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Selective Lewis Acid Complexation of 2-Hydroxyethyl Esters using Competitive Diels–Alder Reactions as a Mechanistic Probe

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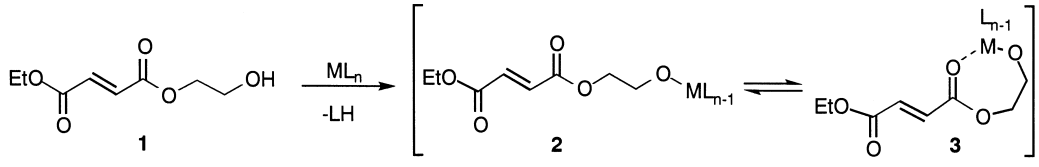
Abstract—Competitive Diels–Alder reactions involving ethyl acrylate, 2-hydroxyethyl acrylate and 2-methoxyethyl acrylate indicate that certain Lewis acids (e.g. $EtAlCl_2$) selectively complex to the 2-hydroxyethyl ester group. Studies using ethyl 2-hydroxyethyl fumarate support these findings. ^{13}C NMR spectroscopy provides some evidence regarding the nature of the interactions between 2-hydroxyethyl esters and $EtAlCl_2$. The influence of $EtAlCl_2$ on the level of diastereocontrol observed in the Diels–Alder reactions of ($2R^*$,$3R^*$)-2-(3-hydroxy)butyl acrylate is described.

As synthetic chemists strive to make increasingly more complex target molecules, the ability to selectively activate one functional group in the presence of other similar chemical functionality is becoming increasingly more important. In pioneering studies, Yamamoto has shown that the highly sterically hindered Lewis acid, methylaluminium bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD), can be used to selectively complex to the least hindered ester carbonyl group of unsymmetrical fumarates (e.g. *tert*-butyl methyl fumarate),[1] as well as other Lewis basic functional groups.[2] Other workers have used small changes in the electronic structure of one of the fumarate carbonyl groups to accomplish selectivity in binding. For example, Brown has shown that complexation to either the ester or the thionoester group of dimethyl monothionofumarate can be accomplished by careful choice of either a hard or soft Lewis acid.[3] Investigations using (*E*)-MeO_2C–CH=CH–COSMe[4] and (*E*)-RCO–CH=CH–COSMe[5] have also been described. In a recent development, it has been demonstrated that (2-pyridyl)methyl esters can be selectively complexed in the presence of benzyl esters using transition metal salts.[6]

We conceived of a simple way to complex and selectively activate 2-hydroxyethyl esters in the presence of other alkyl esters. The concept is illustrated using fumarate **1** in Scheme 1. We envisaged that upon addition of a suitable Lewis acid, a covalent bond between the Lewis acid and fumarate **1** would produce complex **2** as a result of ligand exchange. Subsequent intramolecular complexation of the Lewis acid centre to the carboxyl group would produce chelated complex **3** in which the 2-hydroxyethyl ester has been selectively complexed.[7] These studies were inspired, in part, by the work of Roush et al. who had examined the Lewis acid mediated intramolecular Diels–Alder reactions of highly sensitive triene substrates bearing 2-hydroxyethyl esters.[8] Significantly, we envisaged that products containing 2-hydroxyethyl esters could be chemoselectively cleaved to the corresponding carboxylic acids via the β-haloethyl esters (vide infra).[9]

Results and Discussion

We chose the Diels–Alder reaction as a mechanistic probe for Lewis acid complexation because binding of a Lewis acid to a dienophile is known to dramatically accelerate the rate of the subsequent [4π+2π] cycloaddition reaction.[10] We have performed both intermolecular and



Scheme 1.

Keywords: Diels–Alder reactions; $EtAlCl_2$; ($2R^*$,$3R^*$)-2-(3-hydroxy)butyl acrylate; 2-hydroxyethyl esters; selective Lewis acid complexation.
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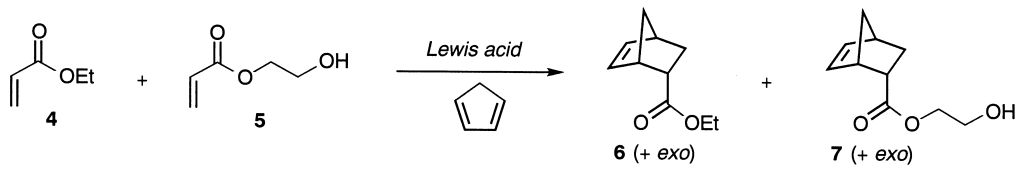
Table 1.



Entry	Reaction conditions[a]	Products (ratio)[b]	Conversion (%)[b]
1	CH_2Cl_2, 0°C	**6**:**7** (50:50)	<1
2	$BF_3.Et_2O$, CH_2Cl_2, 0°C	**6**:**7** (43:57)	14
3	$TiCl_4$, $^iPr_2EtN$, CH_2Cl_2, 0°C	**6**:**7** (19:81)	43
4	$SnCl_4$, $^iPr_2EtN$, CH_2Cl_2, 0°C	**6**:**7** (31:69)	<3
5	$EtAlCl_2$, CH_2Cl_2, 0°C	**6**:**7** (17:83)	10

[a] Reactions performed using 1:1:1 molar ratio of the two acrylates and 1,3-cyclopentadiene.
[b] Determined by GC.

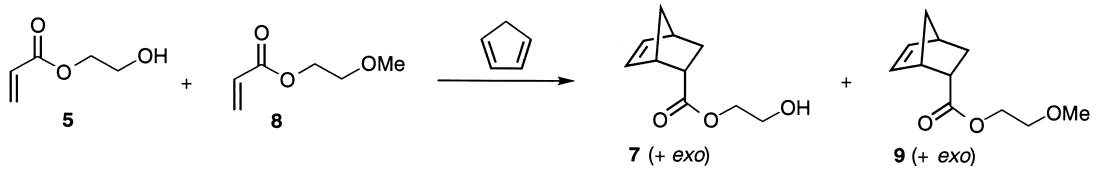
intramolecular competition experiments to ascertain the levels of selectivity that can be accomplished and these studies are described in the following sections.

