Ionic 'Diels–Alder' Reactions of Hexa-3,5-dienyl Trimethylsilyl Ether and Enones: X-Ray Structural Determination of Adduct Stereostructure, and a Stereoselective Approach to *Trans*-fused Octalin Systems

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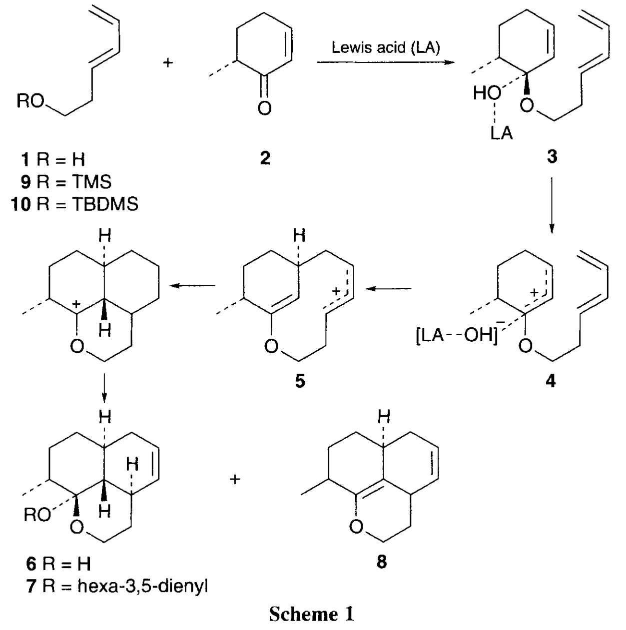
The trimethylsilyl (TMS) and *tert*-butyldimethylsilyl (TBDMS) ethers of hexa-3,5-dien-1-ol react with cyclohexenones and an acyclic enone, methyl vinyl ketone (MVK), in the presence of 5–10 mol% of $Me_3SiOSO_2CF_3$ (TMSOTf) in MeCN to provide *trans*-fused adducts arising *via* ionic (Gassman-type) Diels–Alder reactions; structural confirmation for adduct stereochemistry for this type of reaction is provided by an X-ray structural determination.

Recently, we discovered a new variant of the ionic (Gassman-type) 'Diels–Alder' (DA) reaction wherein hexa-3,5-dien-1-ol **1** and 6-methylcyclohex-2-enone **2** with catalytic $AlCl_3$ in CH_2Cl_2 or $Cu(OSO_2CF_3)_2$ in MeCN undergo a highly stereoselective cycloaddition to provide the *trans*-fused octalin **6**, its acetal **7** and dehydration product **8**, albeit in moderate yields (36–42% overall).[1] In view of the untoward stereochemistry with respect to normal Diels–Alder reactions, we proposed intermediacy of a hemiacetal **3**, which in the presence of the Lewis acid, provides an allylic cation **4** whose stepwise closure leads to the adduct (Scheme 1). The origin of the stereoselectivity was ascribed to addition of the pendant s-*cis* diene in **4** to the less-hindered β-face of the allylic cation followed by closure to the decalyl system from the α-face, which although less favoured sterically than β-closure, was held to be favoured by an electrostatic effect involving the Lewis acid–OH^- complex with the allyl cation moiety in **5**.[1] We herewith disclose further structural data which confirms the stereochemistry of **6**, and results which enhance the synthetic portent of this reaction.

Whilst structures were indicated by DQF 2D COSY NMR experiments at 600 MHz in conjunction with NOE experiments on these adducts and derivatives prepared on the way to (±)-6,9-desdimethylqinghaosu, the data did not permit disclosure of stereochemistry at the acetal carbon atom, C(9a), of importance from a mechanistic viewpoint.[1] We have now obtained crystals of the hemiacetal **6** suitable for a single crystal X-ray structure determination (Fig. 1).† The crystals grew as thin needles out of the vapour phase. Although the small size of the specimen (*ca.* 0.05 × 0.08 × 0.45 mm) limited the quality of the final result, the use of low temperature allowed all hydrogen atoms to be clearly located in difference Fourier maps. The structure reveals two crystallographically independent enantiomerically identical molecules of **6** together with one molecule of water in the asymmetric unit, all of which are hydrogen-bonded together. Geometric parameters for the two molecules are generally in close agreement. The compound is tricyclic with fused pyran, cyclohexene and cyclohexane rings. The hydroxy group at C(9a) is axial, and the C(9) methyl is equatorial. The unsaturation of the cyclohexene is clearly seen in the C(4)–C(5) double bond lengths of 1.310(8) and 1.311(9) Å, the sp^2-like C–C–C angles of between 123 and 125° at the alkene carbons and the torsion angles C(3a)–C(4)–C(5)–C(6) of −1.6 and −2.1°, which are indicative of coplanar vinyl substituents.



Scheme 1

The rationalisation of hemiacetal intermediates and their collapse to cationic intermediates caused us to focus on those catalysts which enhance acetal formation between ketones and alcohols. Nevertheless, use of various combinations of $TiCl_4$–$Ti(OPr^i)_4$, BBr_3, and a wide range of other Lewis acid–solvent combinations were generally ineffectual. Triflic acid provided moderate yields. Mindful of the effectiveness of the Noyori method for generating acetals from carbonyl compounds and trimethylsilyl (TMS) ethers of alcohols with catalytic trimethylsilyl triflate (TMSOTf) in CH_2Cl_2, a reaction which also works well for conjugated enones,[2] we examined the behaviour of the TMS ether **9** and *tert*-butyldimethylsilyl (TBDMS) ether **10** of the alcohol with conjugated enones in the presence of TMSOTf. We are pleased to report that workable yields of ionic DA adducts can now be obtained.

