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Investigation of the asymmetric ionic Diels–Alder reaction for the synthesis of *cis*-decalins

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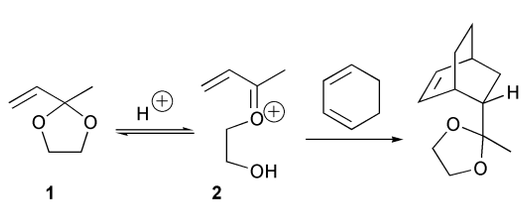
The ionic Diels–Alder reaction, whereby an α,β-unsaturated acetal in combination with a Lewis or Brønsted acid forms an equilibrium concentration of an activated dienophile, has been developed to provide an enantioselective synthesis of *cis*-decalins. Cyclohex-2-enone type chiral acetals of (2*R*,3*R*)-butane-2,3-diol have been screened against Lewis and Brønsted acids with a variety of dienes and are efficient for the synthesis of a limited subset of *cis*-decalin structures. Diastereoselectivities of 73% and 82% have been found for the asymmetric ionic Diels–Alder reaction between the chiral acetal derivatives of cyclohex-2-enone (**6**) and 2-methylcyclohex-2-enone (**18**) with 2,3-dimethyl-1,3-butadiene (**7**). Terminal substituents on the diene partner in general render the system unreactive. However a synthetically useful *cis*-decalin **31**, derived from the reaction of 2-methylcyclohex-2-enone and *Z*-3-*t*-butyldimethylsilyloxypenta-1,3-diene has been prepared in enantiomerically pure form in 74% isolated yield using this asymmetric ionic Diels–Alder protocol.

Introduction

Despite the abundance of natural products containing the *cis*-decalin structure, there have been few reports of asymmetric Diels–Alder studies towards these systems. There are pertinent examples of the use of pre-existing stereocentres to direct facial selectivity in inter-[1,2] and intramolecular[3] Diels–Alder reactions to give *cis*-decalin systems, but these examples suffer from a lack of generality. Despite the excellent advances made in the use of chiral Lewis acids to catalyse enantioselective Diels–Alder reactions[4] with dienophiles such as aldehydes, esters, quinines[5] and bidentate chelating carbonyls,[6] extension of this methodology to simple ketones has been arduous. The high level of oxygen lone pair discrimination required in the metal association step, in order to eliminate multiple transition states, is not so simple for ketone like carbonyls as both oxygen lone pairs are positioned in similar steric and electronic environments. There have been two notable advances of late, but these reports are restricted to the use of cyclopentadiene with cyclic enones.[7] In the meantime we have been concerned with a chiral auxiliary based approach aimed specifically at the enantioselective synthesis of *cis*-decalins.

The observation by Gassman that 1,3-cyclohexadiene underwent dimerisation at 0 °C in the presence of tris(*p*-bromophenyl)aminium hexachloroantimonate led to the development of the ionic Diels–Alder (IDA) reaction.[8] Gassman later discovered that α,β-unsaturated acetals could also undergo ionic Diels–Alder reactions.[9] Protonation of acetal **1** provides an equilibrium concentration of oxonium ion **2**, which is also an activated dienophile and can participate in a Diels–Alder reaction with a diene (Scheme 1).



Scheme 1

Modifications of this procedure using catalytic Lewis acids have been used to prepare simple achiral *cis*-fused decalin systems. Catalysts such as indium trichloride,[10] lithium perchlorate in diethyl ether,[11] the solid acid catalyst Nafion-H[12] and trimethylsilyl triflate[13] have all been shown to give high yields of products under mild conditions. Aldehyde derived chiral acetal acyclic dienophiles under the original Gassman conditions gave poor diastereoselectivities,[14] but the use of the Lewis acid $TiCl_2(O\textit{i}\text{-}Pr)_2$ gave diastereomeric ratios as high as 15 : 1.[13,15]

We reasoned that a chiral cyclohexene acetal **3** upon activation with a Lewis acid would provide at least some partial oxocarbocation character which would activate the substrate towards reaction with an electron rich diene (Fig. 1).[16] Facial bias would be expected to be controlled through the chiral environment associated with the partial generation of the oxocarbocation in **4** and **5**. The extent of diastereoselection would depend upon the relative energies of the Diels–Alder transition states from **4** and **5**. Arguably products derived from **4** would be more favourable as **5** engenders a *syn*-pentane like interaction between substituent R and the pseudo-axial methyl group of the chiral auxiliary. This reasoning is analogous to that derived for stereoselective addition of nucleophiles to carbonyl derivatives controlled by chiral acetals.[17] If the proposed asymmetric Diels–Alder methodology were successful it would provide valuable and flexible methodology for the synthesis of diastereomerically enriched *cis*-decalins with up to four contiguous stereocentres. Although this approach

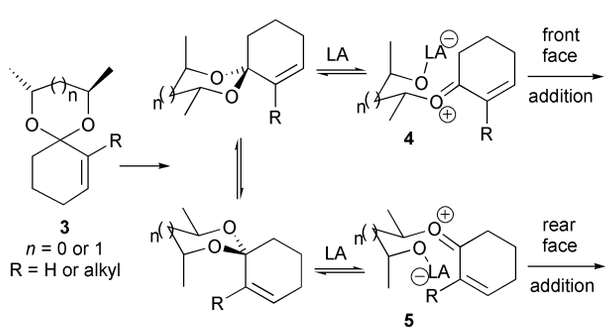


Fig. 1

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† Corresponding authors for X-ray crystal structures.

Table 1 Effect of acid on diastereoselectivity

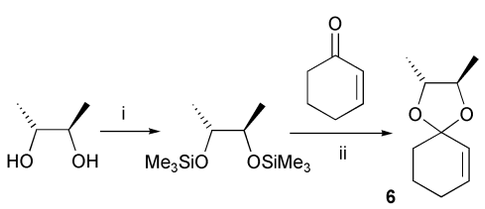
Entry	Acid[a]	Conc./M	*T*/°C	Time/h	Yield (%)[b]	**8** : **9**[c]
1	Me_3SiOTf	0.33	−78	7	> 95	2 : 1
2	$TiCl_4$	0.33	−78 to −25	5	0	—
3	$BiCl_3$	0.33	rt	4	> 95 (91)	1 : 1
4	TfOH	0.33	−78	2	> 95	2 : 1
5	$TiCl_2(O\textit{i}\text{-Pr})_2$	0.33	−78 to rt	24	0	—
6	$InCl_3$	0.33	−20 to rt	24	60	3 : 2
7	CSA[d]	0.33	0	1	> 95	3 : 2
8	CSA[d]	0.33	−20	24	25	2 : 1
9	Me_3SiOTf	0.33	−78	7	> 95	2 : 1
10	Me_3SiOTf	1.00	−78	3	> 95	6 : 1
11[e]	Me_3SiOTf	2.00	−78	3	> 95 (97)	6.5 : 1
12	Me_3SiOTf	10.0	−78	3	70	6 : 1

[a] Standard procedure involved treatment of **6** (1 mmol) with **7** (3 equivalents) and acid (10 mol%) in CH_2Cl_2. [b] Yield measured from ^1H NMR, isolated yield in parentheses. [c] Estimated from ^{13}C NMR.[19] [d] 1 mol% in 4 M $LiClO_4$–Et_2O. [e] Scale increased by factor of 6.

would require the stoichiometric use of enantiomerically pure auxiliary, the acetal group would not only act as a chiral directing group, but also as an activating group for the Diels–Alder reaction and as a carbonyl protecting group for subsequent steps in further synthesis. The eventual removal of the auxiliary would be facile and should not destroy the stereochemical integrity of the diol, which could be recovered.