Intermolecular competition experiments

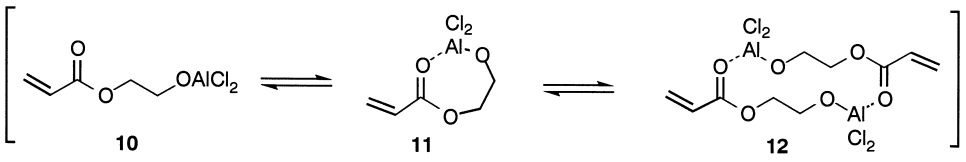
By undertaking intermolecular competition experiments using acrylates bearing different ester groups and analysing the product mixture, we hoped to determine if selective Lewis acid binding to the 2-hydroxyethyl ester group could be achieved. Initial experiments to identify suitable Lewis acids focused on experiments involving ethyl acrylate and 2-hydroxyethyl acrylate, a selection of the results are presented in Table 1. Ethyl aluminium dichloride was found to be the most selective Lewis acid (Entry 5) albeit with only low levels of conversion under these reaction conditions. However, in the absence of ethyl acrylate, 2-hydroxyethyl acrylate **5** can be converted into cycloadduct **7** (*endo*:*exo*; 95:5) in near quantitative yield [$EtAlCl_2$ (1 equiv.), 1,3-cyclopentadiene (3 equiv.) −78°C, 12 h].

To ascertain whether these findings arise from the formation of a genuine complex between the hydroxyl group of the ester and the Lewis acid, and are not simply due to some other electronic effect associated with the β-oxygen substituent, we have undertaken some similar competition experiments between 2-hydroxyethyl acrylate **5** and 2-methoxyethyl acrylate **8** (Scheme 2). While we have observed that cycloadduct **7** is produced as the major product (**7**:**9**; 63:37) even under simple thermal conditions (1,3-cyclopentadiene (1 equiv.), toluene, 110°C), the preference for the formation of this cycloadduct (**7**:**9**; 97:3) is much greater in the presence of ethyl aluminium dichloride (1,3-cyclopentadiene (1 equiv.), CH_2Cl_2, 0°C).

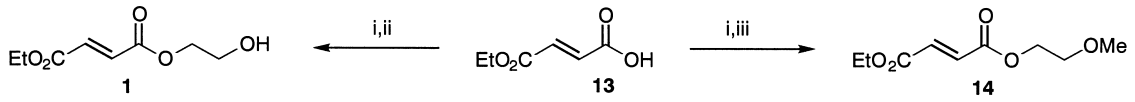
To study the complexation of 2-hydroxyethyl esters by ethyl aluminium dichloride, more directly, we recorded the ^{13}C NMR spectrum of 2-hydroxyethyl acrylate **5** in dideuteriodichloromethane at 25°C. Upon addition of one equivalent of the Lewis acid, significant downfield shifts of the carbonyl group (δ 166.1→171.1, 173.1), one of the olefinics (δ 128.2, 130.6→125.1, 125.8, 140.8, 141.7) and one of the ether carbons atoms (δ 61.0, 66.1→62.9, 63.4, 74.0, 74.7) were observed. These chemical shifts changes are consistent with the formation of a complex such as **11** (Scheme 3). However, to our surprise, two signals in near equal amounts were observed for each carbon atom of the complexed 2-hydroxyethyl ester. This may indicate that we are observing both *s-cis* and *s-trans* conformations of complex **11** on the NMR timescale. Alternatively, we may be observing monomer **11** in equilibrium with a symmetrical dimer



Scheme 2.



Scheme 3.



Scheme 4. Reagents and conditions: (i) $(COCl)_2$, DMF (cat.); (ii) $HOCH_2CH_2OH$, Et_3N, 0°C, DMAP, $CHCl_3$, 69% (from **13**); (iii) $HOCH_2CH_2OMe$, Et_3N, 0°C, DMAP, CH_2Cl_2, 48% (from **13**).

such as **12**. Significantly however, we do not feel that monomeric, non-chelated structure **10** is consistent with the recorded ^{13}C NMR spectrum as no large downfield shift of the carbonyl carbon atom would be expected in this complex.

Intramolecular competition experiments

Using fumarate **1**, we have evaluated the selective complexation of ethyl aluminium dichloride to a 2-hydroxyethyl ester in the presence of an ethyl ester contained within the same molecule. This fumarate was made from commercially available carboxylic acid **13** in 69% yield via the corresponding acid chloride (Scheme 4). In order to evaluate the role of the hydroxyl group within **1**, fumarate **14** containing the corresponding methyl ether was made in an unoptimised 48% yield.

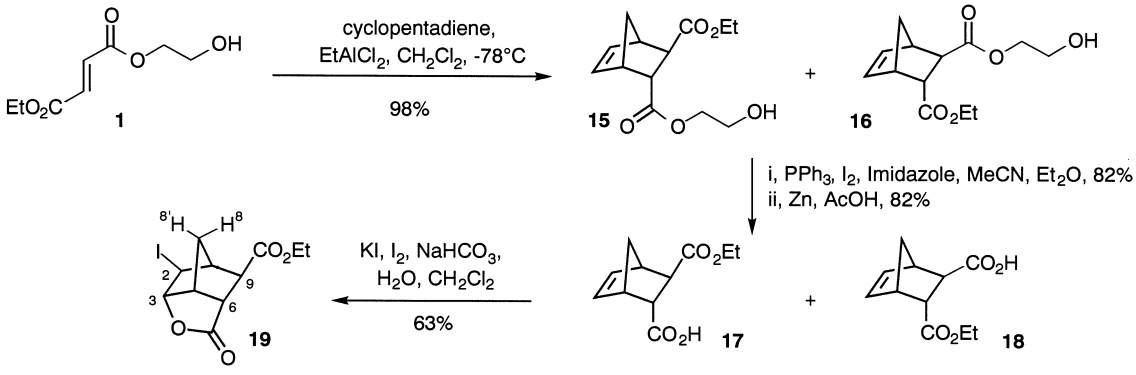
Reaction of fumarate **1** with one equivalent of ethyl aluminium dichloride and 1,3-cyclopentadiene at −78°C overnight furnished cycloadducts **15** and **16** in a 75:25 ratio as judged by ^1H NMR spectroscopy (Scheme 5). In contrast, thermolysis of this fumarate with excess 1,3-cyclopentadiene (110°C, 3 h, 71%) produced essentially equal quantities of these two cycloadducts (51:49 ratio). Unfortunately, cycloadducts **15** and **16** were inseparable by silica gel chromatography, so the relative stereochemistry of the major adduct could not be determined at this point. The mixture was converted into the corresponding monoacids **17** and **18** via the corresponding 2-iodoethyl esters by implementation of a zinc induced β-elimination strategy.[9] Thus, we were able to chemoselectively cleave the 2-hydroxyethyl ester in the presence of a simple ethyl ester group. Subjection of the resulting 72:28 mixture of carboxylic acids **17** and **18** to iodolactonisation conditions resulted in the isolation of a single lactone **19** in 63% yield. In view of relatively high yield, we conclude that this lactone must ultimately be derived from the major cycloadduct.

