ASYMMETRIC INDUCTION IN THE CYCLOADDITION OF 1,3-BUTADIENE TO A POLYMER-BOUND CHIRAL ACRYLATE

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Crosslinked polystyrene resins containing pendant benzyl acrylate or chiral acrylates derived from R-(−)-1,3-butanediol reacted with 1,3-butadiene or 2,3-dimethyl-1,3-butadiene in the presence of the Lewis acid catalysts $TiCl_4$, $TiCl_3(OiPr)$, or $TiCl_2(OiPr)_2$ to yield Diels–Alder adducts. Cleavage of the adducts gave racemic or optically active 3-cyclohexen-1-ylmethanol and 3,4-dimethyl-3-cyclohexen-1-ylmethanol. The polymer-bound Diels–Alder reactions were compared with their analogous reactions in solution. In reactions leading to optically active products the enantiomeric excesses on the polymer were at least as high as those performed in solution.

INTRODUCTION

The use of insoluble polymer supports in operations in synthesis has been explored on a number of fronts since Merrifield's application in the synthesis of a tetrapeptide [1]. The usefulness of the technique in facilitating separations of reactants and products, and the potential for automated processes, are especially attractive features (for reviews see Refs. [2–6]).

A number of applications have been explored in our laboratory, including those in asymmetric syntheses [7,8] and monoblocking of symmetrical difunctional systems [9].

The Diels–Alder reaction remains one of the key types of reactions in organic synthesis. There also are rapidly accumulating examples of asymmetric syntheses through the use of Diels–Alder reactions [10,11]. As well, there have been a number of investigations [12–17] of the mechanistic details of the catalytic effect that Lewis acids exert, in particular, on enone–diene reactions, first reported by Yates and Eaton [17]. In an enone complexed by a Lewis acid, there is pronounced electron deficiency and therefore of reactivity as a dienophile in the Diels–Alder cycloaddition reaction. There also appears to be an enhancement of both stereoselectivity and regioselectivity in such reactions relative to their non-catalyzed counterparts [13–16,18,19].

Lewis acids have been shown to fix the geometry of an acrylate dienophile such that the carbonyl and alkene groups are *anti* with

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each other [10,20]. If a chiral centre is present in the structure of the dienophile, this can lead to enhanced diastereofacial differentiation relative to non-Lewis acid complexed analogues. A complication in the use of the typical Lewis acid, titanium tetrachloride, can be cleavage of acrylate dienophiles as well as polymerization of the acrylate in the presence of traces of water. A milder Lewis acid, titanium dichloride diisopropoxide, was described by Mukaiyama [21]. In our experiences such modified catalysts were capable of catalyzing yet not degrading the acrylate used in the cycloaddition (see below).

A number of acrylates with asymmetric inducing groups have been shown to undergo cycloaddition with butadiene in solution to afford products which can be converted in high e.e. (86–98%) to (*R*)-3-cyclohexen-1-ylmethanol, (*R*)-**1a**, a precursor to the anti-tumour agent sarkomycin [10].

Poll et al. showed, again using chiral acrylate dienophiles, that differing Lewis acids can cause opposing diastereofacial differentiation [22]. It appears that titanium tetrachloride (a type-I Lewis acid) coordinates with available oxygen atoms in the chiral moiety which fixes the conformation of the dienophile, while boron trifluoride etherate (a type-II Lewis acid) only activates the acryloyl group.

The use of polymer supports in Diels–Alder reactions has received relatively little attention. The recent reports of Yedidia and Leznoff [23] and by Gaviña et al. [24,25] were preceeded only by the early work by Blazka and Harwood [26] and by Nieuwstad et al. [27]. These studies have demonstrated the feasibility of using insoluble polymer supports as media for Diels–Alder reactions. It remained to be established, however, if the conditions of low temperature and Lewis acid catalysis using a polymer carrying a chiral auxiliary could result in asymmetric induction during a cycloaddition reaction.

RESULTS AND DISCUSSION

The use of a covalently bound chiral auxiliary on an insoluble polymer support allows facile recovery after the product is released from the polymer compared with the problems of separation and purification following analogous reactions in solution. In the present study, a chiral molecule with a prochiral dienophilic acrylate function was covalently bonded to the polymer derived from 1% crosslinked polystyrene (see below). The target molecule is (*R*)-3-cyclohexen-1-ylmethanol, (*R*)-**1a** (Fig. 1), which was synthesized as an important starting material towards the synthesis of the anti-tumour agent, sarkomycin [28], by Boeckman et al.

In test reactions in solution, benzyl acrylate (**2**) in dichloromethane was treated with butadiene in the presence of titanium tetrachloride at $-20\,^{\circ}C$ to afford benzyl 3-cyclohexen-1-carboxylate (**3a**) in 83% yield (Scheme I). Increased facility in handling 2,3-dimethyl-1,3-butadiene prompted a study of its use. It is known that this diene is very reactive in Lewis acid catalyzed reactions [29] owing to the electron-donating methyl groups. In this case, the milder catalyst, titanium dichloride diisopropoxide, was used. Benzyl 3,4-dimethyl-3-cyclohexene-1-carboxylate (**3b**) was formed in 80% yield. Reductive cleavage of **3a** and **3b** with lithium aluminum hydride gave benzyl alcohol (**4**) and the corresponding 3-cyclohexen-1-ylmethanols, **1a** and **1b**, respectively. Cleavage of **3a** and **3b** with tetra-n-butylammonium hydroxide afforded the corresponding 3-cyclohexene-1-carboxylic

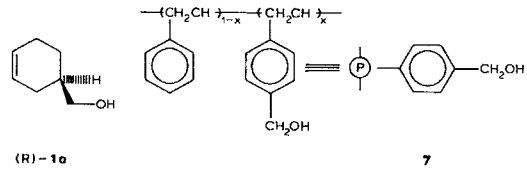
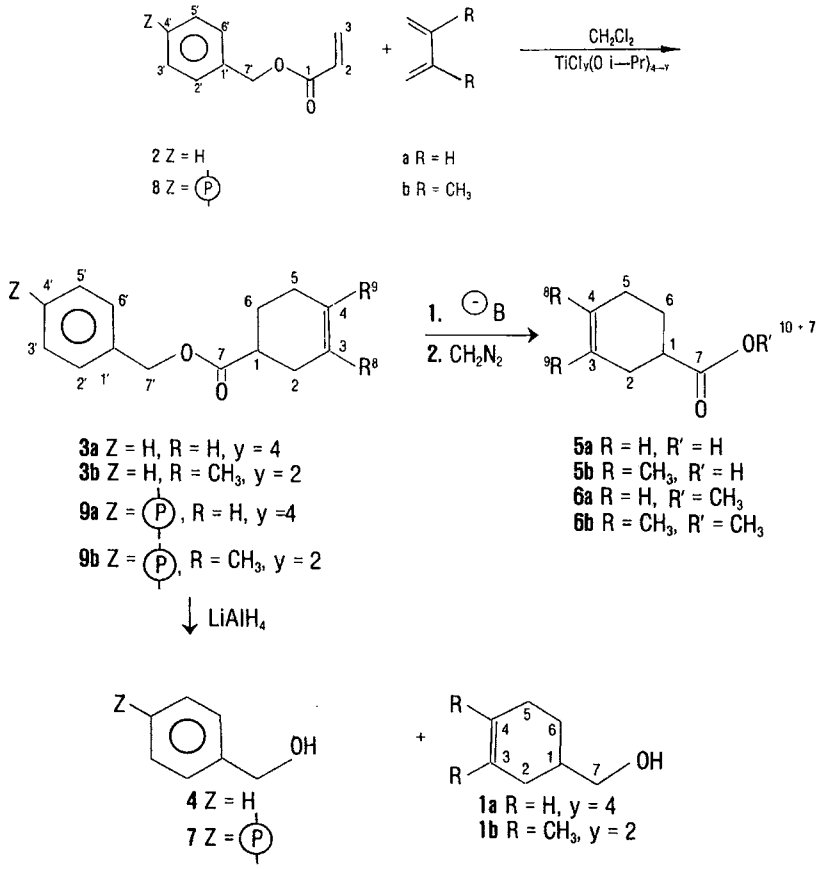