The various conditions and substrates so far tested are given in Table 1. The mildness of the reaction conditions is noteworthy, and, as in our initial observation, diastereoselectivity is fully maintained under these different reaction

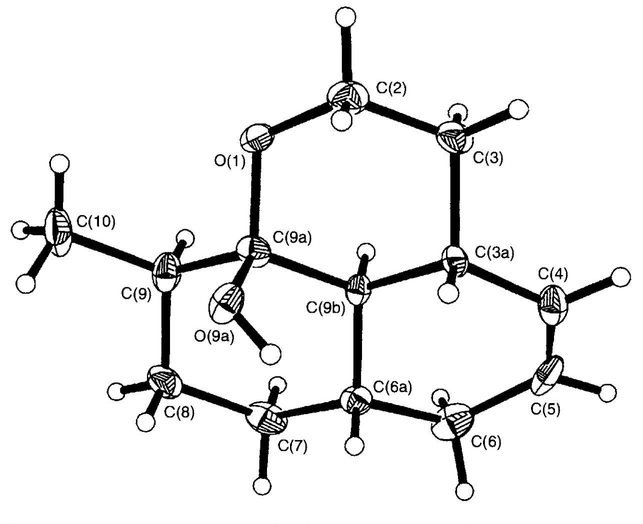


Fig. 1 Molecular structure of **6**, 40% thermal ellipsoids showing atomic labelling scheme of one of the crystallographically independent molecules

conditions, which provide the acetal, rather than the hemiacetal, as the major product. The best conditions for enone **12** involve the use of the TBDMS ether **10** of alcohol **1** in the presence of 5 mol% TMSOTf in MeCN, and give adduct **13** in 64% yield. Whilst exchange of the silyl-bearing group is anticipated, we find that use of TBDMSOTf as catalyst with **10** gave poorer yields of the adduct. The ethylene acetal of cyclohexenone reacted easily with **9** and TMSOTf, although complete acetal exchange also took place, and the yield of the adduct **7** (32%) was lower than in the other reactions.

Table 1 Yields of adducts from enones and dienol TMS ether **9** and dienol TBDMS ether **10**

Enone	TMSOTf (mol%)[a]	Reaction conditions	DA adduct, yield (%)[b]	Conj. adduct, yield (%)[b]
2	2	CH_2Cl_2, −78 °C, 20 h	**7**, 46	**11**, 2
2	5	MeCN, −20 °C, 12 h	**7**, 54	—
12	5	MeCN, −20 °C, 5 h	**13**, 59	—
12	10	Et_2O, −20 °C, 12 h	**13**, 57	—
12	3	toluene, −78 °C, 14 h	**13**, 24	**14**, 18
12	3	CH_2Cl_2, −78 °C, 45 h	**13**, 26	**14**, 23
12	5 (with **10**)	MeCN, −20 °C, 19 h	**13**, 64	—
12 (ethylene acetal)	10	MeCN, −20 °C, 3.5 h	**13**, 32	—
15	10	Et_2O, −78 °C, 10 h, 20 °C, 10 h	**16**, 32	—
15	5	MeCN, −30 °C, 10 h	**16**, 55	**17**, 8
15	6	toluene, −78 °C, 14 h, −20 °C, 10 h	**16**, 31	—
MVK	10	MeCN, −20 °C, 36 h	**18**, 26	—

[a] TMSOTf added to enone (1–2.5 mmol, 2–4 mol dm^{-3}) in indicated solvent under N_2 followed by addition of **9** (2 equiv.) (or **10** where indicated). [b] Isolated yields.

Particularly noteworthy is the intercession of a competing conjugate addition of the TMS ether with the cyclic enones to provide the unstable acetal adducts **11, 14** and **17**. This reaction, not previously recorded, becomes significant for reactions run in toluene or CH_2Cl_2 (Table 1). Remarkably, we also find that protracted treatment of conjugate adduct **14** with TMSOTf (10 mol%) in MeCN converts it into the DA adduct **13** (43%); however, the reaction is far slower than the DA reaction itself involving the enone and TMS ether of the alcohol, and thus, the conjugate addition is a competing reaction in the latter case.

Mechanistically, the results would appear to confirm the cationic mechanism as set out in Scheme 1. The actual mechanism notwithstanding, the reaction provides an effective means of directly constructing *trans*-fused octalin systems, and substantially expands the utility of the ionic DA reaction.[3] Current work focuses on use of chiral acetal-protected enones and chiral catalysis.

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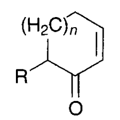
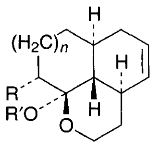
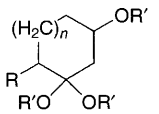


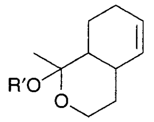
2 *n* = 1, R = Me
12 *n* = 1, R = H
15 *n* = 2, R = H



R′ = hexa-3,5-dienyl
7 *n* = 1, R = Me
13 *n* = 1, R = H
16 *n* = 2, R = H



R′ = hexa-3,5-dienyl
11 *n* = 1, R = Me
14 *n* = 1, R = H
17 *n* = 2, R = H



R′ = hexa-3,5-dienyl
18

Footnote

† *Crystal data* for **6**: $(C_{13}H_{20}O_2)0.5(H_2O)$: $C_{26}H_{42}O_5$, M_r = 434.6, Orthorhombic, $Pna2_1$, a = 24.971(6), b = 6.316(2), c = 14.733(3) Å, V = 2378 Å^3, T = 198 K, D_c = 1.214 g cm^{-3}, μ(Mo-Kα) = 0.82 cm^{-1}, F(000) = 952, R = 0.067, R_w = 0.063, GOOF = 1.46 for 1855 data [$F > 3\sigma(F)$]. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

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