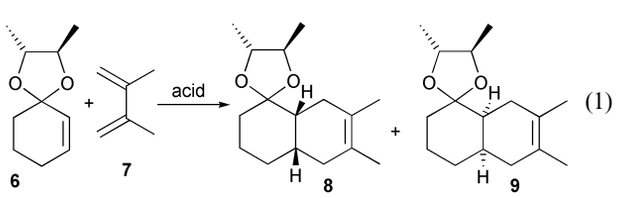
Results and discussion

We began our investigations into the feasibility of this methodology by surveying the cyclohex-2-enone chiral acetal **6** derived from (2*R*,3*R*)-butane-2,3-diol. Conventional acetal formation using various acid catalysts in refluxing benzene under Dean–Stark conditions gave substantial amounts of alkene migration. Using Noyori's conditions acetal **6** was formed in 89% yield (Scheme 2).[18]



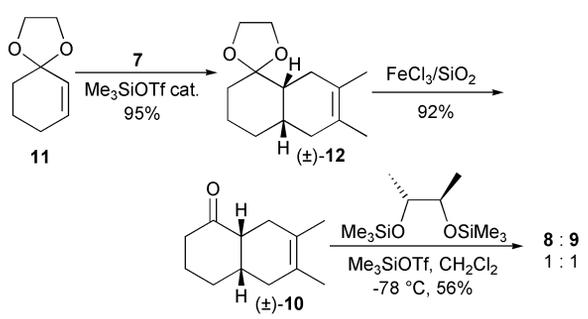
Scheme 2 i, Me_3SiCl, Et_3N, Et_2O, 100%; ii, Me_3SiOTf, CH_2Cl_2, −78 °C, 89%.

To simplify stereochemical analysis we chose 2,3-dimethyl-1,3-butadiene (**7**) as our standard diene as this would avoid any *exo*/*endo* selectivity issues. A range of Lewis and Brønsted acids which have previously been used in ionic Diels–Alder reactions were screened (eqn. (1), Table 1). A range of conditions facilitated this particular ionic Diels–Alder reaction (eqn. (1)), but the diastereocontrol was poor (entries 1–9). However an interesting concentration effect was observed, with a synthetically useful level of selectivity obtained when molar or higher concentrations of **6** were used (entries 10–12). Problems with the viscosity of the mixture were encountered when the concentration was increased to 10 M and no further increase in selectivity was observed. A concentration of 2.0 M in **6** was optimal to obtain a selectivity of 6.5 : 1 in 97% yield.



(1)

To verify that the two products had *cis*-ring junctions and that there had been no interference from a nonconcerted process, an authentic racemic sample of **10** was prepared (Scheme 3). The Me_3SiOTf catalysed ionic Diels–Alder reaction between **11**[18] and **7** gave a 95% yield of **12**. To prevent epimerisation at the ring junction adjacent to the masked carbonyl the acetal was deprotected using $FeCl_3$ adsorbed on silica[20] to give (±)-**10**.[21] Acetalisation using Noyori's conditions as before gave a 1 : 1 mixture of **8** : **9** (56%). This material was spectroscopically identical to that prepared in eqn. (1).



Scheme 3

The sense of diastereoselection of the asymmetric ionic Diels–Alder reactions was determined by X-ray crystallography. A diastereomerically enriched sample of **8** (6 : 1), which was a viscous oil, was dissolved in petrol and cooled slowly to −20 °C. A single crystal was grown which had a low melting point of 15–20 °C, but was amenable to single crystal X-ray structure determination. The structure confirmed the *cis* stereochemistry[22] of the ring junction and the relative stereochemistry of the major diastereoisomer **8** with respect to (2*R*,3*R*)-butane-2,3-diol.‡ This result suggested that **8** was formed from an oxocarbenium ion like **4**, with approach of the diene from the sterically less hindered top face.

Work on asymmetric cyclopropanation on a range of cyclohexenone chiral acetal derivatives showed that the acetal derived from (1*R*,2*R*)-1,2-diphenylethane-1,2-diol gave the best diastereoselectivities.[23] Accordingly the diphenyl analogue **13** was prepared[13] in analogous fashion to **6** (86% yield over two steps) for assay in the ionic Diels–Alder reaction. Treatment of **13** (1 M) in CH_2Cl_2 with **7** (3 equivalents) and Me_3SiOTf (10 mol%) gave *cis*-decalins **14** and **15** as an inseparable mixture (estimated to be *ca.* 2 : 1 from analysis of the complicated ^{13}C NMR spectra) in 96% isolated yield (Scheme 4).

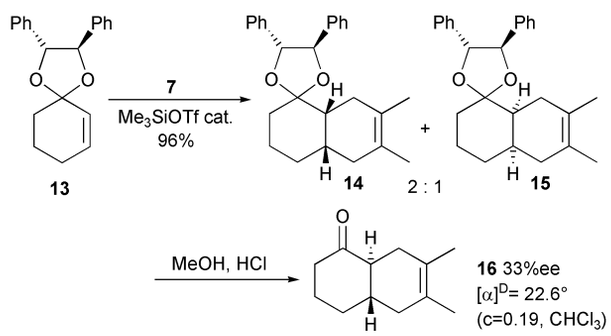
To confirm the sense of diastereoselection it was envisaged that we could convert **14**–**15** to the corresponding dimethyl acetals **8**–**9**. Unfortunately treatment of **14**–**15** under the con-

‡ Crystallographic data (excluding structure factors) for **8**, **22** and **31** have been deposited as supplementary data. CCDC reference numbers 210314–210316. See http://www.rsc.org/suppdata/ob/b3/b305116a/ for crystallographic data in .cif or other electronic format.

Table 2 Optimisation of equation (2)

Entry	Acid[a]	Solvent	*T*/°C	Time/h	Yield (%)[b]	**19** : **20**[c]
1	Me_3SiOTf	CH_2Cl_2	−78 to −40	24	35	2 : 1
2	$BiCl_3$	CH_2Cl_2	rt	6	> 95 (91)	2 : 1
3	BiOCl	CH_2Cl_2	rt	24	—	—
4	$Sc(OTf)_3$	CH_2Cl_2	rt	24	8	3 : 1
5	$InCl_3$	CH_2Cl_2	rt	24	25	1 : 1
6	$ZnCl_2$	CH_2Cl_2	rt	24	90	2 : 1
7	$AlCl_3$	CH_2Cl_2	rt	6	90	1 : 1
8	$Ti(Oi\text{-}Pr)_4$	CH_2Cl_2	rt	24	—	—
9	$TiCl_2(Oi\text{-}Pr)_2$	CH_2Cl_2	−20 to rt	24	—	—
10	TfOH	CH_2Cl_2	−20	5	—	—
11	CSA[d]	Et_2O[e]	0 to rt	5	> 95	2 : 1
12	$TiCl_4$	CH_2Cl_2	rt	1	> 95	5 : 1
13	$TiCl_4$	CH_2Cl_2	−20	2	> 95 (96)	10 : 1
14	$TiCl_4$	CH_2Cl_2	−78 to −60	24	25	10 : 1
15	$TiCl_4$	CH_2Cl_2[f]	−20	2	> 95	10 : 1
16	$TiCl_4$	THF	−20	24	—	—
17	$TiCl_4$	PhMe	−20	24	> 95	5 : 1
18	$TiCl_4$	MeCN	−20	24	50	4 : 1
19	$BF_3{\bullet}OEt_2$	CH_2Cl_2	−20	2	75	1 : 2

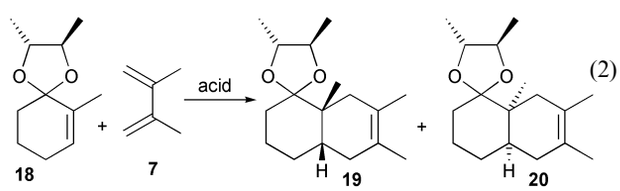
[a] Standard procedure involved treatment of **18** (1 mmol, 0.33 M) with **7** (3 equivalents) and acid (10 mol%). [b] Yield measured from ^{1}H NMR, isolated yield in parentheses. [c] Estimated from ^{13}C NMR.[24] [d] 1 mol%. [e] 4 M $LiClO_4$ in Et_2O. [f] 1 M in **18**.



