Synthesis and characterisation of optically active spiro[4.5]decanes

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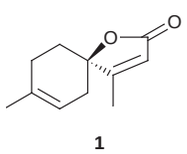
The synthesis of spiro[4.5]decanes through a Diels–Alder cycloaddition between 5-methylenefuran-2(5*H*)-one (protoanemonin) **8**, and chiral dienes 1-[(−)-menthyloxy]-3-trimethylsilyloxybuta-1,3-diene, **5**, 1-[(−)-bornyloxy]-3-trimethylsilyloxybuta-1,3-diene, **6**, and 1-[(+)-isopinocampheyloxy]-3-trimethylsilyloxybuta-1,3-diene, **7**, is reported for the first time. Diastereofacial selectivity together with the preference for an *endo*/*exo* attack are examined. The effect on the diastereofacial selectivity of substituting dienophile **8** by 3-acetoxy-5-methylenefuran-2(5*H*)-one **18** is also discussed. The use of Lewis acids as catalysts to enhance selectivity has been attempted without success.

Introduction

The spiro[4.5]decane ring system is widespread in nature and occurs in many interesting biologically active molecules. Some of them are optically active, such as andirolactone **1**, a spirolactone with biological activity from *Cedrus libanotica* used in folk medicine as a component of cedar wood.[1] Other examples like the acorane sesquiterpene **2** identified in *Rosa rugosa*,[2] and the novel dimeric spiroterpenoids **3** isolated from the Panamanian liverwort *Plagiochila moritziana*[3] also show interesting properties.



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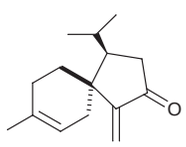

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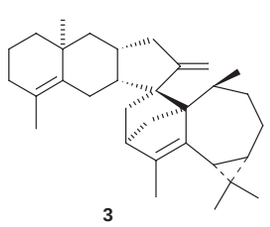

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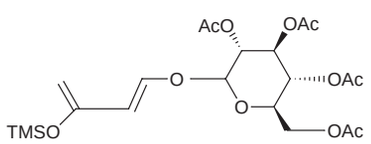
The synthesis of spiro[4.5]decanes is quite accessible through a Diels–Alder reaction between 5-methylenefuran-2(5*H*)-one (protoanemonin) **8**, and classical acyclic and cyclic dienes. This is the case for the synthesis of (±)-andirolactone[4] **1**, which has been synthesised by our group from protoanemonin **8** and isoprene.

Also in a recent publication,[5] we have reported the synthesis of other new polyfunctional 1-oxaspiro[4.5]decanes using this methodology, along with preliminary work towards the synthesis of optically active derivatives.

Most of the studies on asymmetric Diels–Alder reactions published so far have been done using chiral dienophiles[6] rather than chiral dienes.[7] The reactions of dienes bearing optically active auxiliary groups have not been so widely studied as those of dienophiles, and some of the recorded examples are not very efficient. Virtually complete asymmetric induction was observed in the catalysed reaction of juglone with the (*S*)-*O*-methylmandelyl ester of 1-hydroxybutadiene, but reaction with acrolein was found to be much less selective.[8] The asymmetric diene **4** containing a tetraacetyl-D-glucose residue as a chiral auxiliary showed high diastereofacial selectivity in the cycloaddition to benzoquinones,[9] and it was used in the key step in a synthesis of (+)-4-dimethoxydaunomycinone.[10] Some interesting results have also been published on cycloaddition reactions between different chiral dienes and benzaldehyde.[11]



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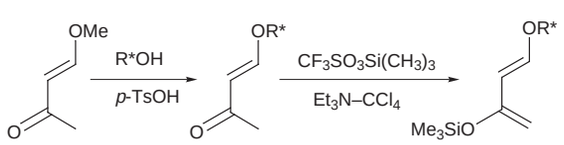
In view of these results, and due to the fact that 3-trimethylsilyloxybuta-1,3-dienes with a chiral auxiliary at the 1-position are relatively easy to synthesise by using Danishefsky's method (Scheme 1), we decided to study the asymmetric version of spiro[4.5]decanes using optically active dienes.



R* = (–)-menthyl, **5**

R* = (–)-bornyl, **6**

R* = (+)-isopinocampheyl, **7**

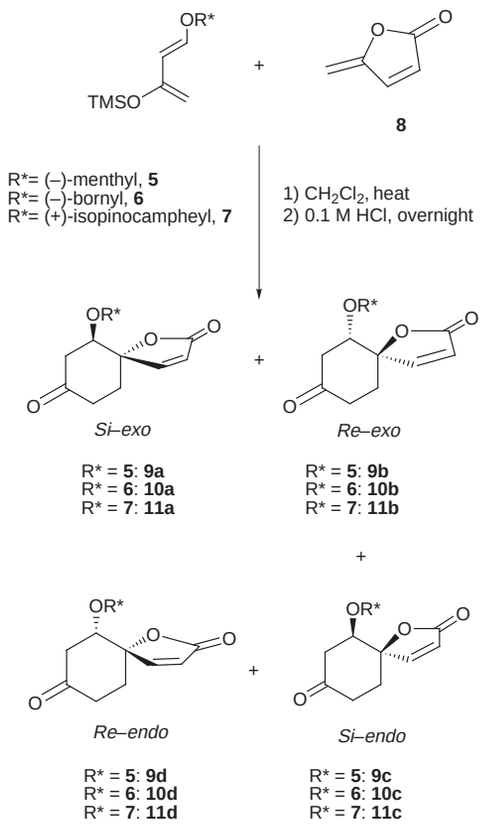
Scheme 1

To this end, we sought to examine the behaviour of dienophile protoanemonin **8**, with chiral dienes 1-[(−)-menthyloxy]-3-trimethylsilyloxybuta-1,3-diene, **5**, 1-[(−)-bornyloxy]-3-trimethylsilyloxybuta-1,3-diene, **6**, and 1-[(+)-isopinocampheyloxy]-3-trimethylsilyloxybuta-1,3-diene, **7** (Scheme 2). Here we report the results of this study.

Results and discussion

Dienophile **8** was synthesised according to a described method,[12] and chiral dienes **5**, **6** and **7** were synthesised according to the general procedure described by Danishefsky[13] starting with 4-methoxybut-3-en-2-one (Scheme 1).

The general procedure for the Diels–Alder reactions was as



Scheme 2

follows. An excess of the chiral diene was made to react with dienophile **8**, by heating the reaction mixture in a sealed tube for 14–18 hours between 120–140 °C in dichloromethane as a solvent. In Table 1 we present only the reaction conditions that led us to the best diastereomeric ratios (see Table 3).