Fig. 1. The target chiral molecule **1a** using polymer **7**.



Scheme I

acids **5a** and **5b**, respectively, which were converted to their methyl esters, **6a** and **6b**, by diazomethane.

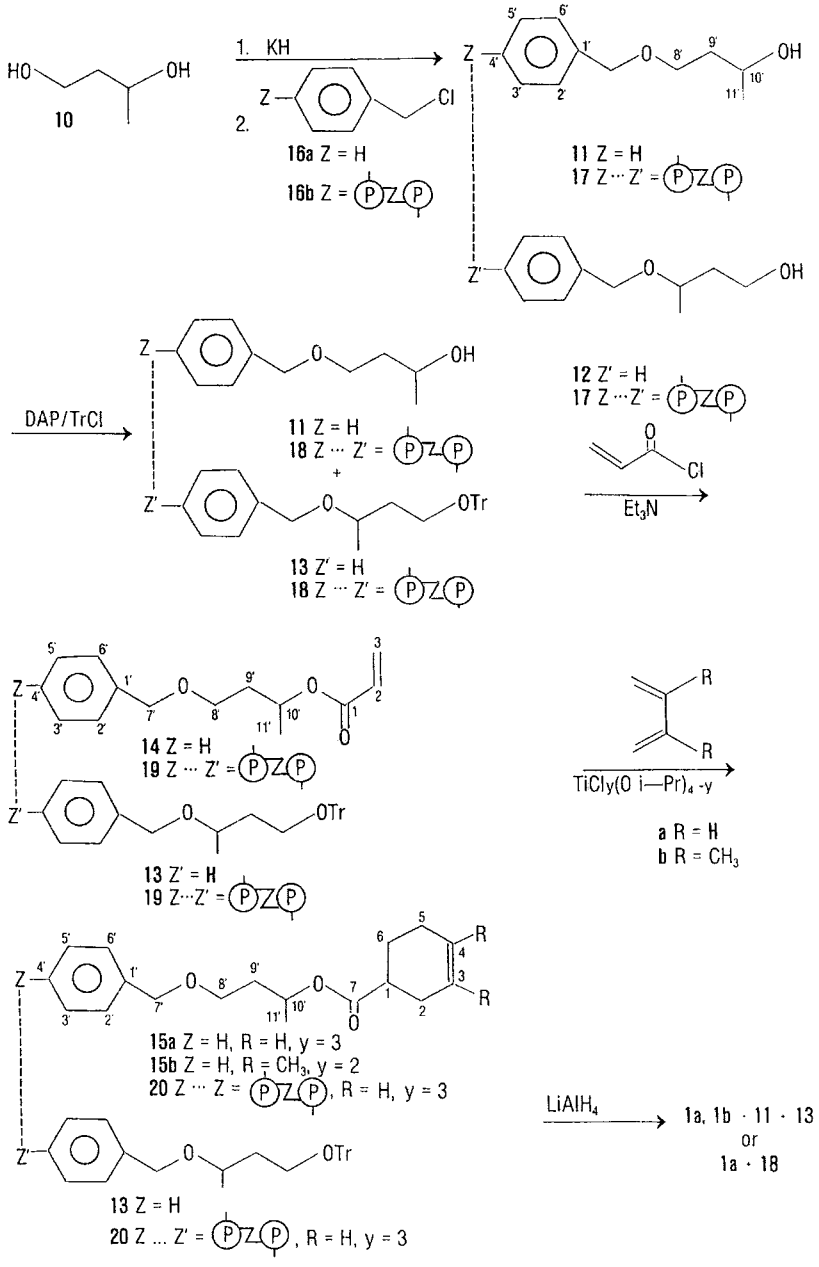
The polymeric analogue of **2** had been previously prepared by Yedidia and Leznoff [23]. Thus, treatment of a hydroxymethylated 1% crosslinked polystyrene–divinylbenzene copolymer (Fig. 1) **7** with acryloyl chloride at $-20\,^{\circ}C$ in the presence of an excess of triethylamine (to prevent addition of hydrogen chloride to the vinylic system) afforded polymer-bound acrylate **8**. Loading was determined to be 0.72 mmol acrylate per gramme of polymer by cleavage with tetrabutylammonium hydroxide to give acrylic acid and regenerated polymer **7**.

Cycloaddition of 1,3-butadiene to **8**, at $-20\,^{\circ}C$, catalyzed by titanium tetrachloride afforded the polymer-bound cyclohexene **9a**. Cleavage of **9a** with lithium aluminum hydride released **1a** and regenerated **7**. The yield of **1a** was determined to be 32% based on the loading on the polymer **8** of 0.72 mmol acrylate g^{-1}. Cleavage of **9a** with tetrabutylammonium hydroxide afforded the carboxylic acid **5a** in 38% yield.

In a similar manner, 2,3-dimethyl-1,3-butadiene underwent cycloaddition, catalyzed by titanium dichloride diisopropoxide, on reaction with the polymer-bound acrylate **8** to afford the dimethylcyclohexenyl derivative **9b**, which underwent cleavage with tetrabutylam-

monium hydroxide to release **5b** in 35% yield.

To introduce a chiral centre near the acrylate function, synthetic approaches to the solution system, 4-benzyloxy-2-butyl acrylate (**14**), were investigated (Scheme II). Reaction of the monopotassium salt of 1,3-butanediol



Scheme II

TABLE 1

Chemical yields and enantiomeric excesses (e.e.) of (*R*)-**1a**

Derived from	Chemical yield (%) [a]	e.e. (%)
15a	86	0
15b	88	0
(*R*)-**15a**	86	20.5
20	30	0
(*R*)-**20**	30	23.4

[a] From corresponding acrylate dienophile.