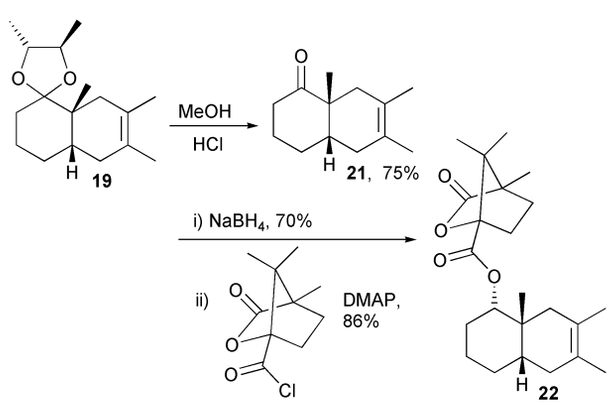
Scheme 4

ditions used for the deprotection of (±)-**12** to ensure no ring junction epimerisation led to only 5% deprotection after 72 h at rt and 24 h at reflux. Heating with aqueous HCl in MeOH effected de-acetalisation, but with concurrent epimerisation at the ring junction to give exclusively the *trans*-decalin **16** [33% *ee* $[\alpha]^D = 22.6°$ ($c = 0.19$, $CHCl_3$)] in 79% yield. Deprotection of a mixture of **8**–**9** (6.5 : 1 ≈ 73% *de*) under identical conditions gave a sample of **16** [73% *ee*, $[\alpha]^D = 48.5°$ ($c = 0.10$, $CHCl_3$), 95% yield]. The identical signs of the optical rotations confirmed that the (*R*,*R*)-diphenyl acetal gave the same facial bias as the (*R*,*R*)-dimethyl acetal, but at a much lower level. The magnitude of the optical rotations also confirmed the enantioexcess of the reactions. As other types of chiral acetal have been shown,[16] on the whole, to be less efficient than the dimethyl and diphenyl derivatives, coupled with the fact that they are not readily available, we decided to continue with (2*R*,3*R*)-butane-2,3-diol as our auxiliary for the asymmetric ionic Diels–Alder reaction.

For synthetic work already underway we were more interested in the use of 2-methylcyclohex-2-enone acetals (*vide infra*). We expected the methyl substituent could possibly enhance diastereoselection in the ionic Diels–Alder reaction as discussed in Fig. 1. Acetalisation of 2-methylcyclohex-2-enone (**17**)[24] with (2*R*,3*R*)-butane-2,3-diol under standard conditions (TsOH cat., PhH, Dean–Stark) gave an 89% yield of dimethyl acetal **18**, the trisubstituted alkene showing no tendency to migrate which was in direct contrast to cyclohex-2-enone. Subjection of **18** to our standard ionic Diels–Alder conditions using diene **7** and catalytic Me_3SiOTf (10 mol%) gave only a disappointing 35% yield of a 2 : 1 mixture of diastereoisomers **19**–**20** (eqn. (2)). We decided to screen a number of Lewis acids to try and increase the yield and diastereoselectivity for this substrate (Table 2).

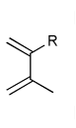
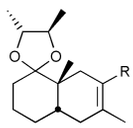
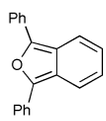
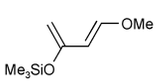
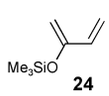
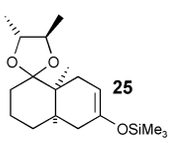


It is interesting that $TiCl_4$ was found to be the best Lewis acid in this survey as it had caused the degradation of acetal **6** in similar experiments. The optimised experiment (entry 13) provided the *cis*-decalin in 96% yield with a diastereomeric ratio of 10 : 1.[25] We were not able to directly determine the sense of diastereoselection, since the viscous oil would not yield to recrystallisation. However, we were eventually able to form a chiral derivative from which a crystal structure could be solved (Scheme 5). Deacetalisation of a pure sample of **19** yielded ketone **21**, which underwent stereoselective reduction with $NaBH_4$ and esterification with camphanic chloride to give ester **22**. Recrystallisation from petrol gave colourless needles from which the X-ray structure was solved. ‡ The structure confirmed the major diastereoisomer from the Diels–Alder reaction to be **19**, with the same sense of relative stereochemistry as **8**. This result again suggested that the major diastereoisomer was formed from the diene approaching from the sterically less hindered face of an oxocarbocation like **4** (Fig. 1). Partial oxocarbocation character or a tight ion pair is assumed, so a chiral environment around the alkene is maintained. The senses of any stereoselectivity observed in Table 2, except for entry 19, were identical. The minor diastereomer could be formed either



Scheme 5

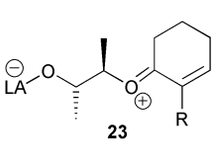
Table 3 Survey of **18** with other dienes

Entry[a]	Diene	*T*/°C	Time/h	Product	Yield (%)[b]	dr[c]
1	 R=Me R=H	−20	2		> 95	10 : 1
2		−20	2		> 95	10 : 1
3		−20	5	—	0	—
4		rt	24	—	0	—
5[d]		rt	24	—	0	—
6		−20	2	—	0	—
7		−20 to rt	24	—	0	—
8		−20	24	Mixture of diastereoisomers	~20	—
9		−20	24	—	0	—
10	 **24**	−20	24	 **25**	40	3 : 2

[a] Standard procedure involved treatment of **18** (1 mmol, 0.33 M) with diene (3 equivalents) and $TiCl_4$ (10 mol%). [b] Yield measured from ^1H NMR. [c] Estimated from ^{13}C NMR.[24] [d] 1 equivalent of diene.

from approach of the diene from the sterically more hindered face of an oxocarbenium ion like **4**, or by approach of the diene to the sterically less hindered face of an oxocarbenium ion like **5** (Fig. 1).

Where no selectivity was observed (entries 5 and 7, Table 2) the complete formation of an oxocarbocation like **23**, where tight ion pairing is absent (Fig. 2), would engender little facial discrimination and would most easily explain these results.

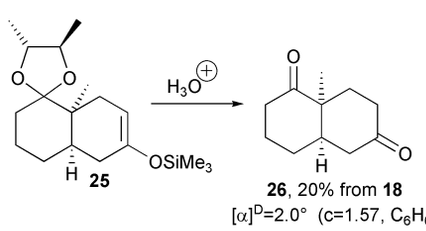


23

Fig. 2

The use of $BF_3{\cdot}Et_2O$ (entry 19, Table 2) reversed the previously observed selectivity. This curious result cannot easily be explained by the arguments outlined in Fig. 1 and above, and shows that a full explanation of diastereoselectivity is probably more complicated than the simple models forwarded.

Having found what we thought was a good chiral auxiliary for the ionic Diels–Alder reaction we then assayed **18** against a range of dienes (Table 3). Not surprisingly isoprene gave a good yield and diastereoselectivity (entry 2) of a *cis*-decalin we assume has the same relative configuration as **19** (*vide supra*). Other dienes were universally poor (entries 3–9). The results clearly show that a group positioned at the terminus of a diene renders them too unreactive. Only 2-trimethylsilyloxy-1,3-butadiene[26] (**24**) showed any useful level of reaction (entry 10). This unoptimised product, formed in around 40% yield,[27] was filtered through a plug of basic alumina and hydrolysed to the diketone **26** in 20% overall yield (eqn. (3)). Comparison of the optical rotation with that of $[\alpha]^D = 12.0°$ ($c = 1.5$, C_6H_6) in the literature[28] determined the sense of diastereoselection and suggested an optical purity of *ca*. 20%, which was in agreement with the measured diastereomeric ratio of **25** that had been estimated from ^{13}C NMR of the crude reaction mixture.



26, 20% from **18**

$[\alpha]^D$=2.0° (c=1.57, C_6H_6)

(3)

The level of diastereoselectivity in this reaction was unexpectedly low and in the opposite sense to what had been observed earlier. The simplest explanation to account for the stereoselectivity in the ionic Diels–Alder reactions leading to **8** and **19** involves the least hindered facial attack of oxocarbenium ion **4** in preference to **5** (Fig. 1). In the formation of **25** the oxygen atom in **24** could also have coordinated to the Lewis acid (Ti in this case) and been delivered from the most hindered face of **4**, thus eroding diastereoselectivity. Alternatively there could be some subtle steric effect with diene **24** compared to **7** which makes the pathway from **5**, albeit very slightly, more favourable.