Reaction evolution as well as the diastereomeric ratio of products was followed by capillary gas chromatography (GC). The reaction was quenched when there was no more dienophile left in the reaction mixture. Hydrolysis of the reaction mixture with 0.1 M HCl at room temp. overnight led to four diastereomeric ketones (Scheme 2) plus the unreacted diene as a chiral enone. The ratio of each diastereomeric ketone was again determined by GC (Table 2) and ^{1}H-NMR. The chiral enone and the diastereomeric mixture were physically separated by flash column chromatography (see the Experimental section for details).

The *Si*/*Re* and *endo*/*exo* stereochemistry for the different adducts was assigned according to Scheme 3.

The assignment of the stereochemistry for each set of diastereomeric ketones, was carried out by 400 MHz ^{1}H-NMR through two-dimensional correlations and NOE difference experiments. The results found for the adducts between protoanemonin **8** and chiral dienes show that the menthyl fragment in the adduct always presents the same rigid conformation, but the conformation of the ketone ring largely depends on the relative configuration of its substituents. The substituent arising from protoanemonin always has the olefinic β-carbon in the equatorial position and the lactone oxygen in the axial position (see Fig. 1). In relation to the ketone ring, H-6 can be either axial or equatorial (chemical shift of H-6 in each adduct: **9a** δ = 3.78 ppm, **9b** δ = 3.70 ppm, **9c** δ = 3.80 ppm, **9d** δ = 3.76 ppm). The ^{1}H-NMR spectra of the adducts **9a** and **9b** show a rather small coupling constant between H-6 and H-7′ (**9a**: $^3J_{6,7} = {}^3J_{6,7'} = 2.6$ Hz; **9b**: $^3J_{6,7} = {}^3J_{6,7'} = 3.3$ Hz) indicating an equatorial–axial relationship between H-6 and H-7′ and an equatorial–equatorial relationship between H-6 and H-7. Also there is an observable coupling constant indicating a zig-zag pathway between H-6 and H-10′ for adduct **9a** ($^4J_{6,10'} = 2.6$ Hz) and between H-6 and H-10 for adduct **9b** ($^4J_{6,10} = 2.0$ Hz) corroborating that H-6 in **9a** and **9b** occupies an equatorial position. On the other hand, ^{1}H-NMR spectra of adducts **9c** and **9d** show a rather large coupling constant between H-6 and H-7 (**9c**: $^3J_{6,7} = 10.5$ Hz; **9d**: $^3J_{6,7} = 11.0$ Hz) indicating an axial–axial relationship between these two protons. Thus, the NOE experiments summarised in Fig. 1 have confirmed the conformation of each adduct.

This ^{1}H-NMR study has also been performed for each set of adducts, *i.e.*, for those adducts arising from cycloadditions of dienophile **8** with dienes **6** or **7**. A mixture of adducts has been used in ^{1}H-NMR experiments whenever physical separation was not attained. However, this has not been an obstacle for their total identification.

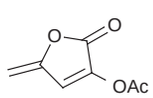
The results on diastereoselectivity for the reaction between protoanemonin **8** and chiral dienes **5**, **6** and **7** are summarised in Tables 3 and 4.

The experimental results show that the highest combined *endo*:*exo* ratio corresponds to entry B in favour of the *exo* attack (Table 4). Entries A and C also give a small preference for the *exo* attack. The fact that the *exo* attack is preferred over the *endo* can be partially justified on the basis of smaller steric repulsions between the OR* group and dienophile **8** for the *exo* attack (see Scheme 3).

Diastereofacial selectivity is good in all three cases studied, favouring the *Si–exo* and the *Re–endo* diastereoisomers. The best selectivity is obtained when the diene carries the bornyl group. It would be quite interesting to explore further this reaction since removal of the auxiliary group from these two main diastereoisomers would lead to the same product, a spiro[4.5]decane with only one stereogenic centre of the same configuration, *i.e.*, to an enantiomerically pure compound (Scheme 4).

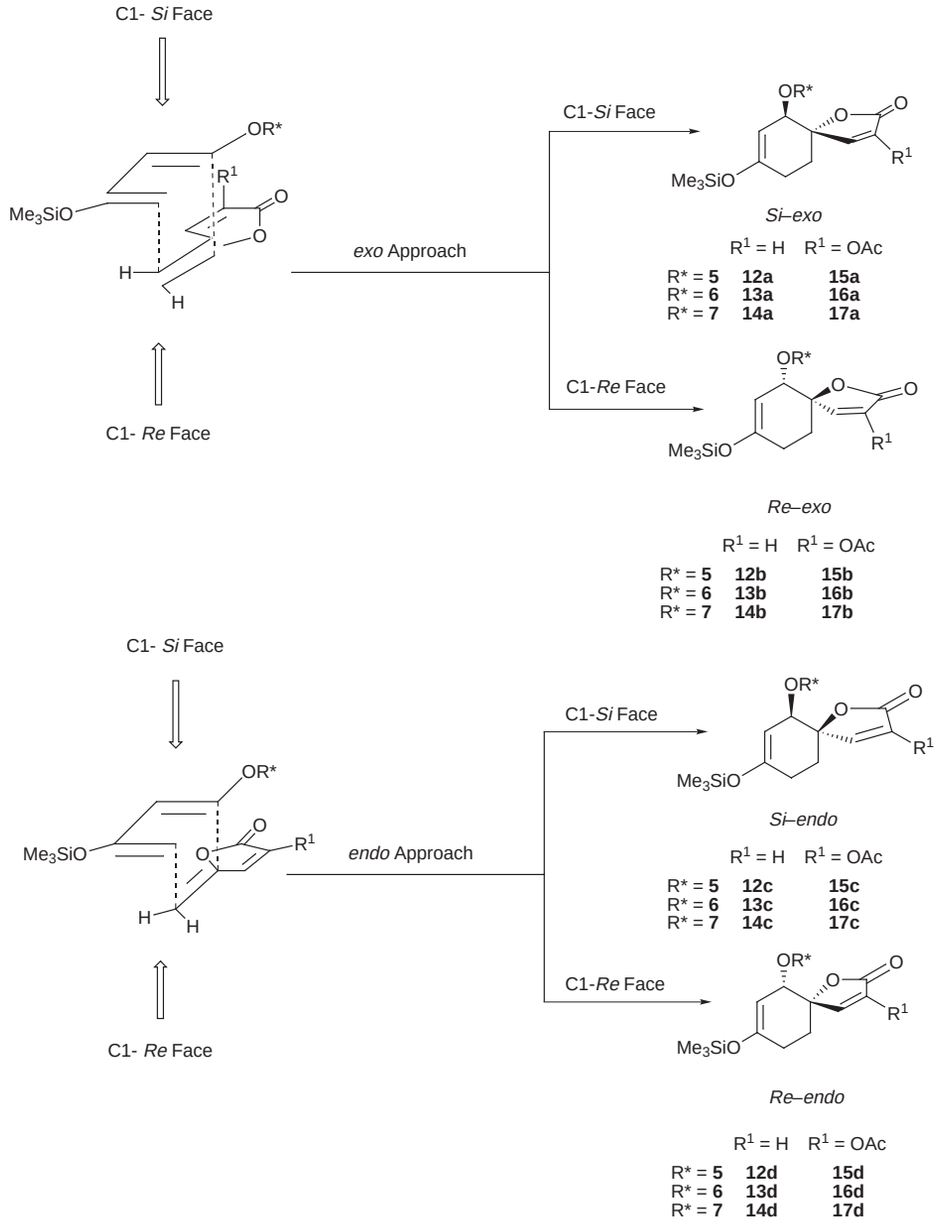
The use of Lewis acids as catalysts to enhance selectivity has been attempted without success. Diethylaluminium chloride (DEAC), boron trifluoride (BF_3) and europium tris-(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyloctane-3,5-dionate) [Eu(fod)$_3$] have been used as catalysts. The cycloaddition of protoanemonin **8** and 1-[(−)-menthyloxy]-3-trimethylsilyloxybuta-1,3-diene **5** (1:2 ratio) employing DEAC (0.5 equiv.) in dichloromethane at −78 °C to room temp. for 23 h or employing BF_3 (1.0 equiv.) at the same temperature for 5 days did not increase the diastereoselectivity of the adducts (Tables 5 and 6). The same result was found when 0.05 equiv. of Eu(fod)$_3$ were used in the cycloaddition (see the Experimental section for details).