(**10**) with benzyl chloride produced a mixture of ether-alcohols 1-benzyloxy-3-butanol (**11**) (86%), and 3-benzyloxy-1-butanol (**12**) (14%). Alcohol **12** was selectively tritylated by the method described by Hernandez et al. [30], which tritylates only primary alcohols, to afford 1-trityloxy-3-benzyloxybutane (**13**), from which the more volatile **11** can readily be separated by distillation. Conversion of **11** to the acrylate ester **14** followed by treatment of **14** with 1,3-butadiene in the presence of titanium tetrachloride resulted in the formation of a complex mixture of polymeric products. Corey et al. [31] explained the cause of instability in similar systems in terms of chelation with the Lewis acid to form a ring structure. This could lead to cleavage and then polymerization. The use of milder Lewis acids such as titanium dichloride diisopropoxide or boron trifluoride etherate alleviated the problem of polymerization, but no cycloaddition occurred either. However, use of titanium trichloride isopropoxide, a Lewis acid of intermediate strength, resulted in the formation of the Diels–Alder adduct **15a** in 86% yield (61% conversion).

Cleavage of **15a** with lithium aluminum hydride produced **1a** and regenerated **11**. The sequence of acryloylation, cycloaddition, and cleavage may be performed in the presence of the trityl ether **13**, which remains unchanged throughout.

TABLE 2

^{13}C NMR chemical shifts in ppm (δ) of some Diels–Alder adducts and derivatives of benzyl acrylate and butadienes

Carbon [a]	Compound							
	1a	**2**	**3a**	**3b**	**5a**	**5b**	**6a**	**6b**
1	34.68	165.76	39.22	40.09	39.08	40.08	40.01	39.80
2	26.69	128.19	27.96	33.56	27.08	33.45	32.97	33.45
3	125.37	130.88	126.56	125.16	126.64	125.36	124.86	124.91
4	124.69		125.04	123.75	124.91	123.73	123.52	122.57
5	23.78		24.96	25.73	24.75	30.87	30.72	30.71
6	23.08		24.39	33.56	24.23	25.60	24.45	25.55
7	64.92		175.47	175.61	182.44	182.73	182.56	175,95
8				18.88		18.94		18.69
9				18.73		18.81		18.46
10							51.44	51.11
1′		135.79	136.11	136.17				
2′		128.43	127.87	127.86				
3′		128.10	127.99	127.96				
4′		128.20	128.41	128.41				
5′		128.10	127.99	127.96				
6′		128.43	127.87	127.86				
7′		66.17	65.94	65.87				

[a] The numbering of the carbon atoms in the compounds listed follows that given for these structures in the schemes and does not follow from the names of the compounds.

In a similar manner, the more reactive diene, 2,3-dimethyl-1,3-butadiene, reacted with **14** in the presence of two equivalents of titanium dichloride diisopropoxide to produce the cycloadduct **15b** in 88% yield (65% conversion). In both systems, two equivalents of the Lewis acid are required for cycloaddition to occur, owing to the two oxygen atoms in the dienophile as points of chelation.

Starting with the optically active, pure (*R*)-(−)-1,3-butanediol, (*R*)-**10**, and using 1,3-butadiene, the product, after cleavage with lithium aluminum hydride, was (*R*)-**1a** in 20.5% e.e.

The polymer-bound systems were formed as shown in Scheme II using the Merrifield polymer (**16b**). The ratio of primary to secondary free alcohol functions in **17** would be expected to be as low as in the solution analogue. Selective blocking of the primary hydroxyl group as the trityl ether [30], which afforded **18**, followed by reaction with acryloyl chloride in the presence of triethylamine, gave the polymer-bound acrylate **19**. Cycloaddition occurred using 1,3-butadiene and titanium trichloride isopropoxide to produce the polymer-bound cyclohexenyl system **20**. Cleavage with lithium aluminum hydride afforded **1a** and regenerated polymer **18**.

The same sequence starting with pure (*R*)-(−)-**10** and the Merrifield polymer afforded the optically active product (*R*)-**1a** in 23.4% e.e. (Table 1). All new products were characterized by spetroscopic data and elemental analysis and the ^{13}C NMR spectra are recorded in Tables 2 and 3.

TABLE 3

^{13}C NMR chemical shifts in ppm (δ) of some Diels–Alder adducts and derivatives of **14** with butadienes and some polymer-bound derivatives, **17**, **19** and **20**

Carbon [a]	Compound						
	11	**14**	**15a**	**15b** [b]	**17** [c]	**19** [c]	**20** [c]
1		165.51	39.42	40.25		–	–
2		128.80	24.39	25.66		–	–
3		130.06	125.17	125.11		–	–
4		126.52	126.84			–	–
5			25.04	30.86		–	–
6			27.30	33.54		–	–
7			175.21	175.37		–	–
1′	138.23	138.19	138.22	138.15	–	–	–
2′	128.36	128.20	128.29	128.23	–	–	–
3′	127.60	127.46	127.60	127.55	–	–	–
4′	127.39	127.37	127.49	127.44	–	–	–
5′	127.60	127.46	127.60	127.55	–	–	–
6′	128.36	128.20	128.30	128.23	–	–	–
7′	73.06	72.86	72.97	72.90	73.18	69.21	68.85
8′	68.54	68.55	68.09	67.98	68.89	68.93	66.67
9′	38.45	35.95	36.03	35.96	38.21	36.51	35.95
10′	66.41	66.37	66.47	66.43	67.49	66.77	66.49
11′	23.44	20.07	20.21	20.15	23.42	20.30	20.28

[a] See footnote a of Table 1.

[b] Methyl groups 8 and 9 adsorb at 18.71 and 18.86, respectively.

[c] Minus signs: these peaks are obscured by the polymer backbone or are too weak to observe.

CONCLUSION

It has been demonstrated that polymer-supported acrylates can act as suitable dienophiles in low temperature, Lewis acid catalyzed, Diels–Alder reactions. The formation, cleavage and isolation of the cycloaddition product was shown to be analogous to the solution-phase reactions. Although the polymer-supported reactions displayed a tendency for lower yields, compared with the solution-phase reactions, the work-up of the reactions were simpler and the chiral substrate was readily recovered.

Cycloaddition of 1,3-butadiene to the solution phase and polymer-bound chiral acrylate produced a slight excess of the *R* isomer. This is consistent with the model presented in Fig. 2, in which there is a predilection for approach of the diene from the si face of the acryloxyl group. Blocking of the re face by the C-1 methyl group is not dominant enough to produce a diastereomeric excess higher than 20.5% in the solution phase reaction. It was hypothesized that the polymer-bound auxiliary may have a higher stereodirecting ability, possibly due to pi–pi interactions with the polystyrene backbone. Although some increase in the e.e. was observed in the polymer-supported cycloaddition to the chiral auxiliary, it is concluded that there is not a great deal of additional stereodirection attained by attachment of the chiral auxiliary to the polymer support. An important consideration is the chelation of one equivalent of the Lewis acid to the ester and ether oxygens, as well as the equivalent that chelates with the carbonyl. This five-membered ring results in a rigid cyclic system that provides a consistent plane about which stereoselection of the ene face can occur.