The structure and relative stereochemistry of lactone **19** were established using a combination of NMR experiments. Assignments were made using HETCOR, COSY and HMQC experiments. Subsequent nOe measurements established the relative stereochemistries within this lactone. Strong enhancements between H-9⟶H-2 (8.3%); H-8⟶H-6 (2.1%); H-8′⟶H-3 (2.1%); H-2⟶H-9 (8.4%) were used in conjunction with other enhancements to confirm the relative spatial disposition of H-2, H-3, H-6 and H-9. Working back from the structure of this lactone, we conclude that the ethyl aluminium dichloride mediated Diels–Alder cycloaddition of fumarate **1** yields diester **15** as the major product. To account for this stereochemical outcome, we suggest selective complexation to the 2-hydroxyethyl ester is occurring such that this ester moiety preferentially adopts the *endo* orientation in the Diels–Alder reaction.[10]

Fumarate **1** was reacted with isoprene under both thermal and ethyl aluminium dichloride mediated conditions. In this case, reasonable levels of regiochemical control were achieved in the presence of one equivalent of the Lewis acid although unfortunately we have not been able to unambiguously determine which regioisomer is predominant (Table 2). Interestingly, when the hydroxyl group of the fumarate was blocked as the corresponding methyl ether (ie **14**) no appreciable regioselectivity was seen.

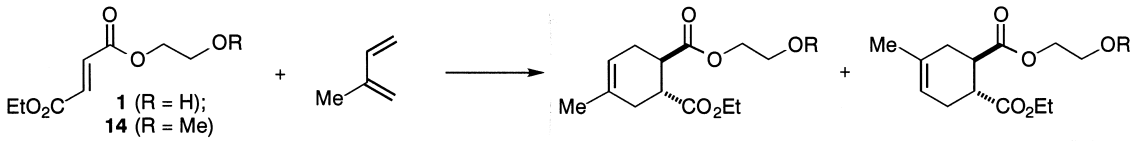
Studies using 2-(3-hydroxy)butyl acrylate

We have briefly examined the possibility of effecting diastereocontrolled Diels–Alder reactions using 2-hydroxyethyl acrylates containing asymmetric centres. Acrylate (2*R**,3*R**)-**20** was made in one step from (2*R**,3*R**)-2,3-dihydroxybutane and acryloyl chloride, albeit in a rather low but unoptimised 21% yield. The major byproduct in this reaction (39% yield) was the corresponding diester of 2,3-dihydroxybutane. Treatment of (2*R**,3*R**)-**20** with 1,3-cyclopentadiene in refluxing toluene yielded cycloadduct **21** as a mixture of all four possible diastereomers (Scheme 6).



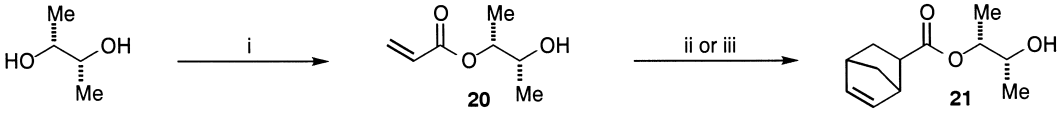
Scheme 5.

Table 2.



Entry	Fumarate	Reaction conditions	Product (ratio)[a]	Yield (%)[b]
1	**1** (R=H)	Toluene, 110°C, 12 h	R=H (52:48)	95
2	**1** (R=H)	$EtAlCl_2$, CH_2Cl_2, 0°C, 12 h	R=H (76:24)	81
3	**14** (R=Me)	Toluene, 110°C, 12 h	R=Me (48:52)	99
4	**14** (R=Me)	$EtAlCl_2$, CH_2Cl_2, 0°C, 12 h	R=Me (52:48)	76

[a] Determined by ^1H NMR analysis.
[b] Yield of isolated material after column chromatography.



Scheme 6. Reagents and conditions: (i) acryloyl chloride, Et_3N, 0°C, CH_2Cl_2, 21%; (ii) toluene, 1,3-cyclopentadiene, 110°C, 99%; (iii) $EtAlCl_2$, 1,3-cyclopentadiene, 0°C, CH_2Cl_2, 82%.

The two *endo* diastereomers were produced as the major products (*endo*:*exo;* 71:29) with a small preference in favour of one of these *endo* diastereomers (ca. 60:40) as determined by ^1H and ^{13}C NMR spectroscopy. Using one equivalent of ethyl aluminium dichloride at 0°C, cycloadduct **21** was produced from acrylate **20** and 1,3-cyclopentadiene in 82% yield with much improved *endo* selectivity (*endo*:*exo*; 9:1). Unfortunately, the two *endo* diastereomers were again produced in near equal quantities (ca. 33:67) indicating that little facial selectivity is being observed in diene addition to Lewis acid complexed acrylate **20**. It is however of interest to note that the major *endo* diastereomer in this cycloaddition was the minor *endo* diastereomer in the thermal reaction.

In conclusion, we have obtained evidence, which indicates that 2-hydroxyethyl esters can be selectively complexed and activated in the presence of other alkyl esters using ethyl aluminium dichloride as the Lewis acid. Furthermore, we have demonstrated that these 2-hydroxyethyl esters can be selectively converted to carboxylic acids via the corresponding β-iodoethyl esters.

Experimental

General

Light petroleum refers to that boiling in the 40–60°C range. Dimethylformamide (DMF) and dichloromethane (DCM) were distilled from CaH_2 under nitrogen, immediately prior to use. Reagents were used as received from commercial sources with the exception of the following; acryloyl chloride which was distilled prior to use; 1,3-cyclopentadiene which was cracked and distilled from $LiAlH_4$ under nitrogen immediately prior to use; triethylamine which was stored over KOH; and diisopropylethylamine which was distilled from CaH_2 and stored over 4 Å molecular sieves. Reactions were performed under an inert atmosphere in oven dried glassware unless otherwise stated. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz on a Bruker ACF-300 instrument, 400 and 100 MHz on a Bruker DRX-400 instrument in *d*-chloroform unless otherwise stated. Chemical shifts are recorded in ppm relative to TMS or residual protic solvent. Mass spectra were recorded on a Kratos Profile HV3 mass spectrometer. Infrared spectra (4000–600 cm^{-1}) were recorded on a Nicolet Magna-550 FT infrared spectrometer using internal calibration, samples were recorded as thin films between sodium chloride plates. Capillary GLC analysis was performed using a Shimadzu GC-14A oven using a BP20 25M column. Injector temperature 150°C, detector temperature 150°C, a ramped oven program was used throughout: 4 min at 70°C then ramped at 10°C/min to 200°C.