Seeing that chiral dienes **5**, **6** and **7** favour diastereofacial selectivity, the Diels–Alder reaction was also carried out with 3-acetoxy-5-methylenefuran-2(5*H*)-one, **18**, a dienophile analogous to compound **8** but with an acetoxy group α to the carbonyl position, in order to check whether the use of a bulkier substituent increases the diastereofacial selectivity.



18

Dienophile **18** was synthesised according to a described method.[14] The general procedure for the Diels–Alder reaction was as follows. An excess of the chiral diene was made to react with dienophile **18**, by heating the reaction mixture in a sealed tube for 12–18 hours between 110–140 °C in dichloromethane as a solvent. Reaction evolution as well as the diastereomeric ratio of products was followed by GC. The reaction was quenched when there was no more dienophile left in the reaction mixture. In Table 7 we present only the reaction conditions that led us to the best diastereomeric ratios (see Table 9). Hydrolysis of the reaction mixture with 0.1 M HCl at room



Scheme 3

Table 1 Reaction conditions for the Diels–Alder reaction between dienophile **8** and chiral dienes **5**, **6** and **7** that led to the best diastereomeric ratio

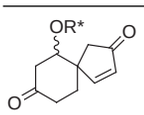
Entry	Diene	*T*/°C	*t*/h	Molar ratio[a]	Yield (%)
A	**5**	120	14	2:1	61
B	**6**	140	18	2:1	36
C	**7**	140	18	2:1	34

[a] Diene : dienophile.

temp. overnight led to four diastereomeric ketones (Scheme 5) plus the unreacted diene as a chiral enone. The ratio of each diastereomeric ketone was again determined by GC (Table 8) and ^{1}H-NMR. The chiral enone and the diastereomeric mixture were physically separated by flash column chromatography (see Experimental section for details).

The assignment of the stereochemistry (Scheme 3) for each set of diastereomeric ketones was done by 400 MHz ^{1}H-NMR through two-dimensional correlations and NOE difference experiments. The results obtained are summarised in Tables 9 and 10. These results show that there is a preference for the *exo vs. endo* attack though the difference is not as noticeable as it

Table 2 Gas chromatography retention times (t_r) for each Diels–Alder adduct (protoanemonin **8** as the dienophile)[a]



	t_r/min			
	(*S*,*R*) *Si–exo*	(*R*,*R*) *Si–endo*	(*R*,*S*) *Re–exo*	(*S*,*S*) *Re–endo*
	(**9a**)	(**9c**)	(**9b**)	(**9d**)
R* = (−)-Menthyl	14.1	14.3	15.3	15.4
	(**10a**)	(**10c**)	(**10b**)	(**10d**)
R* = (−)-Bornyl	14.8	14.9	16.1	16.3
	(**11a**)	(**11c**)	(**11b**)	(**11d**)
R* = (+)-Isopinocampheyl	14.3	14.4	15.4	15.5

[a] Gas chromatography analyses were performed on a Hewlett-Packard model 5890A instrument, using a capillary column Supelco: "cross-linked" 5% phenyl methyl silicone (25 m × 0.2 mm × 0.33 μm), and the conditions: T_{inj} 210 °C, T_{FID} 240 °C, T_1 120 °C, t_1 5 min, rate 5 °C min^{-1}, T_2 240 °C, t_2 30 min.

was for protoanemonin **8**. Diastereofacial selectivity does not differ from that induced by dienophile **8** favouring the *Si–exo* and the *Re–endo* diastereomers.