Table 4 Effect of enol ether protecting group

Entry	Diene[a]	P	Yield (%)[b]	**31** : **32** : **33**[c]
1	**30a**	Me_3Si	21	20 : 5 : < 1
2	**30b**	Et_3Si	40	20 : 5 : < 1
3	**30c**	*t*-$BuMe_2Si$	92	20 : 5 : < 1
4	**30d**	*i*-Pr_3Si	83	20 : 5 : < 1

[a] Standard procedure involved treatment of **18** (1 mmol, 0.33 M) with **30** (1 equivalent) and $TiCl_4$ (10 mol%). [b] Isolated yield. [c] Estimated from ^{13}C NMR.[24]

The impetus for this research was our desire to find an asymmetric Diels–Alder route to decalins of the type **27** (Fig. 3) which are prevalent in many sesquiterpenoid natural products, some of which are the subject of total synthesis programmes within our group. Retro Diels–Alder disconnection of **27** leads to **18** and diene **28**. However from our results in trying to develop this asymmetric ionic Diels–Alder methodology we can postulate that diene **28** is unlikely to react with **18** as it has two terminal substituents and no donor group directly attached to the diene. An alternative strategy involves functional group manipulations of **27** to give **29**, which can then be disconnected to **18** and simplified diene **30**. Diene **30** differs from activated diene **24** only by a methyl group and we were confident this would react in our asymmetric ionic Diels–Alder reaction.

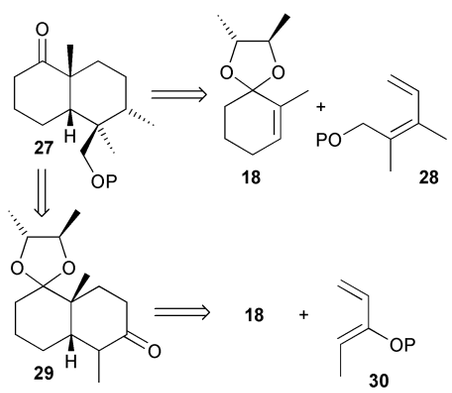
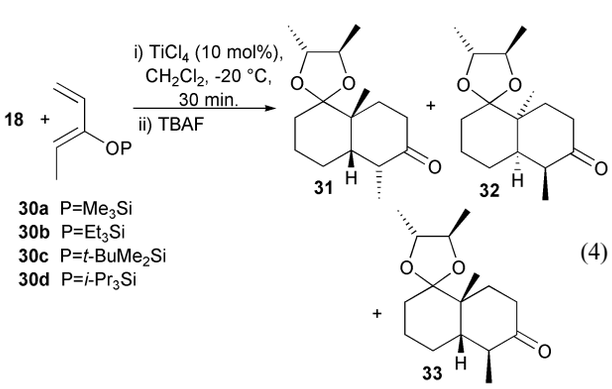


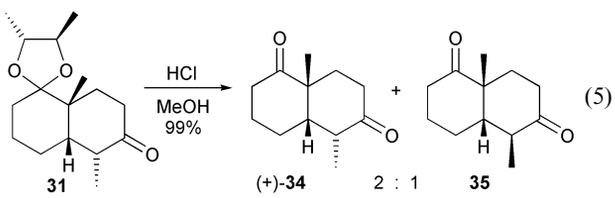
Fig. 3

Dienes with sterically different silicon protecting groups **30a**–**d** were synthesised in order to probe any subtle steric effects.[29] Mixtures of **18** and the dienes **30a**–**d** were treated with catalytic $TiCl_4$ (10 mol%) to give a mixture of three *cis*-decalins (eqn. (4) and Table 4). The crude reaction mixtures were treated with TBAF to give stable ketone products **31**, **32** and **33**. It was determined that the identity of the silicon protecting group did not affect the diastereoselectivity of the reaction, but did have an effect on the stability of the enol ether to the reaction conditions. The *t*-butyldimethylsilyl enol ether was found to give the best yield of Diels–Alder products (92%) with a diastereoselectivity of 77% in favour of **31** (*de* ~60%).

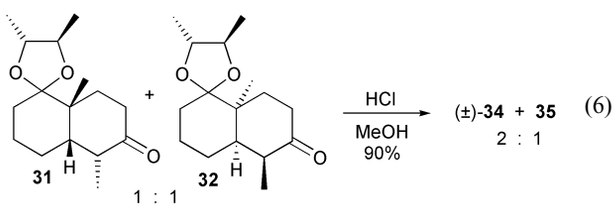


(4)

Stereochemical assignment is based on the fact that **31** was separable from the mixture and a single crystal X-ray structure determination confirmed its relative stereochemistry with respect to (2*R*,3*R*)-butane-2,3-diol.‡ Deacetalisation of a pure sample of **31** gave a 2 : 1 mixture of **34** and **35** (eqn. (5)),[30] with **34** exhibiting $[a]^D = +43.0°$ ($c = 0.52$, $CHCl_3$). Deacetalisation of a 1 : 1 mixture of **31** and **32** gave the same 2 : 1 mixture of **34** and **35**, but this sample of **34** was essentially racemic by polarimetry (eqn. (6)). We infer that **30** and **31** are diastereoisomers arising from *endo* cycloaddition of the diene in two competing pathways whose facial addition is dictated by the chiral acetal. Diastereoisomer **33** could not be isolated in pure form, but we assume this is the C-5 epimer of the major product (**31**) and is formed from *exo* approach of the diene to **18**.



(5)



(6)

Conclusion

The asymmetric ionic Diels–Alder reaction using (2*R*,3*R*)-butane-2,3-diol has been shown to be efficient for the synthesis of a limited subset of *cis*-decalin structures. Diastereoselectivities of 73% and 82% were found for the ionic Diels–Alder reactions between the chiral acetal derivative of cyclohex-2-enone (**6**) and 2,3-dimethyl-1,3-butadiene (**7**) and between the chiral acetal derivative of 2-methylcyclohex-2-enone (**18**) and **7** (and isoprene) in greater than 95% yield. For synthetic purposes we can conclude that we can access a 74% isolated yield of **31** in enantiomerically pure form from the asymmetric ionic Diels–Alder reaction. We believe this synthetic route is comparable in terms of simplicity and efficiency to the synthesis of the ethane-1,2-diol acetal analogue of **31**[31] prepared from enantiomerically pure (−)-Wieland–Miescher ketone.[32] Use of enantiomerically pure **31** as a building block in the synthesis of sesquiterpene natural products will be demonstrated in due course.

Experimental

Unless otherwise stated all reactions were carried out under an atmosphere of nitrogen. All glassware was flame dried and allowed to cool under a stream of nitrogen before use. THF was distilled under an atmosphere of dry nitrogen from potassium benzophenone ketyl. Diethyl ether was distilled under a dry atmosphere of nitrogen from sodium benzophenone ketyl. All other reagents were purified or dried according to standard literature methods. Water was distilled. Thin layer chromatography was performed on Polygram® SIL G/UV_{254} 0.25 mm silica gel precoated plastic sheets with fluorescent indicator. Sheets were visualised using ultra-violet light (254 nm) and/or $KMnO_4$ or anisaldehyde solutions. Flash column chromatography was carried out using Fluorochem silica gel 60, 35–70 μ. ^1H NMR and ^{13}C NMR were as dilute solutions in deuterochloroform unless otherwise stated. All chemical shifts (δ) are quoted in ppm and coupling constants (J) in Hz. Coupling constants are recorded as observed in the spectrum without

averaging. ^{13}C multiplicities were assigned using a DEPT sequence. Residual signals from the solvents were used as an internal reference. Mass spectra were acquired on a VG micromass 70E, VG Autospec or Micromass LCTOF. Melting points are uncorrected and were recorded on a Reichert Melting Point Apparatus. Elemental analyses were performed by the microanalysis service of the School of Chemistry, University of Nottingham on an Exeter Analytical Inc. CE440 elemental analyzer.