Ethyl bicyclo[2.2.1]hept-2-ene-5-carboxylate (6).[11] A solution of ethyl acrylate **4** (0.54 ml, 4.98 mmol) and 1,3-cyclopentadiene (1.2 ml, ca. 14.5 mmol) in toluene (20 ml) was heated under reflux for 3 h and then allowed to cool to room temperature. Removal of the solvent in vacuo and subsequent column chromatography (10% ethyl acetate/90% light petroleum) gave **6** (710 mg, 86%) as a colourless oil and as a 69:31 mixture of *endo*:*exo* isomers as determined by ^1H NMR spectroscopy. ν_{max}/cm^{-1} 2978, 2947, 1733, 1186, 1178; δ_H (300 MHz) 6.18 (0.69H, dd, *J*=5.6, 3.1 Hz), 6.13–6.11 (0.62H, m), 5.92 (0.69H, dd, *J*=5.6, 2.9 Hz), 4.18–4.04 (2H, m), 3.20 (0.69H, br s), 3.03 (0.31 H, br s), 2.96–2.90 (1.69H, m), 2.21 (0.31H, m), 1.94–1.85 (1H, m), 1.56–1.21 (6H, m); δ_C (100 MHz) major *endo* isomer 174.6 (s), 137.6 (d), 132.3 (d), 60.0 (t), 49.5 (t), 45.6 (d), 43.3 (d), 42.5 (d), 29.2 (t), 14.2 (q); *m/z* 167 (M^+), 155, 127. Found (M^+): 166.0992; $C_{10}H_{14}O_2$ requires 166.0994. GC retention times: 11.6 min (*exo*); 11.8 min (*endo*).

2-Hydroxyethyl bicyclo[2.2.1]hept-2-ene-5-carboxylate (7). A solution of 2-hydroxyethyl acrylate **5** (0.57 ml, 4.96 mmol) and 1,3-cyclopentadiene (1.2 ml, ca. 14.5 mmol) in toluene (20 ml) was heated under reflux for 3 h and then allowed to cool to room temperature. Removal of the solvent in vacuo and subsequent column chromatography (40% ethyl acetate/60% light petroleum) gave **7** (882 mg, 98%) as a colourless oil and as a 71:29 mixture of *endo*:*exo* isomers as determined by ^{1}H NMR spectroscopy. ν_{max}/cm^{-1} 3447, 2974, 2948, 2877, 1733, 1456, 1336, 1272, 1177, 1036, 890, 838; δ_H (300 MHz) 6.21 (0.71H, dd, *J*=5.6, 3.0 Hz), 6.19 (0.58H, m), 5.92 (0.71H, dd, *J*=5.6, 2.9 Hz), 4.24 (0.58H, m), 4.18 (1.42H, m), 3.90–3.80 (2H, m), 3.22 (0.71H, br s), 3.05 (0.29H, br s), 3.01–2.97 (1.71H, m), 2.92 (1H, OH), 2.26 (0.29H, m), 1.96–1.88 (1H, m), 1.50–1.23 (3H, m); δ_C (100 MHz) major *endo* isomer 174.8 (s), 137.8 (d), 132.4 (d), 69.7 (t), 60.0 (t), 49.5 (t), 45.7 (d), 43.4 (d), 42.6 (d), 29.3 (t); *m*/*z* 182 (M^+), 117, 66; Found (M^+): 182.0943; $C_{10}H_{14}O_3$ requires 182.0943. GC retention time: 18.5 min (*exo*+*endo*).

2-Methoxyethyl bicyclo[2.2.1]hept-2-ene-5-carboxylate (9). A solution of 2-methoxyethyl acrylate **8** (0.65 g, 4.99 mmol) and 1,3-cyclopentadiene (1.2 ml, ca. 14.5 mmol) in toluene (20 ml) was heated under reflux for 5 h and then allowed to cool to room temperature. Removal of the solvent in vacuo and subsequent column chromatography (15% ethyl acetate/85% light petroleum) gave **9** (0.95 g, 97%) as a colourless oil and as a 70:30 mixture of *endo*:*exo* isomers as determined by ^{1}H NMR spectroscopy. ν_{max}/cm^{-1} 2976, 2947, 2878, 1733, 1450, 1175, 1130; δ_H (300 MHz) 6.17 (0.7H, dd, *J*=5.6, 3.1 Hz), 6.11–6.08 (0.6H, m), 5.92 (0.7H, dd, *J*=5.6, 2.9 Hz), 4.24–4.14 (2H, m), 3.60–3.53 (2H, m), 3.38 (2.1H, s), 3.37 (0.9H, s), 3.21 (0.7H, br s), 3.03 (0.3 H, br s), 3.00–2.94 (0.7H, m), 2.89 (1H, m), 2.26 (0.3H, m), 1.93–1.85 (1H, m), 1.54–1.24 (3H, m); δ_C (100 MHz) major *endo* isomer 174.7 (s), 137.7 (d), 132.3 (d), 70.6 (t), 63.2 (t), 58.9 (q), 49.6 (t), 45.7 (d), 43.2 (d), 42.5 (d), 29.3 (t); *m*/*z* 196 (M^+), 131, 120, 99, 91, 77, 66, 59, 55, 51; Found (M^+): 196.1106; $C_{11}H_{16}O_3$ requires 196.1099. GC retention times: 17.9 min (*exo*); 18.0 min (*endo*).

Intermolecular competition experiments involving ethyl acrylate (4) and 2-hydroxyethyl acrylate (5) in the presence of Lewis acids. All reactions were performed by stirring **4** (5.0 mmol), **5** (5.0 mmol) and the appropriate Lewis acid (5 mmol) in DCM (total volume=15 ml) at 0°C for 15 min. Di(isopropyl)ethylamine (5 mmol) was added to the reactions involving titanium (IV) chloride and tin (IV) chloride. Then, 1,3-cyclopentadiene (5 mmol) was added to the acrylate/Lewis acid mixture. After 1 h at 0°C, an aliquot was removed from the reaction mixture, quenched with saturated sodium bicarbonate solution (ca. 1 ml) and extracted with ether (ca. 1 ml). The ether layer was dried (Na_2SO_4) then analysed by GC to determine the relative amounts of both the acrylates and cycloadducts contained within the mixture. The GC system was calibrated prior to these experiments by injecting mixtures of the acrylates and cycloadducts in predetermined compositions measured using ^{1}H NMR spectroscopy. The results from these competition experiments are presented in Table 1 (see Results and Discussion).