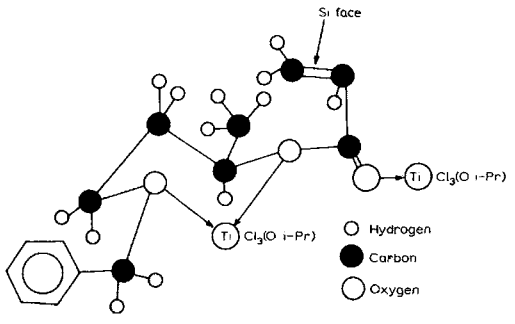


Fig. 2. The geometry of the titanium-catalyzed chiral acrylate.

In the future, it would be of interest to see if replacement of the C-1 methyl group with a bulkier aromatic or t-butyl group would result in higher enantiomeric excesses.

EXPERIMENTAL

Polystyrene containing 1.09 meq Cl/(g of resin) and crosslinked with 1% divinylbenzene, obtained from the Sigma Chemical Company, was used as the starting resin in all resin transformations. In reactions that required 1,3-butadiene, the diene was collected by condensing the gas (Matheson, 99%, L.B.) in a small cold trap at −78°C. After allowing the solid to warm up to −20°C, the required volume of liquid was then quickly transfered via pipette to the reaction flask. Filtration of the resin was accomplished under water aspirator vacuum using sintered glass Buchner funnels. Reactions that required cooling were cooled by a combination cold plate stirrer. Matheson high purity argon was used to maintain inert atmosphere conditions. Solvents required for reactions were dried and distilled before use. All reaction mixtures were stirred with a magnetic stirrer. Distillations were conducted using a Kugelrohr apparatus (bulb-to-bulb) and for these, the temperature range of the heater at which the main fraction was collected, is reported. Flash chromatography was carried out using 20–45 μm silica gel. Melting points (m.p.) were determined using a Kofler hot stage-melting point apparatus and are uncorrected. Optical rotations were determined using a

Perkin–Elmer 141 polarimeter at 21°C ± 2°C, and refer to the sodium D line. Infrared spectra (IR) were recorded on a Pye-Unicam SP1000 infrared spectrophotometer as neat films between NaCl discs for liquids or KBr for solids. Values are reported as the wave number (ν) in reciprocal centimeters (cm^{-1}). Nuclear magnetic spectra for protons (^1H NMR) were recorded on a Varian EM360 (60 MHz) or a Bruker AM300 (300 MHz) spectrometer and are expressed in ppm (δ values) relative to tetramethylsilane (TMS) as an internal reference in deuterochloroform unless specified otherwise. The splitting of the signals are described as singlets (s), broad singlets (bs), doublets (d), triplets (t), quartets (q), doublets of doublets (dd), doublets of triplets (dt), multiplets (m), or multiplets of multiplets (mm). The ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker AM300 (300 MHz) or a Varian FT-80 (80 MHz) and have been assigned using standard correlations. Mass spectra (MS) were recorded at 70 eV on a Perkin–Elmer-Hitachi RMU6E mass spectrometer, attached to a Perkin–Elmer 902 gas chromatograph (GC). The number in parentheses after the indicated ion shows the percentage of the base peak represented by that ion. Other GC analyses were performed on a Tracor 560 utilizing an OV225 stationary phase in a 7-ft. column. Microanalyses were performed by Guelph Chemical Laboratories Ltd., Guelph, Ont.

Benzyl acrylate (2)

A well-stirred solution, under argon, containing benzyl alcohol (10 g, 92 mmol) and triethylamine (20 mL, 144 mmol) in 100 mL of diethyl ether was cooled to −50°C. To this solution was added dropwise, over a period of 1 h, a solution of acryloyl chloride (11.2 mL, 138 mmol, 1.5 eq) in 140 mL of diethyl ether. The light yellow suspension was allowed to warm up to room temperature and then stirred for 4 h. The suspension was subsequently poured into a beaker containing ice and 100 mL of dilute HCl. The ether layer was removed and washed several times with dilute HCl, saturated NaCl solution, collected and dried over $MgSO_4$ and then concentrated to yield (crude) 14 g (86 mmol) of a light yellow liquid. The crude product was distilled (bulb-to-bulb, 1.0 Torr, 106–111°C) to give **2** (13.76 g, 92% yield), a colourless liquid; IR: 1750s (C=O) cm^{-1}; H NMR (60 MHz): 7.20 (s, 5H, C_6H_5), 6.52–5.43 (m, 3H, $CH{=}CH_2$), 5.07 (s, 2H, $C_6H_5CH_2$); MS *m/z*: 162 (M^+, 40), 117 (47), 91 (98), 90 (45), 79 (32), 55 (100), 27 (25).

Benzyl 3-cyclohexene-1-carboxylate (3a)

To a cooled solution (0°C) of $TiCl_4$ (3 mL, 27 mmol, 1.5 eq) in 15 mL of CH_2Cl_2, under argon, was added a solution of **2** (3.0 g, 18.5 mmol) in 20 mL of CH_2Cl_2. After allowing the clear mixture to cool to −20°C, 1,3-butadiene (9 mL, 103 mmol) was added and the clear, dark red solution stirred overnight. The reaction was quenched by pouring the mixture over ice which resulted in the formation of copious amounts of a white precipitate ($Ti[OH]_4$). Stirring and the addition of diethyl ether resulted in the formation of two clear, colourless layers. The organic layer was extracted, washed with brine, dried over $MgSO_4$ and concentrated to yield a light yellow coloured liquid. Distillation (bulb-to-bulb, 0.05 Torr, 97–106°C) gave **3a** (3.32 g, 83% yield); colourless liquid; IR: 1745s (C=O) cm^{-1}; ^1H NMR (300 MHz): 7.33 (s, 5H, C_6H_5), 5.67 (s, 2H, $CH{=}CH$), 5.12 (s, 2H, $C_6H_5CH_2$), 2.30 (m, 2H), 2.11 (m, 4H), 1.71 (m, 1H); MS *m/z*: 216 (M, 5), 125 (24), 92 (16), 91 (100), 81 (18), 79 (42). *Anal.* calcd. for $C_{14}H_{20}O_2$: C 77.75, H, 7.46; found: C 77.35, H 7.72.