(2*R*,3*R*)-2,3-Bis-trimethylsilyloxy-butane

To a mixture of (2*R*,3*R*)-(−)-2,3-butanediol (1.08 g, 12.0 mmol) and imidazole (2.6 g, 39 mmol) in Et_2O (15 mL) at 0 °C was added Me_3SiCl (3.3 mL, 26 mmol). After 30 min the mixture was warmed to rt and stirred overnight. The mixture was filtered through Celite, washed with water (2 × 25 mL) and brine (25 mL), dried over $MgSO_4$ and concentrated *in vacuo* to yield (2*R*,3*R*)-2,3-bis-trimethylsilyloxy-butane (2.81 g, 100%) as a clear oil.[33]

2-Cyclohexenone (2*R*,3*R*)-2,3-butanediol acetal 6

To a pre-cooled (−78 °C) solution of 2-cyclohexenone (1.45 mL, 15.0 mmol) and trimethylsilyl triflate (22 μL, 0.12 mmol) in CH_2Cl_2 (1 mL) was added (2*R*,3*R*)-2,3-bis-trimethylsilyloxy-butane prepared above (2.81 g, 12.0 mmol). The mixture was stirred at −78 °C overnight and quenched with Et_3N (0.1 mL). Volatiles were removed *in vacuo* and the residue was purified by flash column chromatography (SiO_2 neutralised with a 1% Et_3N–petrol solution; elution with 5% EtOAc–petrol) to yield a clear oil of **6** (1.63 g, 84%).[34]

General procedure for the ionic Diels–Alder reaction[35]

To a pre-cooled mixture of acid (0.1 equiv.) and acetal (1 equiv.) in CH_2Cl_2 (3 mL per equiv.) was added the appropriate diene (1–3 equiv.) dropwise and the reaction was stirred for up to 24 h until all acetal was consumed, as determined by TLC or NMR samples. The mixture was filtered through a plug of Al_2O_3, eluted with Et_2O, and concentrated *in vacuo* to yield crude material, which was purified by flash column chromatography (2–10% EtOAc–petrol) where appropriate.

(4a*S*,8a*R*)-6,7-Dimethyl-3,4,4a,5,8,8a-hexahydro-2*H*-naphthalen-1-one (2*R*,3*R*)-2,3-butanediol acetal 8 and (4a*R*,8a*S*)-6,7-dimethyl-3,4,4a,5,8,8a-hexahydro-2*H*-naphthalen-1-one (2*R*,3*R*)-2,3-butanediol acetal 9

The acid catalysed reaction between 2-cyclohexenone (2*R*,3*R*)-2,3-butanediol acetal **6** and 2,3-dimethyl-1,3-butadiene (**7**), according to the general procedure, gave a mixture of *cis*-decalins **8** and **9**, which were not separable by chromatography. From a diastereomerically enriched sample of **8** (6 : 1) a single crystal of **8** was grown (petrol, −20 °C) mp 15–20 °C; ν_{max}-($CHCl_3$)/cm^{-1} 2934–2830, 1438; δ_H (400 MHz) 1.18–1.34 (2H, m, C4-H_2), 1.22 (3H, d, *J* 5.6, CH*Me*), 1.24 (3H, *J* 5.6, CH*Me*), 1.47–2.04 (9H, m), 1.59 (3H, s, *Me*), 1.61 (3H, s, *Me*), 2.24 (1H, br d, *J* 16.1), 3.56–3.66 (2H, m, C*H*MeC*H*Me); δ_C (100 MHz; $CDCl_3$) 17.2 (CH*C*H$_3$), 17.3 (CH*C*H$_3$), 19.0 (*C*H$_3$), 19.2 (*C*H$_3$), 23.0 (*C*3), 26.2 (*C*4), 29.8 (*C*H$_2$), 31.9 (*C*2), 33.1 (*C*4a), 38.0 (*C*H$_2$), 42.6 (*C*8a), 78.1 (*C*H), 78.2 (*C*H), 110.6 (*C*1), 123.0 (q), 123.5 (q); *m*/*z* (EI$^+$) 250.1928 (100% M$^+$, $C_{16}H_{26}O_2$ requires 250.1933), 207 (45%, M$^+$ − (HOCH$_2$CH$_2$OH and CH$_3$)), 160 (82%, M$^+$ − HOCH$_2$CH$_2$OH), 145 (49%), 107 (61%).

A pure sample of **9** could not be obtained. δ_C (100 MHz, determined by subtracting the signals from **8** from an authentic mixture of diastereomers **8** and **9**) 17.1, 17.2, 19.0, 19.2, 23.3, 26.1, 29.8, 31.2, 32.4, 38.1, 42.8, 77.6, 77.9, 110.5, 122.8, 123.5.

Comparisons of the following pairs of ^{13}C NMR signals[24] were used to determine the diastereomeric ratio: 123.0 and 122.8; 110.6 and 110.5; 42.6 and 42.8; 23.0 and 23.3.

Crystal structure determination of compound 8

Crystal data. $C_{16}H_{26}O_2$, *M* = 250.37, orthorhombic, *a* = 6.8589(11), *b* = 10.727(2), *c* = 20.398(3) Å, *U* = 1500.7(7) Å^3, *T* = 150(2) K, space group: $P2_1\,2_1\,2_1$, *Z* = 4, μ = 0.071 mm^{-1}, 4714 reflections measured, 2067 unique (R_{int} = 0.081) which were used in all calculations. The final $wR(F^2)$ was 0.120 (all data).

(4a*S**,8a*R**)-6,7-Dimethyl-3,4,4a,5,8,8a-hexahydro-2*H*-naphthalen-1-one 1,2-ethanediol acetal (±)-12

The Me_3SiOTf catalysed reaction between 2-cyclohexenone 1,2-ethanediol acetal (**11**)[18] (1 mmol) and **7** according to the general procedure at −78 °C gave *cis*-decalin **12** (95%) as a clear oil ν_{max}($CHCl_3$)/cm^{-1} 2938–2831 (C–H), 1730, 1437; δ_H (400 MHz) 1.18–1.36 (2H, m, C4-H_2), 1.45–1.79 (11H, m), 1.86–2.04 (4H, m), 2.25 (1H, br d, *J* 17.2), 3.85–3.95 (4H, m, OCH_2-CH_2O); δ_C (100 MHz) 19.0 (*C*H$_3$), 19.2 (*C*H$_3$), 23.3 (*C*3), 26.1 (*C*4), 29.7 (*C*H$_2$), 29.9 (*C*H$_2$), 33.0 (*C*4a), 38.0 (*C*H$_2$), 41.0 (*C*8a), 64.2 (2C, O*C*H$_2$*C*H$_2$O), 111.5 (*C*1), 122.7 (q), 123.5 (q); *m*/*z* (EI$^+$) 222.1615 (100% M$^+$, $C_{14}H_{22}O_2$ requires 222.1620), 160 (82%, M$^+$ − HOCH$_2$CH$_2$OH), 145 (74%, M$^+$ − (HOCH$_2$-CH$_2$OH and CH$_3$)), 99 (98%).

(4a*S**,8a*R**)-6,7-Dimethyl-3,4,4a,5,8,8a-hexahydro-2*H*-naphthalen-1-one (±)-10

To a solution of (±)-**12** prepared above (647 mg, 2.91 mmol) in 95% aq. acetone (10 mL) was added a preformed $FeCl_3$–SiO_2 mixture[19] (85 mg), and the mixture was stirred at rt overnight. Solvent was removed *in vacuo* and the crude mixture was purified by flash column chromatography (5% EtOAc–hexane) to provide racemic *cis*-decalin ketone (±)-**10** (475 mg, 92%) as a clear oil. Spectroscopic data were identical to the literature.[20]

Formation of 8–9 (1 : 1) from (±)-10

To a solution of (±)-**10** (177 mg, 1.0 mmol) and (2*R*,3*R*)-2,3-bis-trimethylsilyloxy-butane (240 mg, 1.0 mmol) in CH_2Cl_2 (1.5 mL) at −78 °C was added Me_3SiOTf (9 μL, 0.05 mmol). The mixture was stirred at −78 °C overnight and then quenched with Et_3N (0.15 mL). Volatiles were removed *in vacuo* and the residue was purified by flash column chromatography (5% EtOAc–petrol) and gave a combined 1 : 1 mixture of **8**–**9** (140 mg, 56%) whose spectroscopic data were identical to that prepared by the ionic Diels–Alder protocol.