Intermolecular competition reaction involving 2-hydroxyethyl acrylate (5) and 2-methoxyethyl acrylate (8) under thermal conditions. To a stirred solution of 2-hydroxyethyl acrylate **5** (0.57 ml, 4.96 mmol) and 2-methoxyethyl acrylate **8** (0.65 g, ca. 4.99 mmol) in toluene (15 ml) at room temperature, was added 1,3-cyclopentadiene (0.40 ml, 4.86 mmol). The solution was heated to reflux for 3 h then an aliquot was removed from the reaction mixture and the cycloadduct ratio determined by GC (**7**:**9**; 63:37).

Intermolecular competition reaction involving 2-hydroxyethyl acrylate (5) and 2-methoxyethyl acrylate (8) in the presence of ethyl aluminium dichloride. To a stirred solution of 2-hydroxyethyl acrylate **5** (0.57 ml, 4.96 mmol) in DCM (10 ml), at 0°C, was added ethyl aluminium dichloride (1.0 M in hexanes, 5.00 ml, 5.00 mmol). After 10 min, 2-methoxyethyl acrylate **8** (0.65 g, 4.99 mmol) was added and after a further 15 min, 1,3-cyclopentadiene (0.40 ml, ca. 4.86 mmol) was added. After 1 h, an aliquot was removed and poured into saturated sodium bicarbonate solution (ca. 1 ml) and extracted with ether (ca. 1 ml). The ether layer was dried (Na_2SO_4) and the cycloadduct ratio determined by GC (**7**:**9**; 97:3).

Ethyl 2-hydroxyethyl fumarate (1). To a stirred solution of ethyl hydrogen fumarate **13** (14.4 g, 100 mmol) in chloroform (500 ml) at 0°C was added oxalyl chloride (8.72 ml, 100 mmol) and a catalytic amount of DMF (0.20 ml). After 10 min, the solution was allowed to warm to room temperature and stirred overnight. This solution was then added, via cannula, to a stirred solution of ethylene glycol (28.0 ml, 502 mmol), triethylamine (35.0 ml, 251 mmol) and DMAP (1.22 g, 10.0 mmol) in chloroform (1000 ml) at 0°C. After 4 h, aqueous sodium bicarbonate solution was added. The organic layer was separated, washed with brine (200 ml), dried (Na_2SO_4) and the solvent removed in vacuo to give the crude product. Column chromatography (40% ethyl acetate/60% light petroleum) gave **1** (13.0 g, 69%) as a colourless oil. ν_{max}/cm^{-1} 3502, 2983, 1732, 1646, 1302, 1263, 1159; δ_H (400 MHz) 6.87 (2H, m), 4.53 (2H, m), 4.25 (2H, q, *J*=7.1 Hz), 3.87 (2H, m), 3.01 (1H, br s, OH), 1.31 (3H, t, *J*=7.1 Hz); δ_C (100 MHz, CD_2Cl_2) 165.1 (s), 164.9 (s), 134.0 (d), 133.0 (d), 66.8 (t), 61.4 (t), 60.5 (t), 13.8 (q); *m*/*z* 189 (MH^+), 171 (MH^+-H_2O), 145, 127, 117, 99, 85; Found (M^+): 188.0693; $C_8H_{12}O_5$ requires 188.0685.

Ethyl 2-methoxyethyl fumarate (14). To a stirred solution of ethyl hydrogen fumarate **13** (2.00 g, 13.9 mmol) in DCM (50 ml) at 0°C was added oxalyl chloride (1.21 ml, 13.9 mmol) and DMF (2 drops). The solution was stirred at 0°C for 10 min and allowed to warm to room temperature and stirred for another 4.5 h. To this solution at 0°C was then added triethylamine (2.90 ml, 20.8 mmol), DMAP (0.17 g, 1.39 mmol) followed by 2-methoxyethanol (2.20 ml, 27.9 mmol) in DCM (50 ml). After stirring overnight, aqueous sodium bicarbonate solution (50 ml) was added and the mixture extracted with DCM (2×100 ml). The organic layers were combined, washed with brine (50 ml), dried (Na_2SO_4) and the solvent removed in vacuo to give the crude product. Column chromatography (10% ethyl acetate/90% light petroleum) gave **14** (1.34 g, 48%) as a colourless

oil. ν_{max}/cm^{-1} 2984, 1722, 1646, 1299, 1260, 1157, 1039; δ_H (300 MHz) 6.88 (2H, m), 4.36–4.33 (2H, m), 4.25 (2H, q, *J*=7.1 Hz), 3.65–3.62 (2H, m), 3.39 (3H, s), 1.31 (3H, t, *J*=7.1 Hz); δ_C (100 MHz) 164.9 (s), 164.8 (s), 134.0 (d), 133.1 (d), 70.2 (t), 64.2 (t), 61.3 (t), 58.9 (q), 14.0 (q); *m*/*z* 203 (MH^+), 172, 157, 127, 99, 58; Found (M^+): 202.0843; $C_9H_{14}O_5$ requires 202.0841.

Reaction of ethyl 2-hydroxyethyl fumarate (1) with 1,3-cyclopentadiene under ethyl aluminium dichloride mediated conditions. To a solution of fumarate **1** (3.76 g, 20.0 mmol) in DCM (40 ml) was added ethyl aluminium dichloride (1.0 M in hexanes, 20.0 ml, 20.0 mmol) and the solution stirred for 15 min, then cooled to −78°C. 1,3-Cyclopentadiene (3.40 ml, ca. 34 mmol) was added and the solution stirred overnight. Sodium bicarbonate solution (30 ml) was carefully added and the aqueous layer extracted with DCM (2×). The organic layers were combined, dried (Na_2SO_4) and the solvent removed in vacuo. Column chromatography (40% ethyl acetate/60% light petroleum) gave **15** and **16** (4.97 g, 98%) as a colourless oil and as a 75:25 mixture of isomers as determined by ^1H NMR spectroscopy. ν_{max}/cm^{-1} 3447, 2982, 1728, 1456, 1267, 1185, 1033; δ_H (300 MHz) 6.30–6.26 (1H, m), 6.10–6.07 (1H, m), 4.24–4.08 (4H, m), 3.82–3.75 (2H, m), 3.41 (0.75H, t, *J*=4.1 Hz), 3.35 (0.25H, t, *J*=4.1 Hz), 3.28 (1H, br s), 3.19–3.01 (2H, m), 2.70 (0.25H, dd, *J*=4.5, 1.4 Hz), 2.66 (0.75H, dd, *J*=4.4, 1.4 Hz), 1.62–1.61 (1H, m), 1.47–1.44 (1H, m), 1.27 (2.25H, t, 7.1 Hz), 1.26 (0.75H, t, 7.1 Hz); δ_C (100 MHz) (major compound) 174.4 (s), 173.5 (s), 137.5 (d), 135.0 (d), 66.0 (t), 60.8 (t), 60.7 (t), 47.8 (d), 47.6 (d), 47.22 (d), 47.17 (t), 45.6 (d), 14.1 (q); *m*/*z* 254 (M^+), 237 (MH^+-H_2O), 209, 189, 171, 127, 66; Found (M^+): 254.1150; $C_{13}H_{18}O_5$ requires 254.1154.