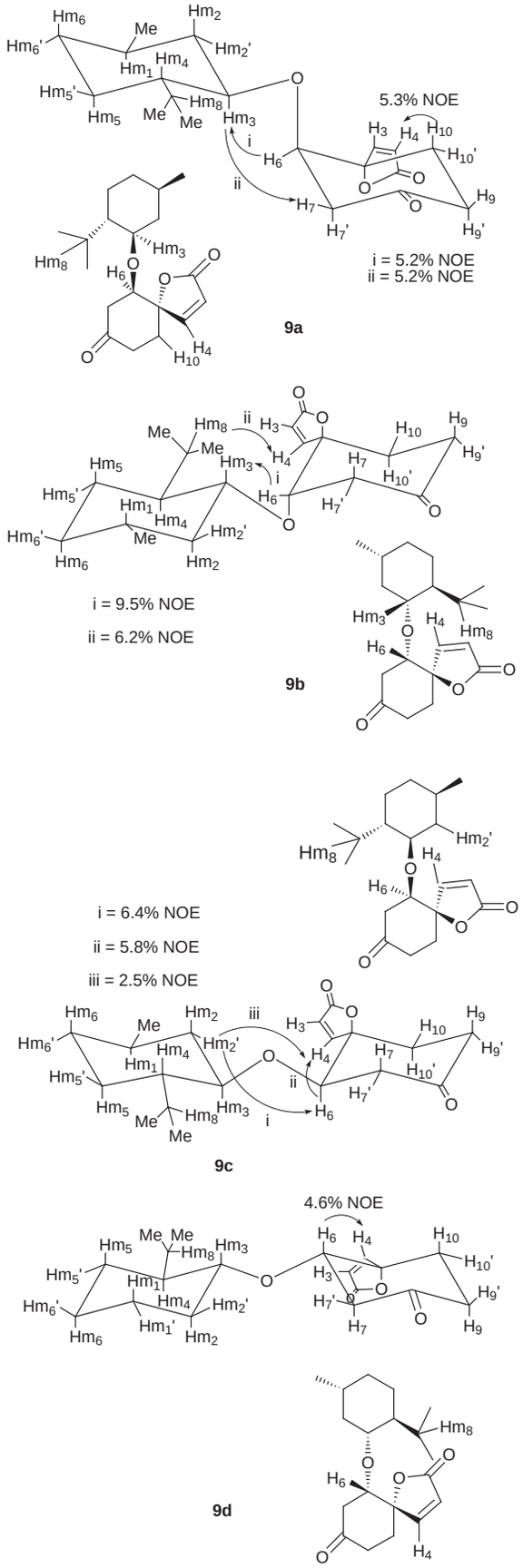


Fig. 1

Conclusions

Asymmetric induction has been observed in the Diels–Alder reaction of protoanemonin **8** with three different chiral dienes. Diastereofacial selectivity has been found to be quite good in all cases (see Table 4). The *Si–exo* and the *Re–endo* diastereomers are the most favoured ones. This is an interesting case to explore further since removal of the auxiliary group from these two main diastereomers leads to the same product, a spiro-[4.5]decane with only one stereogenic centre of the same configuration, *i.e.*, to an enantiomerically pure compound. Substitution of dienophile **8** by dienophile **18** has little effect on the diastereofacial selectivity. The use of Lewis acids as catalysts to enhance selectivity has been attempted without success.

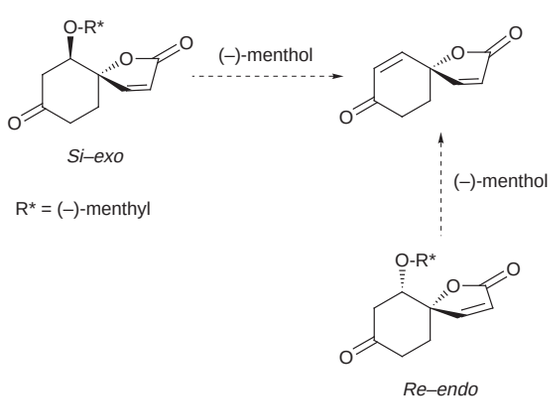
Table 3 Diastereomeric ratios for the different Diels–Alder cycloaddition adducts (protoanemonin **8** as the dienophile)

		Relative yield (%)			
Entry	R*	*Si–exo*	*Re–exo*	*Si–endo*	*Re–endo*
A		(**9a**)	(**9c**)	(**9b**)	(**9d**)
	(−)-Menthyl	42	16	11	31
B		(**10a**)	(**10c**)	(**10b**)	(**10d**)
	(−)-Bornyl	68	4	8	20
C		(**11a**)	(**11c**)	(**11b**)	(**11d**)
	(+)-Isopino-campheyl	47	9	15	29

Table 4 *endo*:*exo* ratios and *endo* and *exo* diastereofacial selectivities (protoanemonin **8** as the dienophile)

Entry	R*	Σ*endo*: Σ*exo*[a]	*exo*(*Si*: *Re*) ds[a]	*endo*(*Si*: *Re*) ds[a]
A	(−)-Menthyl	42:58	72:28	26:74
B	(−)-Bornyl	28:72	95:5	29:71
C	(+)-Isopino-campheyl	44:56	84:16	34:66

[a] Ratios determined by GC and ^{1}H-NMR.



Scheme 4

Experimental

Mps were determined on a hot stage and are uncorrected. Distillation of small amounts of material was effected in a bulb-to-bulb distillation apparatus, with oven temperatures being reported. Electron-impact mass spectra were recorded at 70 eV. All NMR studies were performed at 300 K in a Bruker ARX400 spectrometer. Unambiguous ^{1}H and ^{13}C chemical shift assignments were achieved from 2D-COSY, 2D-HMQC and NOE-1D difference experiments. Chemical shifts in NMR spectra are given in ppm relative to internal TMS (δ scale) and were recorded with a 400 MHz spectrometer. IR spectra were obtained with a Nicolet 5ZDX spectrometer. Gas chromatography analyses were performed on a Hewlett-Packard model 5890A instrument, using a capillary column Supelco: "cross-linked" 5% phenyl methyl silicone (25 m × 0.2 mm × 0.33 μm), and the conditions T_{inj} 210 °C, T_{FID} 240 °C, T_1 120 °C, t_1 5 min,

Table 5 Diastereomeric ratios for the catalysed Diels–Alder cycloaddition of protoanemonin **8** with diene 1-(−)-menthyloxy-3-trimethylsilyloxybuta-1,3-diene **5**

	Relative yield (%)			
Catalyst	*Si–exo* (**9a**)	*Re–exo* (**9c**)	*Si–endo* (**9b**)	*Re–endo* (**9d**)
DEAC	40	15	13	32
BF_3	40	16	12	32
$Eu(fod)_3$	38	15	17	30

Table 6 *endo*:*exo* Ratios and *endo* and *exo* diastereofacial selectivities for the catalysed Diels–Alder cycloaddition between protoanemonin **8** and diene 1-(−)-menthyloxy-3-trimethylsilyloxybuta-1,3-diene **5**

R*	Σ*endo*:Σ*exo*[a]	*exo*(*Si*:*Re*) ds[a]	*endo*(*Si*:*Re*) ds[a]
DEAC	45:55	73:27	29:71
BF_3	44:56	71:29	27:73
$Eu(fod)_3$	47:53	72:28	36:64

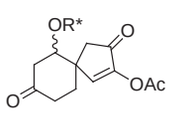
[a] Ratios determined by GC and ^{1}H-NMR.