(4a*S*,8a*R*)-6,7-Dimethyl-3,4,4a,5,8,8a-hexahydro-2*H*-naphthalen-1-one (1*R*,2*R*)-1,2-diphenylethane-1,2-diol acetal 14 and (4a*R*,8a*S*)-6,7-dimethyl-3,4,4a,5,8,8a-hexahydro-2*H*-naphthalen-1-one (1*R*,2*R*)-1,2-diphenylethane-1,2-diol acetal 15

The Me_3SiOTf catalysed reaction between 2-cyclohexenone (1*R*,2*R*)-1,2-diphenylethane-1,2-diol acetal (**13**)[13] (146 mg, 0.50 mmol) and **7**, according to the general procedure at −78 °C for 3 h, gave an inseparable ~2 : 1 mixture of *cis*-decalins **14** and **15** (180 mg, 96%) as a white foam. Data provided are for the mixture of diastereomers. ν_{max}($CHCl_3$)/cm^{-1} 3050–2850 (C–H), 1454, 1353; δ_H (400 MHz; $CDCl_3$) 1.24–2.44 (18H, m), 4.69–4.77 (2H, m), 7.18–7.35 (10H, m); δ_C (100 MHz; $CDCl_3$) 19.0, 19.1, 19.2, 19.3, 22.7, 23.3, 26.1, 26.6, 29.8, 30.0, 31.2, 32.2, 33.2, 33.4, 37.6, 38.2, 42.7, 42.8, 85.1, 85.3, 112.3, 122.3, 122.9, 123.0, 123.7, 124.0, 126.5, 126.8, 126.9, 127.0, 128.2, 128.3, 128.5, 128.5, 137.0, 137.1, 137.2, 137.4; *m*/*z* (EI$^+$) 374.2254 (1% M$^+$, $C_{26}H_{30}O_2$ requires 374.2246), 268 (29%, M$^+$ − PhCHO), 180 (100%, (PhCH)$_2^+$), 167 (43%).

Comparisons of the following pairs of ^{13}C NMR signals[24] were used to estimate the diastereomeric ratio: 42.8 and 42.7.

(4a*S*,8a*S*)-6,7-Dimethyl-3,4,4a,5,8,8a-hexahydro-2*H*-naphthalen-1-one 16

A mixture of *cis*-decalin acetals **14** and **15** prepared above (80 mg, 0.21 mmol) was heated to reflux in MeOH (10 mL) and

2 M HCl (1 mL) overnight. Extraction into ether followed by aqueous washes and purification by column chromatography (5% EtOAc–petrol) provided *trans*-decalin ketone **16** (30 mg, 79%) as a white solid, mp 59–61 °C; (Found C, 80.73; H, 10.51. $C_{12}H_{18}O$ requires C, 80.84; H, 10.18%); [33% *ee*, $[\alpha]^D = +28.6°$ (*c* 0.19, $CHCl_3$)]; $\nu_{max}(CHCl_3)/cm^{-1}$ 2928–2825 (C–H), 1698 (C=O), 1601 (w); δ_H (400 MHz) 1.40 (1H, apt. qd, *J* 13.2, 3.6, C4-H_{ax}), 1.56 (3H, s, *Me*), 1.59 (3H, s, *Me*), 1.55–1.70 (2H, m), 1.84–2.06 (5H, m), 2.11–2.20 (2H, m), 2.33 (1H, apt. td, *J* 13.5, 5.8, C2-H_{ax}), 2.36 (1H, m, C2-H_{eq}); δ_C (100 MHz) 18.7 (*Me*), 19.0 (*Me*), 26.3 (*C*3), 30.9 (*C*8), 32.5 (*C*4), 40.3 (*C*5), 41.0 (*C*4a), 42.0 (*C*2), 51.2 (*C*8a), 124.1 (q), 124.7 (q), 212.7 (*C*1); *m*/*z* (EI^+) 178.1357 (100%, M^+, $C_{12}H_{18}O$ requires 178.1358), 163 (57%, $M^+ - Me$), 145 (51%), 132 (28%), 119 (43%).

Deprotection of a mixture of **8**–**9** (6.5 : 1, 73% *de*) under analogous conditions gave a sample of **16** [73% *ee*, $[\alpha]^D = 48.5°$ (*c* = 0.10, $CHCl_3$), 95% yield].

2-Methyl-2-cyclohexenone (2*R*,3*R*)-2,3-butanediol acetal 18

A mixture of 2-methyl-2-cyclohexenone (**17**)[24] (3.05 g, 27.7 mmol), (2*R*,3*R*)-2,3-butanediol (2.45 g, 27.2 mmol) and *p*-toluenesulfonic acid (*ca*. 50 mg) in benzene (180 mL) was heated to reflux in Dean–Stark apparatus overnight. To the solution was added $NaHCO_3$ (*ca*. 200 mg), and the mixture was filtered and the volatiles removed *in vacuo*. Purification by column chromatography (base-washed SiO_2, 5% EtOAc–petrol) yielded acetal **18** (4.47 g, 90%) as a clear oil, (Found C, 72.57; H, 10.03. $C_{11}H_{18}O_2$ requires C, 72.49; H, 9.95%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3104, 2994–2936 (C–H), 1601, 1432; δ_H (400 MHz) 1.24 (3H, d, *J* 5.7, *Me*), 1.27 (3H, d, *J* 5.7, *Me*), 1.68 (3H, dd, *J* 3.5, 2.0, C=C*Me*), 1.68–1.85 (4H, m), 1.94–1.99 (2H, m), 3.62 (1H, dq, *J* 8.5, 5.7, OC*H*), 3.66 (1H, dq, *J* 8.5, 5.7, OC*H*), 5.66 (1H, m, C=C*H*); δ_C (100 MHz; $CDCl_3$) 16.1 (*Me*), 16.6 (C=C*Me*), 17.5 (*Me*), 20.9 (*C*5), 25.2 (*C*4), 35.7 (*C*6), 77.7 (*C*H), 79.9 (*C*H), 106.6 (C1), 129.1 (C3), 134.8 (C2); *m*/*z* (EI^+) 182.1307 (4%, M^+, $C_{11}H_{18}O_2$ requires 182.1307), 154 (100%), 127 (24%), 82 (52%).

(4a*S*,8a*R*)-6,7,8a-Trimethyl-3,4,4a,5,8,8a-hexahydro-2*H*-naphthalen-1-one (2*R*,3*R*)-2,3-butanediol acetal 19 and (4a*R*,8a*S*)-6,7,8a-trimethyl-3,4,4a,5,8,8a-hexahydro-2*H*-naphthalen-1-one (2*R*,3*R*)-2,3-butanediol acetal 20

The acid catalysed reaction between 2-methyl-2-cyclohexenone (2*R*,3*R*)-2,3-butanediol acetal (**18**) and **7**, according to the general procedure, gave a mixture of *cis*-decalins **19** and **20**, which were not fully separable by chromatography. A pure sample of **19** could be isolated by chromatography (gradient elution 0–2% EtOAc–petrol).

Major diastereomer **19**; (Found C, 77.37; H, 10.80. $C_{17}H_{28}O_2$ requires C, 77.21; H, 10.68%); $\nu_{max}(CHCl_3)/cm^{-1}$ 2867 (C–H), 1456; δ_H (400 MHz) 0.89 (3H, s, C8a*Me*), 1.17–1.29 (2H, m, C4-H_2), 1.22 (3H, d, *J* 6.0, OCH*Me*), 1.26 (3H, d, *J* 6.0, OCH*Me*), 1.52–1.68 (6H, m), 1.59 (6H, s, C*Me*=C*Me*), 1.80 (1H, td, *J* 14.9, 5.5, C2-H_{ax}), 2.16 (1H, br d, *J* 18.0, C5-H_{eq}), 2.26 (1H, br d, *J* 16.0, C8-H_{eq}), 3.57 (1H, dq, *J* 8.6, 6.0, OC*H*), 3.71 (1H, dq, *J* 8.6, 6.0, OC*H*); δ_C (100 MHz) 16.3 (CH*Me*), 18.2 (CH*Me*), 18.3 (C8a*Me*), 19.1 (*Me*), 19.3 (*Me*), 22.6 (*C*3), 28.7 (*C*4), 32.7 (*C*2), 35.9 (*C*5), 36.0 (*C*8), 38.1 (*C*4a), 41.3 (*C*-8a), 77.8 (O*C*H), 79.4 (O*C*H), 112.0 (*C*1), 122.1 (q), 122.1 (q); *m*/*z* (EI^+) 264.2089 (100%, M^+, $C_{17}H_{28}O_2$ requires 264.2089), 175 (92%), 121 (66%).