Reaction of ethyl 2-hydroxyethyl fumarate (1) with 1,3-cyclopentadiene under thermal conditions. A stirred solution of fumarate **1** (188 mg, 1.00 mmol) and 1,3-cyclopentadiene (0.50 ml, ca. 6.1 mmol) in toluene (5 ml) was heated under refluxed for 3 h. The solvent was removed in vacuo to give the crude product. Column chromatography (40% ethyl acetate/60% light petroleum) gave **15** and **16** (180 mg, 71%) as a colourless oil as a 51:49 mixture of isomers as determined by ^1H NMR spectroscopy. All other spectroscopic data in agreement with those described above.

(1*R,2*R**,3*S**,6*R**)-1-Ethyl 2-(2-iodoethyl) bicyclo[2.2.1]-hept-4-ene-1,2-dicarboxylate and (1*R**,2*R**,3*R**,6*S**)-1-ethyl 2-(2-iodoethyl) bicyclo[2.2.1]hept-4-ene-1,2-dicarboxylate.** To a stirred solution of alcohols **15** and **16** (75:25 ratio, 2.00 g, 7.87 mmol) in acetonitrile (40 ml) and ether (80 ml) at 0°C was added imidazole (0.79 g, 11.6 mmol), triphenylphosphine (3.35 g, 12.8 mmol) and iodine (2.20 g, 8.67 mmol). After 20 min, ether (150 ml) was added, the mixture filtered and the solvent removed in vacuo to give the crude product. Column chromatography (5% ether/95% light petroleum) gave the *title* compounds (2.36 g, 82%) as a colourless oil and as a 75:25 mixture of isomers by ^1H NMR spectroscopy. ν_{max}/cm^{-1} 2981, 1728, 1264, 1179; δ_H (400 MHz) 6.30–6.28 (1H, m), 6.12 (0.75H, dd, *J*=5.6, 2.8 Hz), 6.07 (0.25H, dd, *J*=5.6, 2.8 Hz), 4.40–4.26 (2H, m), 4.19–4.05 (2H, m), 3.42 (0.75H, t, *J*=4.1 Hz), 3.36 (0.25H, t, *J*=4.1 Hz), 3.33–3.25 (3H, m), 3.18 (0.25H, m), 3.13 (0.75H, m), 2.73 (0.25H, dd, *J*=4.5, 1.8 Hz), 2.68 (0.75H, dd, *J*=4.5, 1.8 Hz), 1.61 (1H, m), 1.46 (1H, m), 1.28 (2.25H, t, *J*=7.1 Hz), 1.24 (0.75H, t, *J*=7.1 Hz); δ_C (100 MHz) (major compound) 174.2 (s), 172.6 (s), 137.7 (d), 135.1 (d), 64.6 (t), 60.9 (t), 47.8 (d), 47.7 (d), 47.4 (t), 47.3 (d), 45.7 (d), 14.2 (q), 0.4 (t, CH_2I); *m*/*z* 364 (M^+), 319, 299, 155, 66; Found (M^+): 364.0171; $C_{13}H_{17}IO_4$ requires 364.0172.

(1*R,2*R**,3*S**,6*R**)-1-Ethyl bicyclo[2.2.1]hept-4-ene-1,2-dicarboxylate (17) and (1*R**,2*R**,3*R**,6*S**)-1-ethyl bicyclo-[2.2.1]hept-4-ene-1,2-dicarboxylate (18).** To a stirred solution of the iodides produced in the experiment above (75:25 ratio, 1.00 g, 2.75 mmol) in acetic acid (10 ml) was added zinc powder (2.00 g, 30.6 mmol). The suspension was stirred for 15 h, water (10 ml) was then added and the mixture extracted with DCM (3×50 ml). The organic layers were combined, dried (Na_2SO_4) and the solvent removed in vacuo to give the crude product. Column chromatography (20% ethyl acetate/80% light petroleum) gave **17** and **18** (472 mg, 82%) as a colourless oil and as a 72:28 mixture of isomers as determined by ^1H NMR spectroscopy. ν_{max}/cm^{-1} 3400–2800, 2984, 1726, 1701, 1183; δ_H (300 MHz) 6.28 (1H, m), 6.12 (0.72H, dd, *J*=2.6, 5.5 Hz), 6.06 (0.28H, dd, *J*=2.7, 5.5 Hz), 4.19–4.05 (2H, m), 3.43 (0.72H, t, *J*=4.5 Hz), 3.34 (0.28H, t, *J*=3.8 Hz), 3.28 (1H, br s), 3.17 (0.28H, br s), 3.12 (0.72H, br s), 2.72 (0.28H, d, *J*=4.5 Hz), 2.62 (0.72H, d, *J*=4.5 Hz), 1.62–1.59 (1H, m), 1.47–1.44 (1H, m), 1.29–1.19 (3H, m), carboxylic acid hydrogen not observed; δ_C (100 MHz) (major isomer) 179.4 (s), 174.2 (s), 137.7 (d), 135.2 (d), 61.0 (t), 47.9, 47.8, 47.3, 47.2, 45.6 (4×d, 1×t), 14.2 (q); *m*/*z* 210 (M^+), 192 (M^+-H_2O), 165, 145, 66; Found (M^+): 210.0892; $C_{11}H_{14}O_4$ requires 210.0892.

