclohexenone (287 mg, 2.61 mmol) in acetonitrile (1.5 mL) containing TMSOTf (5 mol%) at -20 °C under nitrogen was treated with the 4:1 mixture of the 3*E*:3*Z* mixture of the TMS ether (906 mg, 4.58 mmol). The mixture was stirred at -20 °C for 65 h and then quenched with dry pyridine. After removal of solvent, the residue was purified by flash chromatography (1% ethyl acetate/hexanes) to give (3*S*,3a*S*,6*S*,6a*S*,9*S*,9a*S*,9b*R*)-9a-[(5*E*)-3',5'-heptadienoxy]-3,6,9-trimethyl-2,3,3a,6,-6a,7,8,9,9a,9b-decahydro-1-oxa-1*H*-phenalene (177 mg, 22%) **34** as diastereomers isomeric in the acetal dienyl side chain as a colourless liquid. ^{13}C NMR (100 MHz) (major isomer) δ 13.36; 13.89; 16.76; 17.45; 18.02; 22.19; 27.29; 31.68; 32.82; 34.86; 35.93; 36.99; 37.66; 38.36; 62.74; 67.66; 100.03; 126.23; 127.48; 129.52; 131.77; 133.35; 134.79.

The acetal (80.5 mg, 0.234 mmol) in THF-water (5:1, 6 mL) containing *p*-toluenesulfonic acid (a few crystals) was stirred overnight at room temperature. It was then poured onto water (5 mL) containing triethylamine (3 drops), and the mixture was extracted with diethyl ether (3 x 5 mL). The combined extracts were washed with water (10 mL) and brine (5 mL), and then dried (MgSO$_4$). After evaporation of the solvent, the residue was submitted to flash chromatography (5% ethyl acetate/hexanes) to provide (3*S*,3a*S*,6*S*,6a*S*,9*S*,9a*S*,9b*R*)-9a-hydroxy-3,6,9-trimethyl-2,3,3a,-6,6a,7,8,-9,9a,9b-decahydro-1-oxa-1*H*-phenalene **35** (39.7 mg, 72%) as colourless needles, m.p. 76.1 °C, $[\alpha]_D^{21}$ +102° (c 0.61, $CHCl_3$); ^1H NMR (400 MHz) δ 0.86 (3H, d, *J* = 6.3 Hz, Me); 0.88 (3H, d, *J* = 6.8 Hz, Me); 1.04 (3H, d, *J* = 7.3 Hz, Me); 1.25-1.32 (1H, m, H7); 1.40 (1H, dd, *J* = 10.8 Hz, *J* = 10.8 Hz,, H9b); 1.43-1.51 (3H, m, H3, H7 and H8); 1.55 (s, OH); 1.73-1.78 (2H, m, H6a and H9); 1.99 (1H, dddd, *J* = 4.4 Hz, *J* = 4.4 Hz, *J* = 13.2 Hz, *J* = 13.2 Hz, H8); 2.11 (1H, ddd, *J* = 2.0 Hz, *J* = 10.7 Hz, *J* = 10.7 Hz, H3a); 2.16-2.19 (1H, m, H6); 3.56 (1H, dd, *J* = 4.9 Hz, *J* = 11.2 Hz, H2); 3.7 (1H, dd, *J* = 11.2 Hz, *J* = 11.2 Hz, H2); 5.61 (1H, ddd, *J* = 2.9 Hz, *J* = 4.4 Hz, *J* = 10.3 Hz, H5); 5.70 (1H, dd, *J* = 1.5 Hz, *J* = 9.8 Hz, H4); ^{13}C NMR (100 MHz) δ 13.25, Me; 13.45, Me; 16.36, Me; 22.19, C7; 28.06, C8; 32.34, C6; 34.86, C6a; 35.91, C3; 37.50, C9b; 37.83, C3a; 40.30, C9; 67.22, C2; 97.70, C9a; 125.46, C4; 133.13, C5; ν_{max} (CCl_4) 3454 br. s; 3020 s; 2943 vs; 2871 s; 1654 w; 1457 s; 1401 m; 1380 m; 1225 m; 1167 s; 1127 s; 1077 s; 1042 vs cm^{-1}; mass spectrum (EI): m/z 236 (M^+, 6%); 218 (100%); found M^+ 236.1762; $C_{15}H_{24}O_2$ requires 236.1776; Anal. calcd. for $C_{15}H_{24}O_2$ C 76.23, H 10.23; found C 76.31, H 10.21.

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34 Treatment of **14** with TMSOTf in acetonitrile resulted in slow conversion into Diels-Alder adduct **13**, presumably via loss of two moles of hexadienol to generate the allylic cation equivalent to **7**.

35. A more favorable result may obtain with the six-membered enone acetal corresponding to **20**, where lower ring strain may encourage closure in the acetal corresponding to **25**.

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