A pure sample of minor diastereomer **20** could not be obtained. δ_C (100 MHz) was determined by subtracting the signals from major diastereomer from an authentic 1 : 1 mixture of diastereomers: 16.2, 18.2, 18.7, 19.1, 19.3, 23.1, 28.2, 31.9, 35.8, 36.4, 37.9, 41.3, 77.4, 79.7, 112.3, 122.1, 122.3.

Comparisons of the following pairs of ^{13}C NMR signals[24] were used to determine the diastereomeric ratio: 112.0 and 112.3; 79.7 and 79.4; 38.1 and 37.9; 32.7 and 31.9; 28.7 and 28.2; 22.6 and 23.1.

(4a*S*,8a*R*)-6,7,8a-Trimethyl-3,4,4a,5,8,8a-hexahydro-2*H*-naphthalen-1-one 21

A mixture of acetal **19** (790 mg, 3.0 mmol) in MeOH (30 mL) and 2 M HCl (3 mL) was heated to reflux for 4 h. An ethereal extraction and purification by column chromatography (5% EtOAc–petrol) provided ketone **21** (418 mg, 73%) as a clear oil, the spectroscopic data of which were identical to racemic data in the literature.[36] $[\alpha]^D = -86.5°$ (*c* 1.19, $CHCl_3$).

(1*S*,4a*S*,8a*S*)-6,7,8a-Trimethyl-1,2,3,4,4a,5,8,8a-octahydronaphthalen-1-ol

A solution of ketone **21** (418 mg, 2.17 mmol) in THF (5 mL) was added dropwise to a cooled (0 °C) suspension of $NaBH_4$ (250 mg, 6.5 mmol) in THF (15 mL). The mixture was allowed to warm slowly to rt and stirred for 96 h. The reaction was poured into sat. aq. $NaHCO_3$ soln. (50 mL) and extracted into ether (3 × 50 mL). The combined organics were dried ($MgSO_4$) and the volatiles were removed *in vacuo*. Purification by column chromatography (10% EtOAc–petrol) yielded the alcohol (294 mg, 70%) as a clear oil. $[\alpha]^D = -9.7°$ (*c* 1.49, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3615 (O–H), 2928, 2860 (C–H), 1601; δ_H (400 MHz) 1.00 (3H, d, *J* 0.6, C8a*Me*), 1.18–1.76 (16H, m), 2.14 (1H, br d, *J* 17.1), 2.33 (1H, br d, *J* 17.5), 3.30 (1H, dd, *J* 11.2, 4.6, C1*H*); δ_C (100 MHz; $CDCl_3$) 19.1 (*Me*), 19.4 (*Me*), 23.6 (C8a*Me*), 24.0 (*C*H_2), 28.8 (*C*H_2), 30.6 (*C*H_2), 32.4 (*C*H_2), 35.7 (*C*H_2), 37.8 (*C*8a), 40.0 (*C*4a), 78.2 (*C*1), 121.7 (q), 122.2 (q); *m*/*z* (EI^+) 194.16704 (27%, M^+, $C_{13}H_{22}O$ requires 194.16707), 176 (72%, $(M - H_2O)^+$), 119 (100%).

Camphanic acid (1*S*,4a*S*,8a*S*)-6,7,8a-trimethyl-1,2,3,4,4a,5,8,8a-octahydronaphthalen-1-yl ester 22

To a cooled (0 °C) solution of camphanic chloride (130 mg, 0.60 mmol) and DMAP (trace) in CH_2Cl_2 (1 mL) was added a solution of the alcohol prepared above (98 mg, 0.50 mmol) in CH_2Cl_2 (1 mL) and the mixture was stirred at rt for 24 h and then heated to reflux for a further 72 h. The volatiles were removed *in vacuo* and the crude material was purified by column chromatography (10% EtOAc–petrol) to yield **22** as a clear oil (160 mg, 86%), which solidified upon standing. Recrystallisation from petrol provided colourless needles, mp 102–104 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 2980–2850, 1784, 1723; δ_H (500 MHz; $CDCl_3$) 0.92 (3H, s, C8a*Me*), 0.98 (3H, s, camphanic *Me*), 1.08 (3H, s, camphanic *Me*), 1.13 (3H, s, camphanic *Me*), 1.24–1.84 (16H, m), 1.92 (1H, ddd, *J* 13.1, 10.9, 4.5), 2.03 (1H, ddd, *J* 12.5, 9.4, 4.5), 2.28 (1H, br d, *J* 18.3), 2.33 (1H, br d, *J* 16.9), 2.43 (1H, ddd, *J* 13.3, 10.9, 4.2), 4.74 (1H, dd, *J* 11.4, 4.8, C1*H*); δ_C (125 MHz) 9.8 (camphanic *Me*), 16.9 (camphanic *Me*), 17.0 (camphanic *Me*), 19.1 (*Me*), 19.4 (*Me*), 23.6 (*C*H_2), 23.7 (C8a*Me*), 27.2 (*C*H_2), 28.4 (*C*H_2), 29.0 (*C*H_2), 30.7 (*C*H_2), 33.1 (*C*H_2), 35.5 (*C*H_2), 36.9 (*C*8a), 40.0 (*C*4a), 54.1 (q), 54.9 (q), 82.1 (*C*1), 91.5 (q), 121.5 (q), 122.1 (q), 167.3 (ester C=O), 178.6 (lactone C=O); *m*/*z* (CI^+) 374.2468 (42%, M^+, $C_{23}H_{34}O_4$ requires 374.2457), 177 (100%).

Crystal structure determination of compound 22

Crystal data. $C_{16}H_{26}O_3$, *M* = 266.37, orthorhombic, *a* = 5.9429(10), *b* = 12.548(2), *c* = 20.128(4) Å, *U* = 1500.9(8) Å^3, *T* = 150(2) K, space group: $P2_1\,2_1\,2_1$, *Z* = 4, μ = 0.079 mm^{-1}, 3413 reflections measured, 2110 unique (R_{int} = 0.040) which were used in all calculations. The final $wR(F^2)$ was 0.0876 (all data).

(4a*S*,8a*R*)-6,8a-Dimethyl-3,4,4a,5,8,8a-hexahydro-2*H*-naphthalen-1-one (2*R*,3*R*)-2,3-butanediol acetal

The $TiCl_4$ catalysed reaction between **18** and 2-methyl-1,3-butadiene (entry 2, Table 3), according to the general procedure, gave (4a*S*,8a*R*)-6,8a-dimethyl-3,4,4a,5,8,8a-hexahydro-2*H*-naphthalen-1-one (2*R*,3*R*)-2,3-butanediol acetal as the major

diastereoisomer (by analogy with **19**). ν_{max}($CHCl_3$)/cm^{-1} 3054–2855 (C–H), 1433; δ_H (400 MHz) 1.16–1.30 (2H, m, C4-H_2), 1.21 (3H, d, *J* 6.0, CH*Me*), 1.24 (3H, d, *J* 6.0, CH*Me*), 1.47–1.83 (10H, m), 2.15–2.25 (2H, m), 3.50–3.72 (2H, m), 5.23 (1H, m, C=C*H*); δ_C (100 MHz; $CDCl_3$) 16.3 (*Me*), 18.1 (*Me*), 18.2 (*Me*), 22.6 (*C*3), 23.8 (C8a*Me*), 28.7 (*C*4), 29.8 (CH_2), 32.7 (CH_2), 34.2 (CH_2), 37.9 (*C*4a), 40.3 (*C*8a), 77.7 (OC*H*), 79.5 (OC*H*), 112.1 (*C*1), 118.0 (*C*7), 130.5 (*C*6); *m*/*z* (EI^+) 250.1939 (100%, M^+, $C_{16}H_{26}O_2$ requires 250.1933), 161 (67%), 127 (58%), 107 (46%).