Table 7 Reaction conditions for the Diels–Alder reaction between dienophile **18** and chiral dienes **5**, **6** and **7** that led to the best diastereomeric ratio

Entry	Diene	*T*/°C	*t*/h	Molar ratio[a]	Yield (%)
D	**5**	120	14	1.5:1	52
E	**6**	110	12	1.5:1	98
F	**7**	140	18	1.5:1	46

[a] Diene:dienophile.

Table 8 Gas chromatography retention times (t_r) for each Diels–Alder adduct (3-acetoxy-5-methylenefuran-2(5*H*)-one **18** as the dienophile)[a]



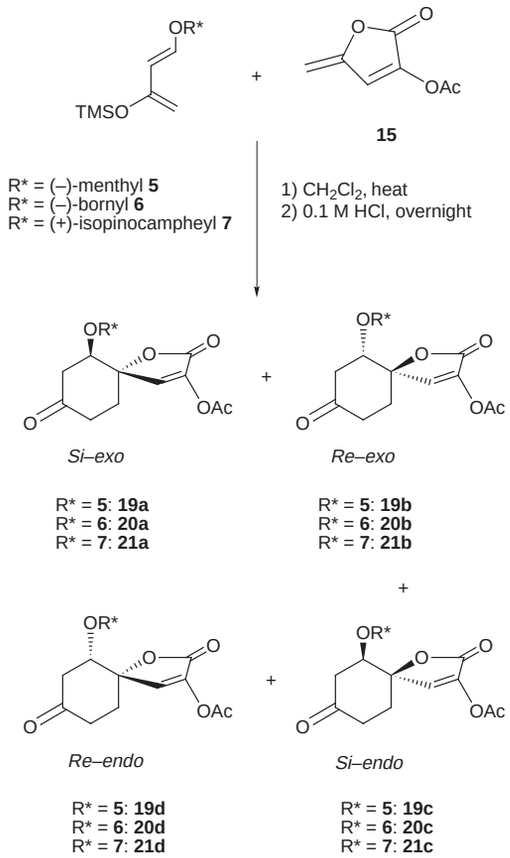
	t_r/min			
	(*S*,*R*) *Si–exo*	(*R*,*R*) *Si–endo*	(*R*,*S*) *Re–exo*	(*S*,*S*) *Re–endo*
	(**19a**)	(**19c**)	(**19b**)	(**19d**)
R* = (−)-Menthyl	22.1	22.3	23.1	24.4
	(**20a**)	(**20c**)	(**20b**)	(**20d**)
R* = (−)-Bornyl	25.7	25.9	27.3	28.3
	(**21a**)	(**21c**)	(**21b**)	(**21d**)
R* = (+)-Isopinocampheyl	19.6	19.8	20.7	20.9

[a] Gas chromatography analyses were performed on a Hewlett-Packard model 5890A instrument, using a capillary column Supelco: "cross-linked" 5% phenyl methyl silicone (25 m × 0.2 mm × 0.33 μm), and the conditions: T_{inj} 210 °C, T_{FID} 240 °C, T_1 120 °C, t_1 5 min, rate 5 °C min^{-1}, T_2 240 °C, t_2 30 min.

rate 5 °C min^{-1}, T_2 240 °C, t_2 30 min (see Tables 2 and 8 for retention times). Unless otherwise noted, all starting materials were either from commercial suppliers and used without further purification or were prepared according to literature procedures (**8**,[12] **5**, **6**, **7**[13] and **18**[15]). Unless otherwise noted, organic extracts were dried over $MgSO_4$ and filtered. Flash column chromatography was carried out under air pressure using SDS silica gel (Type 60, 230–400 mesh). Reactions and chromatography fractions were analysed using precoated Merck silica gel 60 F_{254} TLC plates.

Diels–Alder reactions of dienophiles 8 and 18 with chiral dienes 5, 6 and 7

A solution of dienophile (1 equiv.) and diene (1.4–2 equiv.) in CH_2Cl_2 (0.3 M) was introduced into a sealed tube, and heated in an oil bath (see Tables 1 and 7 for the particular reaction



Scheme 5

Table 9 Diastereomeric ratios for the different Diels–Alder cycloaddition adducts from 3-acetoxy-5-methylenefuran-2(5*H*)-one **18**

		Relative yield (%)			
Entry	R*	*Si–exo*	*Re–exo*	*Si–endo*	*Re–endo*
D		(**19a**)	(**19c**)	(**19b**)	(**19d**)
	(−)-Menthyl	38	14	13	35
E		(**20a**)	(**20c**)	(**20b**)	(**20d**)
	(−)-Bornyl	54	7	11	28
F		(**21a**)	(**21c**)	(**21b**)	(**21d**)
	(+)-Isopinocampheyl	45	6	8	41

Table 10 *endo*:*exo* Ratios and *endo* and *exo* diastereofacial selectivities (3-acetoxy-5-methylenefuran-2(5*H*)-one **18** as the dienophile)

Entry	R*	Σ*endo*:Σ*exo*[a]	*exo*(*Si*:*Re*) ds[a]	*endo*(*Si*:*Re*) ds[a]
D	(−)-Menthyl	48:52	73:27	27:73
E	(−)-Bornyl	39:61	89:11	28:72
F	(+)-Isopinocampheyl	49:51	88:12	16:84

[a] Ratios determined by GC and ^{1}H-NMR.

conditions: molar ratio, temperature and time). Reaction evolution was followed by TLC and diastereomeric ratio of products by GC. The reaction was quenched, when there was no more dienophile left in the reaction mixture, by immersion in a dry ice–acetone bath to afford a crude containing the mixture of adducts and the excess of diene. The crude was diluted to the appropriate volume (1 M) in THF, then 0.1 M HCl (4 equiv.) was added and the resultant solution was stirred at room temperature overnight. The reaction mixture was poured into saturated aqueous sodium bicarbonate and extracted with dichloromethane. The combined extracts were dried and the

solvents were evaporated at reduced pressure. The residue was chromatographed on silica gel eluting with 4 : 1 hexane–ethyl acetate to afford a mixture of four diastereomeric ketones plus the unreacted diene as a chiral enone. The diastereomeric ratio in each mixture was determined by GC and by ^{1}H-NMR spectroscopy. Flash column chromatography (8 : 1 hexane–ethyl acetate) of the mixture of diastereomeric ketones did not lead to complete separation in all cases. The following characterisation data are only for compounds that have been fully isolated.