Ethyl 2-iodo-5-oxo-4-oxa-tricyclo[4.2.1.0^{3,7}]nonane-9-carboxylate (19). To a stirred solution of acids **17** and **18** (72:28 ratio, 319 mg, 1.52 mmol) in DCM (5 ml) was added sodium hydrogen carbonate (0.60 g, 7.14 mmol), water (15 ml), potassium iodide (2.37 g, 14.3 mmol) and iodine (1.20 g, 4.73 mmol). The mixture was stirred for 18 h, then saturated sodium thiosulfate solution (10 ml) was added. The mixture was extracted with DCM (2×50 ml). The organic layers were combined, washed with water (20 ml), dried (Na_2SO_4) and the solvent removed in vacuo to give the crude product. Column chromatography (10% ethyl acetate/90% light petroleum) gave **19** (326 mg, 63%) as a colourless solid (mp 103–104°C). ν_{max}/cm^{-1} 3056, 2986, 1798, 1784, 1732, 1265, 1244, 1195, 1008; δ_H (400 MHz) 5.10 (1H, d, *J*=5.0 Hz, H-3), 4.16 (2H, m, OCH_2), 3.87 (1H, d, *J*=2.7 Hz, H-2), 3.19 (1H, m, H-7), 3.07 (1H, br d, *J*=4.8 Hz, H-6), 2.99 (1H, br s, H-1), 2.80 (1H, br s, H-9), 2.29 (1H, m, H-8), 1.95 (1H, m, H-8′), 1.25 (3H, t, *J*=7.1 Hz); δ_C (100 MHz) 177.2 (s, lactone), 170.1 (s), 88.4 (d, C-3), 61.9 (t), 50.5 (d, C-1), 50.3 (d, C-9), 46.1 (d, C-7), 40.9 (d, C-6), 35.0 (t, C-8), 28.0 (d, C-2), 14.1 (q); *m*/*z* 336 (M^+), 291, 209, 181, 153, 135, 123, 107, 91, 69, 55; Found (M^+): 335.9866; $C_{11}H_{13}IO_4$ requires 335.9859.

Reaction of ethyl 2-methoxyethyl fumarate (14) with isoprene under thermal conditions. A solution of fumarate **14** (203 mg, 1.00 mmol) and isoprene (1.00 ml, 10.0 mmol)

in toluene (10 ml) was heated under reflux for 12 h and then allowed to cool to room temperature. Removal of the solvent in vacuo and subsequent column chromatography (10% ethyl acetate/90% light petroleum) gave (1*R**,2*R**)-2-ethyl 1-(2-methoxyethyl) 4-methylcyclohex-4-ene-1,2-dicarboxylate and (1*R**,2*R**)-1-ethyl 2-(2-methoxyethyl) 4-methylcyclohex-4-ene-1,2-dicarboxylate (270 mg, 99%) as a colourless oil and as a 48:52 mixture of isomers as determined by ^{1}H NMR. ν_{max}/cm^{-1} 2973, 2931, 1735, 1446, 1181; δ_H (300 MHz) 5.36 (1H, m), 4.23–4.19 (2H, m), 4.15–4.08 (2H, m) 3.57–3.54 (2H, m), 3.36 (1.44H, s), 3.35 (1.56H, s), 2.91–2.76 (2H, m), 2.42–2.00 (4H, m), 1.64 (3H, br s), 1.23 (1.56H, t, *J*=7.1 Hz), 1.22 (1.44H, t, *J*=7.1 Hz); δ_C (100 MHz) 175.0 (s), 174.82 (s), 174.80 (s), 174.7 (s), 132.2 (s), 132.1 (s), 119.0 (d), 118.9 (d), 70.4 (t, 2 carbons coincident), 63.5 (t, 2 carbons coincident), 60.50 (t), 60.47 (t), 58.9 (q, 2 carbons coincident), 41.8 (d), 41.7 (d), 41.2 (d), 41.1 (d), 32.5 (t), 32.4 (t), 28.1 (t), 28.0 (t), 23.0 (q, 2 carbons coincident), 14.1 (q, 2 carbons coincident); *m*/*z* 270 (M$^+$), 225, 194, 166, 93; Found (M$^+$): 270.1469; $C_{14}H_{22}O_5$ requires 270.1467.

Reaction of ethyl 2-methoxyethyl fumarate (14) with isoprene under ethyl aluminium dichloride mediated conditions. To a stirred solution of fumarate **14** (203 mg, 1.00 mmol) in DCM (3 ml) at 0°C was added ethyl aluminium dichloride (1.0 M in hexanes, 1.05 ml, 1.05 mmol). After 15 min, isoprene (1.0 ml, 10.0 mmol) was added and the solution stirred for 12 h at 0°C. Sodium bicarbonate solution (10 ml) was added cautiously, and the mixture extracted with DCM (2×50 ml). The organic layers were combined, washed with brine (20 ml), dried (Na_2SO_4) and the solvent removed in vacuo to give the crude product. Column chromatography (10% ethyl acetate/90% light petroleum) gave (1*R**,2*R**)-2-ethyl 1-(2-methoxyethyl) 4-methylcyclohex-4-ene-1,2-dicarboxylate and (1*R**,2*R**)-1-ethyl 2-(2-methoxyethyl) 4-methylcyclohex-4-ene-1,2-dicarboxylate (205 mg, 76%) as a colourless oil and as a 52:48 mixture of isomers as determined by ^{1}H NMR. Other spectroscopic data as described above.

Reaction of ethyl 2-hydroxyethyl fumarate (1) with isoprene under thermal conditions. A stirred solution of fumarate **1** (200 mg, 1.06 mmol) and isoprene (0.30 ml, 3.00 mmol) in toluene (10 ml) was heated under reflux for 12 h and then allowed to cool to room temperature. Removal of the solvent in vacuo and subsequent column chromatography (40% ethyl acetate/60% light petroleum) gave (1*R**,2*R**)-2-ethyl 1-(2-hydroxyethyl) 4-methylcyclohex-4-ene-1,2-dicarboxylate and (1*R**,2*R**)-1-ethyl 2-(2-hydroxyethyl) 4-methylcyclohex-4-ene-1,2-dicarboxylate (257 mg, 95%) as a colourless oil and as a 52:48 mixture of isomers as determined by ^{1}H spectroscopy. Other spectroscopic data as described below.