An impurity, assumed to be (4a*R*,8a*S*)-6,8a-dimethyl-3,4,4a,5,8,8a-hexahydro-2*H*-naphthalen-1-one (2*R*,3*R*)-2,3-butanediol acetal, had characteristic signals in the ^{13}C NMR at δ_C (100 MHz; $CDCl_3$) 28.3, 30.3, 34.0, 37.7, 77.5, 79.7, 112.4, 118.2.

(4a*R*,8a*S*)-8a-Methylhexahydronaphthalene-1,6-dione 26

The $TiCl_4$ catalysed reaction between **18** and 2-(trimethylsilyloxy)-1,3-butadiene[26] (**24**) (entry 10, Table 3) yielded a mixture of starting materials and products (~40% by ^1H NMR). The diastereomeric ratio was estimated by comparison of characteristic peaks in the ^1H NMR spectra δ_H(400 MHz) 0.91 (9/5 H, s), 0.92 (6/5 H, s) and the ^{13}C NMR spectra. The following pairs of signals were observed in a ~3 : 2 ratio:[24] δ_C(100 MHz) 101.8 and 101.7; 112.2 and 112.0; 147.6 and 147.6.

The crude mixture was directly hydrolysed in a warmed (50 °C, 1 h) solution of MeOH (3 mL) and 2 M HCl (2 mL) to provide diketone **26** (36 mg, 20%) after standard work-up and column chromatography (25% EtOAc–petrol) as a white solid, mp 63–65 °C (lit. mp[28] 50–51 °C). $[a]^D$ = 2.0° (*c* 1.57, C_6H_6), lit.[28] $[a]^D$ = 12° (*c* 1.5, C_6H_6).

(4a*S*,5*R*,8a*R*)-5,8a-Dimethylhexahydronaphthalene-1,6-dione 1-((2*R*,3*R*)-2,3-butanediol) acetal 31, (4a*R*,5*S*,8a*S*)-5,8a-dimethylhexahydronaphthalene-1,6-dione 1-((2*R*,3*R*)-2,3-butanediol) acetal 32, (4a*S*,5*S*,8a*R*)-5,8a-dimethylhexahydronaphthalene-1,6-dione 1-((2*R*,3*R*)-2,3-butanediol) acetal 33

The Diels–Alder reactions were performed according to the general procedure. The crude products from the Diels–Alder reactions were treated with tetrabutylammonium fluoride (1 M in THF, 1 equiv.) and stirred for 5 min. The volatiles were removed *in vacuo,* and purification by column chromatography (5% EtOAc–petrol) yielded mixtures of diastereomers which were only partially separable by chromatography. Pure major isomer could be isolated in 74% yield.

Major diastereomer **31** recrystallised from petrol to give colourless needles mp 71–73 °C; (Found C, 72.14; H, 9.86. $C_{16}H_{26}O_3$ requires C, 72.14; H, 9.84%); ν_{max}($CHCl_3$)/cm^{-1} 2980–2872 (C–H), 1704 (C=O); δ_H(400 MHz; $CDCl_3$) 0.84, (1H, ap qd, *J* 13.4, 4.0, C4-H_{ax}), 0.95 (3H, d, *J* 6.7, C5-*Me*), 1.23 (3H, d, *J* 5.8, OCH*Me*), 1.26 (3H, d, *J* 5.8, OCH*Me*), 1.29 (3H, s, C8a-*Me*), 1.43–1.72 (5H, m), 1.76 (1H, dd, *J* 13.6, 7.3, C8-H_{eq}), 1.98 (1H, br d, *J* 13.4, C4a-*H*), 2.08 (1H, ap td, *J* 13.6, 5.3, C8-H_{ax}), 2.25 (1H, ddd, *J* 14.6, 5.3, 1.6, C7-H_{eq}), 2.43 (1H, ap td, *J* 14.5, 7.3, C7-H_{ax}), 2.86 (1H, ap qu, *J* 6.7, C5-*H*), 3.62 (1H, dq, *J* 8.6, 6.0, OC*H*), 3.68 (1H, dq, *J* 8.6, 6.0, OC*H*); δ_C(100 MHz; $CDCl_3$) 12.0 (C5-*Me*), 16.3 (*Me*), 17.1 (*Me*), 18.2 (*Me*), 22.1 (CH_2), 22.3 (CH_2), 29.2 (*C*8), 31.9 (*C*2), 37.9 (*C*7), 42.7 (*C*8*a*), 44.0 (*C*5), 49.4 (*C*4*a*), 78.0 (O*CH*), 79.8 (O*CH*), 111.6 (*C*1), 213.7 (*C*6); *m*/*z* (EI^+) 266.1887 (13%, M^+, $C_{16}H_{26}O_3$ requires 266.1882), 237 (33%), 140 (45%), 127 (100%).

Crystal structure determination of compound 31

Crystal data. $C_{23}H_{34}O_4$, *M* = 374.50, orthorhombic, *a* = 6.1489(9), *b* = 14.787(2), *c* = 23.008(3) Å, *U* = 2092.0(5) $Å^3$, *T* = 120(2) K, space group: $P2_1\,2_1\,2_1$, *Z* = 4, μ = 0.079 mm^{-1}, 9146 reflections measured, 2361 unique (R_{int} = 0.136) which were used in all calculations. The final $wR(F^2)$ was 0.1767 (all data).

Minor diastereomer. 32: ν_{max}($CHCl_3$)/cm^{-1} 2960–2871 (C–H), 1704 (C=O); δ_H(400 MHz; $CDCl_3$) 0.83 (1H, ap qd, *J* 13.4, 4.1, C4-H_{ax}), 0.95 (3H, d, *J* 6.7, C5-*Me*), 1.22 (3H, d, *J* 6.0, OCH*Me*), 1.26 (3H, d, *J* 5.8, OCH*Me*), 1.29 (3H, s, C8a-*Me*), 1.43–1.83 (6H, m), 1.97 (1H, br d, *J* 13.0, C4a-*H*), 2.16 (1H, ap td, *J* 13.6, 5.4, C8-H_{ax}), 2.27 (1H, ddd, *J* 14.6, 5.4, 1.7, C7-H_{eq}), 2.44 (1H, ap td, *J* 13.6, 7.3, C7-H_{ax}), 2.86 (1H, ap qu, *J* 6.7, C5-*H*), 3.62 (1H, dq, *J* 8.6, 6.0, OC*H*), 3.68 (1H, dq, *J* 8.6, 6.0, OC*H*); δ_C(100 MHz; $CDCl_3$) 12.0 (C5-*Me*), 16.2 (*Me*), 17.5 (*Me*), 18.3 (*Me*), 22.0 (CH_2), 22.7 (CH_2), 29.6 (*C*8), 31.2 (*C*2), 38.0 (*C*7), 42.7 (*C*8*a*), 43.8 (*C*5), 48.9 (*C*4*a*), 77.8 (O*CH*), 80.0 (O*CH*), 111.9 (*C*1), 213.8 (*C*6); *m*/*z* (EI^+) 266.1874 (51%, M^+, $C_{16}H_{26}O_3$ requires 266.1882), 237 (67%), 140 (80%), 127 (93%), 114 (100%).

The third diastereomer **33** was not separable from **31**, but contained peaks in the ^{13}C NMR spectra at δ_C 112.7, 79.2, 78.0, 50.5, 43.8, 32.7 and 17.5.

De-acetalisation of 31

A pure sample of **31** (25 mg, 0.09 mmol) was hydrolysed in a warmed (50 °C, 16 h) solution of MeOH (4 mL) and 2 M HCl (2 mL) to provide a *ca.* 2 : 1 mixture of diketones **34** and **35** (18 mg, 99%) after standard work-up. The spectroscopic data were in accord with the literature.[30] A pure sample of **34** (5.2 mg) was obtained by chromatography (20% EtOAc–pet) mp 100–102 °C; $[a]^D$ = +43.0° (*c* 0.52, $CHCl_3$).

De-acetalisation of 31–32 (1 : 1) as above.

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