(5*S*,6*R*)-6-Menthyloxy-1-oxaspiro[4.5]dec-3-ene-2,8-dione 9a. Crystals, mp 113–114 °C; $[a]_D$ −104.5 (c = 2.35, chloroform); IR (KBr) 1775, 1718, 1593 cm^{-1}; MS, *m/e* (%) 182 (80), 164 (52), 138 (23), 97 (24), 83 (100), 55 (62); 400 MHz ^{1}H-NMR ($CDCl_3$) δ 0.6–1 (complex absorption, 10H), 1.1 (m, 1H), 1.3 (m, 1H), 1.63 (m, 4H), 1.85 (m, 2H), 1.99 (m, 1H), 2.39 (m, 1H), 2.52 (dt, J = 14 Hz, J' = 4.9 Hz, 1H), 2.61 (dt, J = 2.6 Hz, J' = 15.25 Hz, 1H), 2.70 (1H), 2.73 (dd, J = 15.25 Hz, J' = 3 Hz, 1H), 3.51 (dt, J = 10.4 Hz, J' = 4.3 Hz, 1H), 3.78 (q, J = 2.6 Hz, 1H), 6.12 (d, J = 5.5 Hz, 1H), 7.62 (d, J = 5.5 Hz, 1H); 100 MHz ^{13}C-NMR ($CDCl_3$) δ 15, 21, 22, 22, 24, 29, 31, 34, 37, 39, 42, 48, 76, 87, 102, 121, 159, 171, 207. Anal. Calcd. for $C_{19}H_{28}O_4$: C, 71.20; H, 8.82. Found: C, 71.15; H, 8.85%.

(5*R*,6*S*)-6-Menthyloxy-1-oxaspiro[4.5]dec-3-ene-2,8-dione 9b. Crystals, mp 142–143 °C; $[a]_D$ +58.62 (c = 1.88 chloroform); IR (KBr) 1775, 1725, 1593 cm^{-1}; MS, *m/e* (%) 182 (80), 138 (21), 123 (7), 97 (20), 83 (100), 55 (53); 400 MHz ^{1}H-NMR ($CDCl_3$) δ 0.5–1.0 (m, 10H), 1.15–1.35 (m, 2H), 1.60 (m, 4H), 1.80 (m, 1H), 1.90 (m, 1H), 2.0 (m, 1H), 2.35–2.75 (complex absorption, 4H), 2.90 (dd, J = 15 Hz, J' = 3 Hz, 1H), 3.07 (dt, J = 10 Hz, J' = 4 Hz, 1H), 3.70 (q, J = 3.3 Hz, 1H), 6.14 (d, J = 5 Hz, 1H), 7.62 (d, J = 5 Hz, 1H); 100 MHz ^{13}C-NMR ($CDCl_3$) δ 15, 21, 22, 22, 25, 29, 31, 34, 37, 42, 45, 48, 80, 80, 87, 121, 158, 171, 207. Anal. Calcd. for $C_{19}H_{28}O_4$: C, 71.20; H, 8.82. Found: C, 71.23; H, 8.85%.

(5*R*,6*R*)-6-Menthyloxy-1-oxaspiro[4.5]dec-3-ene-2,8-dione 9c. Crystals, mp 99–100 °C; $[a]_D$ +12.80 (c = 1.50 chloroform); IR (KBr) 1775, 1725, 1593 cm^{-1}; MS, *m/e* (%) 182 (80), 138 (21), 123 (7), 97 (20), 83 (100), 55 (53); 400 MHz ^{1}H-NMR ($CDCl_3$) δ 0.5–0.9 (m, 10H), 1.05 (m, 1H), 1.25 (complex absorption, 1H), 1.60 (m, 4H), 1.80 (m, 1H), 2.0 (m, 2H), 2.35 (m, 1H), 2.75 (m, 4H), 3.02 (dt, J = 10 Hz, J' = 4 Hz, 1H), 3.80 (dd, J = 10.5 Hz, J' = 5.5 Hz, 1H), 6.12 (d, J = 5.5 Hz, 1H), 7.25 (d, J = 5.5 Hz, 1H); 100 MHz ^{13}C-NMR ($CDCl_3$) δ 15, 21, 22, 22, 24, 29, 31, 34, 37, 39, 42, 48, 75, 76, 87, 121, 159, 171, 207. Anal. Calcd. for $C_{19}H_{28}O_4$: C, 71.20; H, 8.82. Found: C, 71.18; H, 8.85%.

(5*S*,6*S*)-6-Menthyloxy-1-oxaspiro[4.5]dec-3-ene-2,8-dione 9d. Crystals, mp 134–135 °C; $[a]_D$ −73.6 (c = 1.50 chloroform); IR (KBr) 1768, 1743, 1450 cm^{-1}; MS, *m/e* (%) 279 (1), 182 (54), 138 (31), 123 (30), 95 (63), 83 (100), 55 (91); 400 MHz ^{1}H-NMR ($CDCl_3$) δ 0.5–1.0 (m, 10H), 1.15 (m, 1H, H_{m4}), 1.25 (complex absorption, 1H), 1.58 (m, 4H), 1.90–2.05 (complex absorption, 3H), 2.40 (m, 1H), 2.80 (m, 2H), 2.85 (m, 2H), 3.0 (dt, J = 10.4 Hz, J' = 4.0 Hz, 1H), 3.76 (dd, J = 11.0 Hz, J' = 4.9 Hz, 1H), 6.15 (d, J = 5.5 Hz, 1H), 7.35 (d, J = 5.5 Hz, 1H); 100 MHz ^{13}C-NMR ($CDCl_3$) δ 16, 21, 22, 23, 24, 30, 31, 34, 36, 41, 47, 48, 75, 79, 88, 123, 155, 170, 207. Anal. Calcd. for $C_{19}H_{28}O_4$: C, 71.20; H, 8.82. Found: C, 71.21; H, 8.86%.

(5*S*,6*R*)-6-Isopinocampheyloxy-1-oxaspiro[4.5]dec-3-ene-2,8-dione 11a. Oil, 400 MHz ^{1}H-NMR ($CDCl_3$) δ 0.85 (s, 3H), 0.91 (m, 1H), 1.03 (d, J = 7.37 Hz, 3H), 1.18 (s, 3H), 1.50 (ddd, 1H), 1.76 (m, 1H), 1.80 (m, 1H), 1.90 (m, 1H), 1.91 (m, 1H), 2.26 (m, 1H), 2.33 (m, 1H), 2.40 (m, 1H), 2.55 (m, 1H), 2.72 (m, 1H), 2.73 (m, 1H), 2.83 (dd, J = 8 Hz, J' = 2.40 Hz, 1H), 3.71 (q, J = 1.9 Hz, 1H), 3.73 (m, 1H), 6.14 (d, J = 5.7 Hz, 1H), 7.67 (d, J = 5.7 Hz, 1H); 100 MHz ^{13}C-NMR ($CDCl_3$) δ 20, 24, 27, 30, 34, 35, 37, 38, 41, 42, 45, 47, 76, 77, 87, 121, 159, 170, 207.