Benzyl 3,4-dimethyl-3-cyclohexene-1-carboxylate (3b)

To 10 mL CH_2Cl_2, under argon, containing $TiCl_4$ (1 mL, 9.3 mmol) was added

$Ti(OiPr)_4$ (2.8 mL, 9.3 mmol). The mixture was cooled to 0 °C and stirred 0.5 h to yield a clear solution containing $TiCl_2(OiPr)_2$ (18.6 mmol, 1.5 eq). To this mixture was added a solution of **2** (2 g, 12.4 mmol) in 125 mL CH_2Cl_2, which was cooled to −20 °C and stirred for 1 h. 2,3-Dimethyl-1,3-butadiene (3 mL, 26.5 mmol, 2 eq) was then added to the clear, slightly yellow solution, and the mixture allowed to stir at −20 °C for 20 h. The reaction was worked up in a manner similar to that described for **3a** to yield a viscous, yellow liquid. Distillation (bulb-to-bulb, 0.05 Torr, 136–140 °C) gave **3b** (2.4 g, 80% yield); colorless, viscous liquid; IR: 1750s (C=O) cm^{-1}; ^1H NMR (300 MHz): 7.33 (s, 5H, C_6H_5), 5.12 (s, 2H, $C_6H_5CH_2$), 2.56 (m, 1H) 2.29–2.09 (m, 2H), 1.98 (m, 2H), 1.74–1.59 (m, 8H); MS *m/z*: 244 (M^+, 0.05), 153 (99), 125 (28), 107 (99), 91 (100), 67 (30), 43 (50). *Anal.* calcd. for $C_{16}H_{20}O_2$: C 78.65, H 8.25; found: C 78.20, H 8.30.

*3-Cyclohexen-1-ylmethanol (**1a**)*

To a cooled (0 °C) suspension of $LiAlH_4$ (0.14 g, 3.7 mmol, 4 eq) in 25 mL THF, under argon, was added **3a** (800 mg, 3.7 mmol) dissolved in 10 mL THF. The mixture was stirred at room temperature for 3 h and then the contents of the reaction vessel were poured over ice containing dilute HCl. The aqueous layer was saturated with NaCl and then extracted several times with ether. The combined ether extracts were dried over $MgSO_4$ and concentrated. Distillation (bulb-to-bulb, 1.0 Torr, 35–40 °C, collected over dry ice–acetone, {lit. b.p. 79–83 °C, 12 mmHg [32]}) gave **1a** (373 mg, 90% yield); IR: 3550b (CH_2OH) cm^{-1}; ^1H NMR (300) MHz: 5.68 (m, 2H, C*H*=C*H*–), 3.52 (m, 2H), 2.08 (m, 3H), 1.78 (m, 3H), 1.27 (m, 1H); MS *m/z*: 112 (M^+, 4), 94 (91), 81 (68), 77 (33), 53 (38), 41 (45), 39 (38).

*3-Cyclohexene-1-carboxylic acid (**5a**) and methyl-3-cyclohexene-1-carboxylate (**6a**)*

Using a method described by Yedidia and Leznoff [23], the ester **3a** (1 g, 4.6 mmol) underwent base cleavage by stirring for 24 h at room temperature with $(nBu)_4NOH$ (15 mL, 40% aqueous solution) in 40 mL of THF. Routine isolation of the acid yielded **5a** (545 mg, 94% yield), which was purified by distillation (bulb-to-bulb, 1.0 Torr, 55–60 °C, lit. b.p. 129 °C, 20 Torr [33]); colourless liquid; IR: 2960b (O–H), 1720s (C=O) cm^{-1}; ^1H NMR (300 MHz): 9.32 (b, 1H, O–*H*), 5.70 (s, 2H, C*H*=C*H*–), 2.29 (m, 2H), 2.07 (m, 4H), 1.71 (m, 1H); MS *m/z*: 126 (M^+, 40), 108 (48), 81 (100), 80 (77), 79 (59), 54 (55), 41 (49). Esterification with CH_2N_2 gave the sweet-smelling methyl ester, **6a**, which was purified by distillation (bulb-to-bulb, 1.0 Torr, 35–39 °C, lit. b.p. 73–73.5 °C, 20 Torr [33]); colourless liquid; IR: 1750s (C=O) cm^{-1}; ^1H NMR (60 MHz): 5.72 (s, 2H, –C*H*=C*H*–), 3.70 (s, 3H, –OCH_3), 2.30 (m, 2H), 2.11 (m, 4H), 1.71 (m, 1H); MS *m/z*: 140 (M^+, 15), 108 (38), 81 (100), 80 (96), 79 (46), 53 (15), 41 (15).

*3,4-Dimethyl-3-cyclohexene-carboxylic acid (**5b**) and methyl 3,4-dimethyl-3-cyclohexene-1-carboxylate (**6b**)*

In a manner similar to that described above, **3b** (1 g, 4.1 mmol) was stirred with a solution of aqueous $(nBu)_4NOH$ in THF to give, after isolation and distillation (bulb-to-bulb, 1.0 Torr, 89–93 °C, 607 mg, 96% yield) of **5b**, a low melting, white crystal (m.p. 79–80 °C, lit. m.p. 80–82 °C [33]); IR: 3220b (O–H), 1732s (C=O) cm^{-1}; ^1H NMR (60 MHz): 10.86 (b, 1H, O–*H*), 2.07 (m, 7H), 1.66 (s, 6H, –CCH_3=CCH_3–). Esterification with CH_2N_2 gave the methyl ester, **6b**, which was purified by distillation (bulb-to-bulb, 1.0 Torr, 60–62 °C, lit. b.p. 104–106 °C, 20 Torr [33]); colourless liquid; IR: 1751s (C=O) cm^{-1}; ^1H

NMR (60 MHz): 3.68 (s, 3H, O–CH_3), 2.07 (m, 7H), 1.66 (s, 6H, –CCH_3=CCH_3–); MS *m/z*: 168 (M^+, 27), 109 (72), 108 (100), 93 (72), 87 (37), 41 (28), 39 (19).

Preparation of polymer-bound acrylate ***8***

Polymer **7** was prepared by a method previously described [34,35]. In addition, to further facilitate the complete drying of the resin, after hydrolysis of the acetate, the polymer was suspended in benzene and refluxed in a Soxhlet apparatus containing molecular sieves for 24 h. The hydroxy polymer (25 g, approx. 1.0 mmol $-CH_2OH$/g) was suspended in 300 mL of THF to which was added 25 mL of triethylamine (180 mmol, approx. 7 eq). To the cooled suspension (−20 °C) was added, dropwise, 10 mL (123 mmol, in 50 mL of THF) of acryloyl chloride. The mixture was stirred at room temperature, under argon, for 18 h. The polymer was then filtered and washed several times with THF, THF/water (1 : 1), THF/water (1 : 3, with 1% HCl), THF/water, THF (until polymer swells to full capacity), and then methanol. The polymer was then extracted in a Soxhlet extractor for 48 h with THF over molecular sieves, and then thoroughly dried by agitating and heating (75–80 °C) the polymer (Kugelrohr apparatus) under vacuum (1.0 Torr) for 18 h to give the white resin, **8**; IR (KBr): 1725s (C=O), 1635 and 1415 (C=C) cm^{-1}.

To determine the amount of loading, the polymer, **8** (5 g), underwent base hydrolysis with $(n\text{-}Bu)_4NOH$ to yield the regenerated polymer, **7** (complete removal of C=O absorption at 1725 cm^{-1}) and acrylic acid (259 mg, 3.6 mmol). Hence the resin, **8**, had a loading capacity of 0.68 mmol acrylate per gramme polymer.