Reaction of ethyl 2-hydroxyethyl fumarate (1) with isoprene under ethyl aluminium dichloride mediated conditions. To a stirred solution of fumarate **1** (188 mg, 1.00 mmol) in DCM (3 ml) was added ethyl aluminium dichloride (1.0 M in hexanes, 1.05 ml, 1.05 mmol) and the resulting solution was stirred for 15 min before being cooled to 0°C. Isoprene (1.0 ml, 10.0 mmol) was added and the solution stirred for 12 h. After which time, aqueous sodium bicarbonate solution was added cautiously, the layers separated, and the aqueous layer further extracted with DCM (2×). The organic layers were combined, dried (Na_2SO_4) and the solvent removed in vacuo to give the crude product. Column chromatography (40% ethyl acetate/60% light petroleum) gave (1*R**,2*R**)-2-ethyl 1-(2-hydroxyethyl) 4-methylcyclohex-4-ene-1,2-dicarboxylate and (1*R**,2*R**)-1-ethyl 2-(2-hydroxyethyl) 4-methylcyclohex-4-ene-1,2-dicarboxylate (207 mg, 81%) as a colourless oil and as a 76:24 mixture of isomers as determined by ^{1}H NMR. ν_{max}/cm^{-1} 3446, 2961, 2934, 1733, 1446, 1379, 1312, 1235, 1184, 1075, 1035; δ_H (300 MHz) 5.34 (1H, m), 4.25–4.07 (4H, m), 3.75 (2H, m), 2.89–2.66 (3H, m), 2.32–1.96 (4H, m), 1.64 (3H, s), 1.21 (2.28H, t, *J*=7.1 Hz), 1.20 (0.72H, t, *J*=7.1 Hz); δ_C (100 MHz) (major isomer reported) 175.3 (s), 175.1 (s), 132.2 (s), 118.9 (d), 66.2 (t), 60.9 (t), 60.8 (t), 42.1 (d), 41.4 (d), 32.5 (t), 28.2 (t), 22.9 (q), 14.1 (q); *m*/*z* 256 (M$^+$), 238, 211, 182, 166, 93; Found (M$^+$): 256.1312; $C_{13}H_{20}O_5$ requires 256.1311.

(2*R,3*R**)-2-(3-Hydroxy)butyl acrylate (20).** To a stirred solution of (2*R**,3*R**)-2,3-dihydroxybutane (6.80 ml, 75.1 mmol), triethylamine (11.2 ml, 80.4 mmol) in DCM (200 ml), at 0°C, was added acryloyl chloride (6.1 ml, 75.1 mmol) dropwise in DCM (200 ml). After stirring overnight, water (100 ml) was added, the organic layer separated and the aqueous layer reextracted with DCM (2×). The combined organic layers were washed with water (50 ml), dried (Na_2SO_4), and the solvent removed in vacuo to give the crude product. Column chromatography (40% ethyl acetate/60% light petroleum) gave **20** (2.22 g, 21%) as a colourless oil. ν_{max}/cm^{-1} 3447, 2982, 2940, 1708, 1637, 1407, 1296, 985; δ_H (300 MHz) 6.42 (1H, dd, *J*=17.3, 1.5 Hz), 6.13 (1H, dd, *J*=17.3, 10.3 Hz), 5.83 (1H, dd, *J*=10.3, 1.5 Hz), 4.95 (1H, dq, *J*=3.3, 6.5 Hz), 3.92 (1H, m), 1.90 (1H, br s, OH), 1.25 (3H, d, *J*=6.5 Hz), 1.18 (3H, d, *J*=6.5 Hz); δ_C (100 MHz) 165.8 (s), 130.9 (t), 128.6 (d), 74.6 (d), 69.5 (d), 17.9 (q), 14.2 (q); *m*/*z* 127 (MH$^+$−H$_2$O); Found (M$^+$): 144.0780; $C_7H_{12}O_3$ requires 144.0786.

Reaction of 2-(3-hydroxy)butyl acrylate (20) with 1,3-cyclopentadiene under thermal conditions. A stirred solution of acrylate (2*R**,3*R**)-**20** (200 mg, 1.39 mmol) and 1,3-cyclopentadiene (0.40 ml, ca. 4.8 mmol) in toluene (15 ml) was heated under reflux for 3 h and then allowed to cool to room temperature. Removal of the solvent in vacuo and subsequent column chromatography (40% ethyl acetate/60% light petroleum) gave **21** (288 mg, 99%) as a colourless oil and as a 71:29 mixture of *endo*:*exo* isomers, with the two *endo* diastereomers produced in ca. 60:40 ratio as determined by ^{1}H and ^{13}C NMR spectroscopy. ν_{max}/cm^{-1} 3446, 2978, 2943, 1730, 1192, 1090; δ_H (400 MHz) 6.20 (0.71H, m), 6.16–6.09 (0.58H, m), 5.93 (0.71H, m), 4.90–4.76 (1H, m), 3.88–3.81 (1H, m), 3.21 (0.71H, br s), 3.03 (0.29H, br s), 3.00–2.91 (1.71H, m), 2.24–2.21 (0.29H, m), 2.03–1.86 (2H, m), 1.55–1.26 (3H, m), 1.24–1.13 (6H, m); *m*/*z* 210 (M$^+$), 166, 145, 121, 66; Found (M$^+$): 210.1259; $C_{12}H_{18}O_3$ requires 210.1256.

Reaction of 2-(3-hydroxy)butyl acrylate (20) with 1,3-cyclopentadiene using ethyl aluminum dichloride. To a stirred solution of **20** (720 mg, 4.99 mmol) in DCM (10 ml)

was added ethyl aluminium dichloride (1.0 M in hexanes, 5.0 ml, 5.00 mmol). The solution was cooled to 0°C and 1,3-cyclopentadiene (1.5 ml, ca. 18.2 mmol) was added. After stirring overnight, the reaction was quenched with aqueous sodium bicarbonate solution and the mixture extracted with DCM (2×50 ml). The organic layers were combined, dried (Na_2SO_4) and the solvent removed in vacuo to give the crude product. Column chromatography (40% ethyl acetate/60% light petroleum) gave **21** (859 mg, 82%) as a colourless oil and as a 9:1 mixture of *endo*:*exo* isomers, with the two *endo* diastereomers produced in ca. 33:67 ratio as determined by ^1H and ^{13}C NMR spectroscopy. δ_C (100 MHz) major *endo* diastereomer 174.3 (s), 137.9 (d), 132.2 (d), 74.1 (d), 69.7 (d), 49.6 (t), 45.8 (d), 43.6 (d), 42.5 (d), 29.2 (t), 17.8 (q), 14.2 (q); other spectroscopic data as described above.

2-Hydroxyethyl acrylate (5) with ethyl aluminium dichloride. To a stirred solution of 2-hydroxyethyl acrylate **5** (57.0 μl, 4.96 μmol) in dideuterodichloromethane (1.00 ml) was added ethyl aluminium dichloride (1.0 M in hexanes, 0.50 ml, 0.50 mmol). After 0.25 h, the solution (0.5 ml) was transferred to an oven dried NMR tube, via syringe and analysed by ^{13}C NMR spectroscopy. δ_C (100 MHz) 173.1 (s), 171.1 (s), 141.7 (t), 140.8 (t), 125.8 (d), 125.1 (d), 74.7 (t), 74.0 (t), 63.4 (t), 62.9 (t).

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