(5*R*,6*S*)-6-Isopinocampheyloxy-1-oxaspiro[4.5]dec-3-ene-2,8-dione 11b. Oil, 400 MHz ^{1}H-NMR ($CDCl_3$) δ 0.84 (s, 3H), 0.94 (m, 1H), 1.02 (d, J = 6.45 Hz, 3H), 1.23 (s, 3H), 1.72 (m, 1H), 1.74 (m, 1H), 1.83 (m, 1H), 1.87 (m, 1H), 1.91 (m, 1H), 2.29 (m, 1H), 2.39 (m, 1H), 2.40 (m, 1H), 2.54 (m, 1H), 2.70 (m, 1H), 2.88 (dd, J = 7.89 Hz, J' = 2.37 Hz, 1H), 3.70 (m, 1H), 3.74 (q, J = 1.8 Hz, 1H), 6.14 (d, J = 5.6 Hz, 1H), 7.65 (d, J = 5.6 Hz, 1H); 100 MHz ^{13}C-NMR ($CDCl_3$) δ 21, 24, 27, 30, 33, 37, 38, 39, 41, 43, 45, 48, 79, 80, 87, 121, 171, 159, 207.

(5*S*,6*R*)-3-Acetoxy-6-[(−)-menthyloxy]-1-oxaspiro[4.5]dec-3-ene-2,8-dione 19a. Oil, IR (film) 1785, 1724, 1450, 1188 cm^{-1}; MS, *m/e* (%) 240 (19), 198 (32), 83 (100), 81 (23), 69 (54), 57 (39), 55 (82); 400 MHz ^{1}H-NMR ($CDCl_3$) δ 0.68 (q, J = 11.6 Hz, 1H), 0.70 (d, J = 6.90 Hz, 3H), 0.77 (m, 1H), 0.82 (d, J = 7.16 Hz, 3H), 0.85 (d, J = 6.6 Hz, 3H), 0.92 (m, 1H), 1.11 (m, 1H), 1.25 (m, 1H), 1.58 (m, 1H), 1.60 (m, 1H), 1.83 (m, 1H), 1.87 (d, J = 13 Hz, 1H), 1.97 (m, 1H), 2.28 (s, 3H), 2.39 (m, 1H), 2.53 (dt, J = 14.20 Hz, J' = 5.26 Hz, 1H), 2.60 (dt, J = 15.3 Hz, J' = 2.63 Hz, 1H), 2.67 (m, 1H), 2.76 (dd, J = 15.4 Hz, J = 3.18 Hz, 1H), 3.16 (dt, J = 10.35 Hz, J' = 4.24 Hz, 1H), 3.80 (q, J = 1.6 Hz, 1H), 7.36 (s, 1H); 100 MHz ^{13}C-NMR ($CDCl_3$) δ 16, 20, 21, 22, 23, 25, 30, 31, 34, 37, 40, 42, 48, 76, 77, 83, 137, 138, 166, 167, 207. Anal. Calcd. for $C_{21}H_{30}O_6$: C, 66.68; H, 7.99. Found: C, 66.52; H, 8.19%.

(5*R*,6*S*)-3-Acetoxy-6-[(−)-menthyloxy]-1-oxaspiro[4.5]dec-3-ene-2,8-dione 19b. Oil, IR (film) 1787, 1725, 1650, 1187 cm^{-1}; 400 MHz ^{1}H-NMR ($CDCl_3$) δ 0.74 (d, J = 6.9 Hz, 3H), 0.80 (m, 1H), 0.89 (d, J = 6.63 Hz, 3H), 0.87 (m, 1H), 0.88 (d, J = 6.37 Hz, 3H), 0.91 (q, 1H), 1.18 (m, 1H), 1.28 (m, 1H), 1.58 (m, 1H), 1.60 (m, 1H), 1.85 (m, 1H), 1.90 (m, 1H), 2.06 (m, 1H), 2.29 (s, 3H), 2.40 (m, 1H), 2.55 (m, 1H), 2.57 (m, 1H), 2.68 (dt, J = 13.8 Hz, J' = 6.37 Hz, 1H), 2.90 (dd, J = 14.96 Hz, J' = 3.18 Hz, 1H), 3.12 (dt, J = 10.61 Hz, J' = 4.51 Hz, 1H), 3.72 (q, J = 1.59 Hz, 1H), 7.39 (s, 1H); 100 MHz ^{13}C-NMR ($CDCl_3$) δ 16, 20, 21, 22, 23, 25, 30, 31, 34, 37, 42, 45, 49, 76, 80, 84, 136, 137, 166, 167, 207.

(5*R*,6*R*)-3-Acetoxy-6-[(−)-menthyloxy]-1-oxaspiro[4.5]dec-3-ene-2,8-dione 19c. Oil, IR (film) 1775, 1722, 1371, 1198 cm^{-1}; 400 MHz ^{1}H-NMR ($CDCl_3$) δ 0.66 (q, J = 11.92 Hz, 1H), 0.67 (d, J = 7.09 Hz, 3H), 0.75 (m, 1H), 0.81 (d, J = 6.96 Hz, 3H), 0.85 (d, J = 6.56 Hz, 3H), 0.89 (m, 1H), 1.07 (m, 1H), 1.24 (m, 1H), 1.56 (m, 1H), 1.59 (m, 1H), 1.81 (m, 1H), 1.99 (dt, J = 13.15 Hz, J' = 4.73 Hz, 1H), 2.02 (m, 1H), 2.12 (m, 1H), 2.30 (s, 3H), 2.38 (m, 1H), 2.74 (m, 1H), 2.74–2.80 (AB system, 2H), 3.04 (dt, J = 10.44 Hz, J' = 4.28 Hz, 1H), 3.79 (dd, J = 10.03 Hz, J' = 5.75 Hz, 1H), 7.10 (s, 1H); 100 MHz ^{13}C-NMR ($CDCl_3$) δ 16, 20, 21, 22, 23, 25, 31, 32, 34, 37, 40, 44, 48, 73, 77, 84, 134, 138, 166, 167, 207.