*Polymer-bound benzyl 3-cyclohexene-1-carboxylate (**9a**)*

Polymer **8** (20 g), which had been previously cleaned by Soxhlet extraction (CH_2Cl_2, 24 h), was suspended in 200 mL CH_2Cl_2. To the cooled suspension (0 °C), under argon, was added freshly distilled $TiCl_4$ (2.24 mL, 20.4 mmol, 1.5 eq). The red coloured suspension was cooled to −20 °C and stirred for 1 h. To the slurry was added 10 mL (115 mmol, 8 eq) of 1,3-butadiene and the mixture was then stirred at −20 °C for 72 h. After the required period, the polymer was filtered, washed several times with CH_2Cl_2, and then transfered to a Soxhlet extraction apparatus and cleaned overnight under an argon atmosphere, with refluxing CH_2Cl_2. The polymer was filtered and dried under vacuum to yield the red coloured polymer, **9a**; IR (KBr) 1740s cm^{-1}.

*Polymer-bound benzyl 3,4-dimethyl-3-cyclohexene-1-carboxylate (**9b**)*

To a 10 mL solution of $TiCl_2(OiPr)_2$ (10.2 mmol, 1.5 eq) was added, under argon, 10 g of polymer **8**. The orange coloured polymer was cooled to −20 °C and stirred for 1 h. To the slurry was added 4 mL (34 mmol, 5 eq) of 2,3-dimethyl-1,3-butadiene and the reaction mixture stirred for 72 h. The polymer was filtered, washed several times with CH_2Cl_2, filtered and then dried under vacuum to give polymer **9b**; IR (KBr) 1750s (C=O) cm^{-1}.

*Reductive cleavage of polymer **9a**: Isolation of 3-cyclohexene-1-methanol*

The thoroughly dried polymer **9a** (5 g) was added, under argon, to a suspension of 150 mg $LiAlH_4$ (4 mmol, approx. 4 eq) in 50 mL THF. The slurry immediately became dark grey in colour. After stirring at room temperature for 24 h, the polymer was filtered and washed successively, several times with THF, THF/dilute HCl (1 : 1), THF and then methanol to give a cloudy grey filtrate and an off-white coloured polymer. After removing the organic phase of the filtrate, the remain-

ing aqueous phase was saturated with NaCl and extracted with ether. The combined ether extracts were dried over $MgSO_4$, concentrated, and then distilled (bulb-to-bulb) to give **1a** (129 mg, 1.15 mmol, 32% yield based on 0.72 mmol acrylate per gramme polymer).

*Base cleavage of polymer **9a**: Isolation of 3-cyclohexene-1-carboxylic acid*

Using the established method, 1.0 g of polymer **9a** was suspended in 100 mL of THF containing 10 mL 40% $(nBu)_4NOH$. The suspension was stirred for 24 h. The polymer was filtered and washed successively, several times each, with THF, THF/water (1:1), THF/water (1:3), THF/water (1:9), THF and then methanol to give an off-white coloured polymer and approximately 500 mL of a red coloured filtrate. The organic solvents in the filtrate were removed by a rotary evaporator and the remaining aqueous solution acidified and extracted several times with ether. The combined extracts were dried over $MgSO_4$ and then concentrated to give a viscous oil. The extract was then partially purified by base extraction and distilled (bulb-to-bulb) to give the acid, **5a** (347 mg, 2.6 mmol, 38% yield based on 0.72 mmol acrylate per gramme polymer). Examination of the cleaved polymer IR did not exhibit any carbonyl absorption, thus indicating that polymer 7 was regenerated. The presence of acid **5a** was further verified by esterification with CH_2N_2 to give the methyl ester, **6a**, which was identified by GC/MS.

*Base cleavage of polymer **9b**: Isolation of 3,4-dimethyl-3-cyclohexene-1-carboxylic acid*

In a manner identical to that described above, 5 g of polymer **9b** was suspended in 50 mL THF containing 5 mL 40% (aq) $(nBu)_4NOH$. After stirring for 24 h, the crude acid was isolated and then purified by distillation (bulb-to-bulb) to give **5b** (192 mg, 1.26 mmol, 35% yield based on 0.72 mmol acrylate per gramme polymer). The corresponding ester, **6b**, was formed by treatment with CH_2N_2 and identified by GC/MS. The IR spectrum of the cleaved polymer revealed no absorption due to carbonyl and hence polymer 7 was regenerated.

*4-Benzyloxy-2-butanol (**11**) and 3-benzyloxy-1-butanol (**12**)*

To a cooled suspension (0 °C) of potassium hydride (7.84 g, 195 mmol) in 100 mL ether, protected by a drying tube, was added dropwise 1,3-butanediol (**10**) (17.7 g, 195 mmol). Following the vigorous evolution of hydrogen, the resulting brown slurry was refluxed for 6 h. Dimethylformamide (10 mL) was added to the mixture followed by a solution of benzyl chloride (34 mL, 293 mmol) in 100 mL of diethyl ether. The resulting mixture was stirred for 8 h and then refluxed for an additional 2 h. After cooling, the mixture was poured over ice and neutralized with 2 *M* HCl. The ether layer was separated and the remaining aqueous layer extracted with ether (2 times 50 mL). The ethereal phases were combined, dried over $MgSO_4$ and concentrated. Distillation (bulb-to-bulb, 1.0 Torr, 100–110 °C) furnished 30.23 g (168 mmol, 86% yield) of **11** and **12**.

*Selective tritylation of the mixture of alcohols **11** and **12***

As described by Hernandez et al. [30], to 50 mL of ether containing trityl chloride (freshly recrystallized from benzene containing acetyl chloride, 2.68 g, 9.6 mmol) was added dimethylaminopyridine (1 g, 8.1 mmol). After stirring overnight, under rigorously anhydrous conditions, the dimethylaminopyridine–trityl chloride salt (DAP–TrCl) was formed as a white precipitate. To the slurry was added 10 g of the alcohol mixture (8.6 g **11**, 48 mmol, 1.4 g of **12**, 8.0 mmol) in 50 mL

of ether. The resulting mixture was refluxed overnight to give a cloudy suspension, which was then poured into 200 mL of dilute HCl. The ether layer was separated, washed several times with dilute HCl, dried over $MgSO_4$ and concentrated. Distillation (bulb-to-bulb, 1.0 Torr, 100–110 °C, lit. b.p. 99–102 °C, 1.5 Torr [36]) gave the secondary alcohol, **11** (8.4 g, 46 mmol, 96% yield) in the collection bulb, while 4.2 g of the crude mixture containing **13** remained in the distillation bulb. Subsequent GC analysis of the distilled alcohol showed that more than 99% of the primary alcohol had been selectively tritylated. Characterisation of **11**: colourless liquid; IR: 3420b (O–H), 1112s (C–O–C) cm^{-1}; ^1H NMR (60 MHz): 7.32 (s, 5H, C_6H_5), 4.50 (s, 2H, $C_6H_5CH_2$), 4.19–3.43 (m, 4H), 1.72 (q, 2H, $J = 6$ Hz, $OCH_2CH_2CH(OH)CH_3$), 1.20 (d, 2H, $J = 6$ Hz, $BzOCH_2CH_2CH(OH)CH_3$); MS *m/z*: 180 (M^+, 1.3), 107 (77), 92 (27), 91 (100), 79 (21), 56 (36), 28 (21).

*2-(4-Benzyloxybutyl) acrylate (**14**)*

In a manner similar to the synthesis of **2**, to a mixture containing triethylamine, the secondary alcohol **11** (5 g, 27.7 mmol) and the trityl-protected primary alcohol **13** (1.6 g, 3.7 mmol) in ether was added acryloyl chloride (3.38 mL, 41.1 mmol). The work-up gave a viscous yellow liquid (crude yield, 7.2 g) containing the acrylate ester and the intact trityl-protected alcohol (as identified by TLC). The crude product was partially purified by flash column chromatography [37] (1% ethyl acetate/hexane) to yield 6 g of a colorless liquid. Careful distillation (bulb-to-bulb, 0.05 Torr, 102–107 °C, polymerizes readily) gave the pure acrylate ester, **14** (4.6 g, 71% yield) as a colorless liquid; IR: 1735s (C=O), 1650m, 1630m, 1211s cm^{-1}; ^1H NMR (300 MHz): 7.33 (s, 5H, C_6H_5), 6.36 (dd, 1H, HCH=CH, $J_{AC}[cis] = 10.3$ Hz), 6.07 (dd, 1H, HCH=CH, $J_{BC}[trans] = 17.2$ Hz), 5.76 (dd, 1H, HCH=CH, $J_{AB}[geminal] = 1.6$ Hz), 5.19 (m, 1H, $OCH_2CH_2CHCH_3$), 4.48 (s, 2H, $C_6H_5CH_2$), 3.52 (t, 2H, OCH_2CH_2, $J = 5.8$ Hz), 1.92 (m, 2H, OCH_2CH_2), 1.27 (d, 3H, $OCH_2CH_2CHCH_3$, $J = 6.4$ Hz); MS *m/z*: 234 (M^+, 6), 162 (60), 161 (55), 107 (55), 91 (100), 56 (67), 55 (76).

*The Diels–Alder adduct 2-(4-benzyloxybutyl) 3-cyclohexene-1-carboxylate (**15a**)*

To a rigorously dried flask containing $Ti(OiPr)_4$ (1.93 mL, 6.5 mmol) in 20 mL CH_2Cl_2, under argon, was added, quickly, $TiCl_4$ (2.14 mL, 19.5 mmol). As the mixture stirred for 1 h a fine yellow precipitate was formed. As a solution in 10 mL of CH_2Cl_2, of the dienophile, **14** (2 g, 8.5 mmol, 0.75 eq), and of **13** (0.5 g, 0.25 eq, 1.18 mmol), was added to the slurry, the precipitate disappeared and a clear yellow-orange solution remained. The mixture was cooled to −20 °C and stirred for 1 h. 1,3-Butadiene (10 mL, excess) was then added, and the stirred reaction mixture was monitored by gas chromatography over a period of 48 h. The contents of the flask were poured over ice and extracted with ether. The combined extracts were dried over $MgSO_4$, then concentrated to give 2.3 g of a viscous liquid. A TLC (5% EtOAc/hex.) of the crude product revealed that the trityl ether **13** remained unchanged (R_f of **13** = 0.6); there was no indication of cleavage of **12**. Careful distillation (bulb-to-bulb, 0.05 Torr, 102–107 °C) gave **14** (0.6 g, 2.6 mmol). Further distillation (bulb-to-bulb, 0.05 Torr, 147–150 °C) gave **15a** (1.47 g, 5.1 mmol, 61% yield, 86% yield based upon incomplete conversion of **14**; colorless liquid; IR: 1740s (C=O), 1465s, 1390s, 930m, 655s cm^{-1}; ^1H NMR (300 MHz): 7.32 (s, 5H, C_6H_5), 5.66 (s, 2H, CH=CH), 5.10 (m, 1H, CH_2CHCH_3), 4.48 (s, 2H, $ArCH_2$), 3.49 (t, 2H, $ArCH_2OCH_2$, $J = 6.5$ Hz), 2.45 (m, 1H, CH_2CHCH_3), 2.23 (m, 2H, $CHCH_2CH$=CH–CH_2), 2.07 (m, 2H, $CHCH_2CH$=$CHCH_2$), 1.86 (m, 4H, $CH_2CHCH_3OCOCHCH_2CH$=

$CHCH_2CH_2$), 1.25–1.22 (d, 3H, CH_2CHCH_3, $J = 6.3$ Hz); MS m/z: 288 (M^+, 0.9), 162 (84), 125 (87), 91 (100), 81 (99), 78 (78), 56 (60), *Anal.* calcd. for $C_{18}H_{24}O_3$: C 74.97, H 8.39; found: C 75.24, H 8.54.

The Diels–Alder adduct 2-(4-benzyloxybutyl) 3,4-dimethyl-3-cyclohexene-1-carboxylate (15b)

In a manner similar to that described above for **15a**, the dienophile, **14** (1 g, 4.3 mmol, and 284 mg (0.7 mmol) **13**) was added to 20 mL CH_2Cl_2 containing $TiCl_2(OiPr)_2$ formed by adding $TiCl_4$ (0.72 mL, 6.45 mmol) to a solution of $Ti(OiPr)_4$ (1.92 mL, 6.45 mmol) in CH_2Cl_2. After cooling to −20 °C, 2,3-dimethyl-1,3-butadiene (3 mL, 6.45 mmol) was added to the clear, yellow solution, which was then stirred for 48 h. The usual work-up gave 1.2 g of a viscous liquid which was fractionally distilled to give 0.23 g of **14**. Further distillation (bulb-to-bulb, 0.05 Torr, 169–170 °C) gave **15b** (0.871 mg, 65% yield, 88% yield based upon incomplete conversion of **14**. Clear, viscous liquid; IR: 1745 (C=O), 1510m, 1525s, 745s, 710s cm^{-1}; ^1H NMR (300 MHz): 7.31 (s, 5H, C_6H_5), 5.09 (m, 1H, CH_2CHCH_3), 4.47 (s, 2H, $ArCH_3$), 3.49 (t, 2H, $ArCH_2OCH_2$, $J = 6.5$ Hz), 2.48–1.67 (mm, 9H, $CH_2CH_2CHCH_3OCOCHCH_2$–CCH_3=$CCH_3CH_2CH_2$), 1.24–1.21 (d, 3H, CH_2CHCH_3, $J = 6.3$ Hz); MS m/z: 316 (M^+, 2.5), 225 (34), 153 (99), 109 (57), 108 (95), 107 (99), 91 (100). *Anal.* calcd. for $C_{20}H_{28}O_3$: C 75.91, H 8.92; found: C 75.55, H 9.20.