(5*S*,6*S*)-3-Acetoxy-6-[(−)-menthyloxy]-1-oxaspiro[4.5]dec-3-ene-2,8-dione 19d. Oil, IR (film) 1778, 1722, 1458, 1194 cm^{-1}; 400 MHz ^{1}H-NMR ($CDCl_3$) δ 0.59 (d, J = 6.9 Hz, 3H), 0.78 (m, 1H), 0.81 (d, J = 6.9 Hz, 3H), 0.81 (q, 1H), 0.84 (m, 1H), 0.86 (d, J = 6.37 Hz, 3H), 1.12 (m, 1H), 1.24 (m, 1H), 1.55 (m, 1H), 1.58 (m, 1H), 1.91 (m, 1H), 1.98 (m, 1H), 2.01 (m, 1H), 2.11 (ddd, J = 14.33 Hz, J' = 6.37 Hz, J'' = 3.71 Hz, 1H), 2.28 (s, 3H), 2.37 (m, 1H), 2.69 (ddd, J = 14.33 Hz, J' = 5.04 Hz, J'' = 1.85 Hz, 1H), 2.76 (m, 1H), 2.84 (dd, J = 13.69 Hz, J' = 10.88 Hz, 1H), 3.05 (dt, J = 10.34 Hz, J' = 4.24 Hz, 1H), 3.74 (dd, J = 10.61 Hz, J' = 4.77 Hz, 1H), 7.10 (s, 1H); 100 MHz ^{13}C-NMR ($CDCl_3$) δ 15, 20, 21, 22, 23, 24, 31, 32, 34, 37, 41, 47, 49, 75, 80, 85, 132, 138, 166, 167, 207.

(5*S*,6*R*)-3-Acetoxy-6-[(+)-isopinocampheyloxy]-1-oxaspiro-[4.5]dec-3-ene-2,8-dione 21a. Oil, IR (film) 1784, 1719, 1373, 1192 cm^{-1}; 400 MHz ^{1}H-NMR ($CDCl_3$) δ 0.86 (m, 3H), 0.93 (m, 1H), 1.04 (m, 3H), 1.18 (m, 3H), 1.57 (m, 1H), 1.76 (m, 1H), 1.87 (m, 1H), 1.91 (m, 1H), 1.92 (m, 1H), 2.26 (m, 1H), 2.30 (s, 3H), 2.34 (m, 1H), 2.41 (m, 1H), 2.72 (m, 1H), 2.73 (m, 1H), 2.84 (m, 1H), 3.73 (m, 1H), 3.77 (m, 1H), 7.41 (s, 1H); 100 MHz ^{13}C-NMR ($CDCl_3$) δ 20, 21, 24, 27, 31, 34, 35, 37, 38, 41, 42, 45, 47, 76, 78, 83, 137, 138, 166, 167, 207.

Diels–Alder reactions of dienophile 8 with chiral diene 5 in the presence of a catalyst

(a) Catalyst: diethylaluminium chloride (DEAC). To a stirred solution of diene **5** (2 equiv.) and protoanemonin **8** (1 equiv.) in anhydrous CH_2Cl_2 (0.3 M) at −78 °C was added 0.5 equiv. of diethylaluminium chloride (1.80 M in toluene). The mixture was stirred for 2 h at −78 °C and then was allowed to warm to ambient temperature. The reaction was monitored by GC and ^{1}H-NMR for the disappearance of the dienophile **8**. After 23 h the reaction was complete. The crude was diluted to the appropriate volume (1 M) in THF, then 0.1 M HCl (4 equiv.) was added and the resultant solution was stirred at room temperature overnight. The reaction mixture was poured into saturated aqueous sodium bicarbonate and extracted with dichloromethane. The combined extracts were dried and the solvents were evaporated at reduced pressure. The residue was chromatographed on silica gel eluting with 4:1 hexane–ethyl acetate to afford a mixture of diastereomeric ketones **9a**, **9b**, **9c**, **9d** plus the unreacted diene as a chiral enone. The diastereomeric ratio mixture was determined by GC and by ^{1}H-NMR spectroscopy and the ketones were characterised as before.

(b) Catalyst: boron trifluoride (BF_3). To a stirred solution of diene **5** (2 equiv.) and protoanemonin **8** (1 equiv.) in anhydrous CH_2Cl_2 (0.3 M) at −78 °C was added 1 equiv. of boron trifluoride (20% in MeOH). The mixture was stirred for 2 h at −78 °C and then was allowed to warm to ambient temperature. The reaction was monitored by GC and ^{1}H-NMR for the disappearance of the dienophile **8**. After 5 days the reaction was complete. The crude was diluted to the appropriate volume (1 M) in THF, then 0.1 M HCl (4 equiv.) was added and the resultant solution was stirred at room temperature overnight. The reaction mixture was poured into saturated aqueous sodium bicarbonate and extracted with dichloromethane. The combined extracts were dried and the solvents were evaporated at reduced pressure. The residue was chromatographed on silica gel eluting with 4:1 hexane–ethyl acetate to afford a mixture of diastereomeric ketones **9a**, **9b**, **9c**, **9d** plus the unreacted diene as a chiral enone. The diastereomeric ratio mixture was determined by GC and by ^{1}H-NMR spectroscopy and the ketones were characterised as before.

(c) Catalyst: europium tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyloctane-3,5-dionate) [Eu(fod)$_3$]. To a solution of diene **5** (2 equiv.) and protoanemonin **8** (1 equiv.) in CH_2Cl_2 (0.3 M) at room temperature was added a catalytic amount of Eu(fod)$_3$ (0.05 equiv.). The reaction was allowed to remain at room temperature and monitored by GC and ^{1}H-NMR for the disappearance of the dienophile **8**. After 20 h the reaction was complete. The crude was diluted to the appropriate volume (1 M) in THF, then 0.1 M HCl (4 equiv.) was added and the resultant solution was stirred at room temperature overnight. The reaction mixture was poured into saturated aqueous sodium bicarbonate and extracted with dichloromethane. The combined extracts were dried and the solvents were evaporated at reduced pressure. The residue was chromatographed on silica gel eluting with 4:1 hexane–ethyl acetate to afford a mixture of diastereomeric ketones **9a**, **9b**, **9c**, **9d** plus the unreacted diene as a chiral enone. The diastereomeric ratio mixture was determined by GC and by ^{1}H-NMR spectroscopy and the ketones were characterised as before.

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Paper 8/05096A