Preparation of (R)-3-cyclohexen-1-ylmethanol (R)-1a

In a manner identical to that described for the synthesis of racemic **11**, *R*-(−)-1,3-butanediol, (*R*)-**10** (5 g, 55 mmol $[\alpha]^{21} = -24.6°$, $c = 1$, EtOH) was added to a suspension of potassium hydride (2.5 g, 62 mmol) in THF containing DMF. Addition of excess benzyl chloride to the alkoxide mixture, refluxing overnight, and subsequent purification gave a mixture of primary and secondary alcohols, (*R*)-**12** and (*R*)-**11**. Selective tritylation of the primary alcohol, (*R*)-**12**, with DAP–TrCl, followed by distillation, gave pure (*R*)-**11** (8.2 g, 83% yield, $[\alpha]^{21} = -3.81°$, $c = 4.07$, CH_2Cl_2). Esterification of (*R*)-**11**, with acryloyl chloride, in the manner described for **11**, gave (*R*)-**14** ($[\alpha]^{21} = -29.2°$, c 4.56, CH_2Cl_2). After formation of the Diels–Alder adduct (*R*)-**15a**, reductive cleavage of (*R*)-**15a** with $LiAlH_4$ in THF, in a manner identical to that described in the formation of **1a** from **3a**, gave (*R*)-**1a** (2.0 g, 17.8 mmol in 32% overall yield from *R*-(−)-1,3-butanediol, $[\alpha]^{21} = +20.6\,°C$, $c = 3.22$, MeOH (lit. for (*S*)-**1a** [38] $[\alpha]^{21} = -100.4°$, $c = 1.7$, MeOH)) and **11** (3.3 g, 18.3 mmol, 92% cleavage). Hence, the enantiomeric excess (e.e.) of (*R*)-**1a** was assessed at 20.5%.

Polymer-bound 4-benzyloxy-2-butanol (17)

To a cooled (0 °C) suspension of potassium hydride (3.6 g, 90 mmol), under argon, in 175 mL THF, was added 1,3-butanediol (**10**) (8.2 g, 91 mmol). After stirring overnight at room temperature, 10 g of the chloromethylated polymer (1.04 mmol $-CH_2Cl\ g^{-1}$) (**16**), 25 mL DMF and a catalytic amount of dibenzo-18-crown-6-ether was added and the resulting slurry refluxed overnight. The polymer was then collected, filtered and washed several times each with THF, 1% HCl in THF, THF/water (1 : 1), THF/water (1 : 3), THF, methanol and then finally THF. To ensure thorough cleansing, the polymer was extracted in a Soxhlet extractor over refluxing THF for 48 h and dried under vacuum (1.0 Torr, 65–70 °C) overnight to give the white polymer, **1**; IR: 3500b (O–H), 1100s (C–O–C) cm^{-1}.

Selective tritylation of polymer-bound primary alcohol (17) to give tritylated polymer 18

In a manner similar to that described above for alcohols **11** and **12**, 10 g of polymer **17** in

200 mL THF was added to a solution of DAP–TrCl (1 g, 2.5 mmol) in 50 mL THF. After stirring overnight at room temperature, the polymer was filtered, washed several times with THF, THF/water (1 : 1), THF/water (1 : 3), THF, methanol and then THF. Extraction using a Soxhlet apparatus (48 h over refluxing THF) and drying (overnight, 1.0 Torr, 60–65 °C) gave the white polymer, **18** (no noticeable change in the IR spectrum).

To determine the amount of protection of the polymer-bound primary alcohol, 1.0 g of **18** was refluxed overnight in 25 mL of THF containing 1 *M* HCl. The polymer was filtered, washed several times with THF, and the filtrates combined and concentrated to yield impure trityl alcohol and **17**. Recrystallization of the trityl alcohol in benzene gave 22 mg (0.092 mmol) of the white crystal, indicating a 70% loading of the 1,3-butanediol on the polymer, assuming that there was 100% tritylation of the polymer-bound primary alcohol.

*Polymer-bound 2-(4-benzyloxybutyl) acrylate (**19**)*

In a manner identical to that described in the formation of polymer **7**, 10 g of polymer **18** was suspended in 150 mL THF containing 10 mL triethylamine. The suspension was cooled to −20 °C, and a solution of acryloyl chloride (5 mL in 60 mL THF) was added dropwise. After addition of the acid chloride, the slurry was allowed to warm up to ambient temperature and stirred for 18 h. The polymer was then filtered and washed with THF, extracted in a Soxhlet extractor with refluxing THF and then dried to give the white resin, **19**; IR (KBr): 1725s (C=O) cm^{-1}.

*Formation of the polymer-bound Diels–Alder adduct (**20**)*

In a manner similar to that described above for **3a**, 10 g of polymer **19** was added to a previously prepared solution of $TiCl_3(OiPr)$ in 150 mL CH_2Cl_2. After cooling the resultant slurry to −20 °C, excess 1,3-butadiene (7 mL) was added and the mixture stirred at −20 °C for 48 h. The filtered polymer was washed several times with CH_2Cl_2, then extracted in a Soxhlet extractor overnight with CH_2Cl_2 to give the orange coloured polymer, **20**; IR (KBr): 1740s (C=O) cm^{-1}.

*Reductive cleavage of **20** to yield the alcohol **1a***

Cleavage of **20** followed the procedure described previously for **3a**. The thoroughly dried polymer (10 g) was added to a suspension of $LiAlH_4$ (300 mg, 8 mmol) in 150 mL THF. The dark grey slurry was stirred for 24 h whereupon the regenerated polymer, **18**, was filtered and washed. After removal of the organic phases, the aqueous layer was saturated with NaCl and extracted with ether. The combined extracts were dried over $MgSO_4$ and concentrated to yield a cloudy crude product. Distillation gave **1a** (128 mg, 30% yield based on 0.38 mmol acrylate per gramme polymer, $[\alpha]^{21} = 0.0$ °C, $c = 3.1$, MeOH). The IR spectrum exhibited no carbonyl absorption, indicating complete cleavage of the ester.

*Formation of polymer (R)-**19**, of polymer-bound Diels–Alder adduct (R)-**20**, and reductive cleavage to yield polymer (R)-**18** and (R)-3-cyclohexen-1-ylmethanol, (R)-**1a***

Synthesis of resins (*R*)-**19** and (*R*)-**20** were identical to the procedures developed for **19** and **20**. However, in this instance commercially available (Aldrich) *R*-(−)-1,3-butanediol (*R*)-**10** was substituted for the racemic diol **10**. Reductive cleavage of (*R*)-**20** (14 g) and subsequent filtration of the regenerated polymer, (*R*)-**18**, gave (after concentration and distillation) the alcohol, (*R*)-**1a** (251 mg, 32% yield based on 0.38 mmol acrylate per gramme polymer, $[\alpha]^{21} = +23.5°$, $c = 3.1$,

MeOH). Hence, the enantiomeric excess (e.e.) of the chiral alcohol (*R*)-**1a** is 23.4% based on lit. [38] for (*S*)-**1a**, $[\alpha]^{21} = -100.4°$, $c = 1.7$, MeOH.

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