Enzymic Polymerisation of an Unactivated Diol/Diacid System

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The polyesterification of adipic acid and butane-1,4-diol by a commercial lipase (Lipozyme IM-20) has been studied using a two-chamber reactor and molecular sieve as a dehydrating agent. The lower oligomeric products were identified and a low-dispersity polyester averaging 20 repeat units was produced.

The pioneering work of Klibanov[1] and others over the past 15 years has firmly established enzyme catalysis as a versatile tool in organic synthesis. The discovery that hydrolase enzymes such as the lipases can show enhanced activity and stability in organic, almost anhydrous media[2-5] has focused attention on enzyme-catalysed condensations. Immobilised lipase systems, already widely used for fat processing, are finding new applications in the synthesis of esters and amides.

Biocatalysis is also a promising technique for certain categories of polyester production since linear polyesterification of diols and diacids is inefficient[6] and high temperatures, typically over 200 °C, are required for acceptable polymer yields. Such conditions are expensive in energy and limit the chemical and structural characteristics of the product: reactive functional groups will be destroyed by heat, and extensive *cis*/*trans* isomerisation of unsaturated monomers will lead to poor crystallinity of the product. The harnessing of lipases could not only provide methodology for the production of polymers under mild conditions, but could also offer the advantages of enhanced selectivity, giving rise to a narrower molecular weight distribution, a more uniform and hence stronger structure, and, for chiral monomers, optically active products.

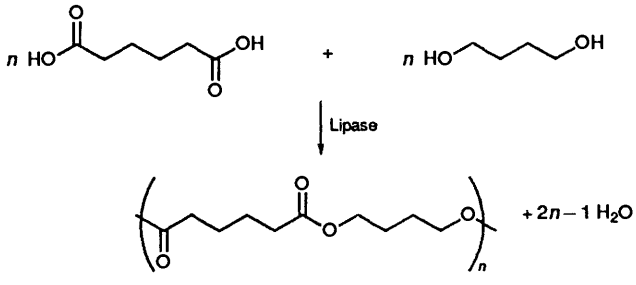
It has been shown that lipases in organic media will promote the formation of linear chain products, using direct esterification or transesterification protocols, in both one- and two-species systems.[7-10] The potential for stereoselective polycondensation[11] and the use of unsaturated[12] and aromatic[13] substrates has also been confirmed. However, the early work demonstrated that product molecular weights were quite low, tending to remain in the oligomer range (< 1000 Daltons).

The highest molecular weights reported for a two-species polycondensation were achieved by Wallace and Morrow,[14,15] who identified and sought to optimise the factors governing the efficiency of the reaction. Hence, they employed high concentration and ambient temperatures (to discourage cyclisation), anhydrous solvents (to prevent hydrolysis), primary alcohols (to minimise steric hindrance), and a strictly equimolar reactant mixture (to maintain the correct balance of functional groups). Most significant, though, was the use of diesters containing halogenated alcohol moieties. In trials with various substrates and solvents, using porcine pancreatic lipase and reaction times between 74 and 144 h, the highest molecular weight averages (M_n 11 700, M_w 15 100) were given by polyfluoroglutarate diester and butane-1,4-diol in diethyl and diisopropyl ethers, and the lowest dispersity (1.06) by a halogenoadipate diester and butane-1,4-diol in diethyl ether. It is noteworthy that when the same technique was applied to a chiral epoxyadipate diester, almost optically pure polyester was generated.[16]

Whilst the use of activated diesters gives excellent results, it cannot easily be applied in an industrial context. The starting materials are expensive, and are often not commercially available; the halogeno alcohols formed as by-products are toxic and thus present disposal problems. Potential industrial users need a biocatalytic technique which is widely applicable and gives good results using low-cost, readily available materials. Our aim in this study has been to achieve significant polyesterification in the simple adipic acid/butane-1,4-diol system, since such a biocatalytic process generating low dispersity, linear polyesters could find commercial application as a step in the manufacture of polyurethanes. The principal gains would be reduced energy demand during formation of the prepolymer and enhanced crystallinity of the final product.

Results and Discussion

The polyesterification of adipic acid and butane-1,4-diol (Scheme 1) was studied under various conditions:



Scheme 1 Polycondensation of adipic acid and butane-1,4-diol

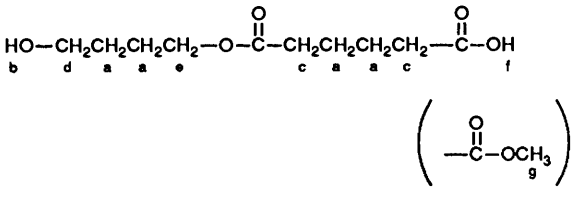
Progress of the reactions was monitored qualitatively by thin-layer chromatography using dichloromethane and ethanol (10:1 v/v) as the eluting phase. Both the starting diol and the ester products are visualised by *para*-anisaldehyde, the diol appearing at R_f 0.18 and the esters at a range of values up to R_f 0.70, reflecting a drop in polarity with increasing molecular weight. The slight difference in polarity between homologues allowed the lower oligomers to be isolated in sufficiently pure form for unambiguous characterisation. The most abundant single species formed by the esterification was found to be the hydroxy-terminated oligomer, BAB (where A represents the adipic acid moiety and B the butane-1,4-diol residue).

^{1}H NMR spectroscopy allowed the length of the oligomer chains to be estimated. The relevant chemical shifts are shown in Table 1. The number of repeat units can be calculated from the integration of the end group signals, the final diol methylene signal [entry (4) in Table 1] being the most reliable for this purpose. This method was accurate for oligomers up to four units in length. Assignments were verified by mass spectrometry (using chemical ionisation) to an upper limit of 600–700 Daltons, above which the chains tended to fragment.

Table 1 ^{1}H NMR resonances of poly(butane-1,4-diyl adipate) esters

	Multiplicity	δ	Assignment (H)
1	m	1.66–1.68	a
2	s	1.70–2.10[a]	b
3	m	2.33–2.34	c
4	t	3.66–3.70	d
5	t	4.10–4.14	e
6	s br	7.00[a]	b & f
(7	s	3.68–3.70	g)

[a] Exchangeable.



Residues from the trial reactions were analysed by gel permeation chromatography (GPC). Since all the products have very similar structures, the differences in molecular volume correspond closely to differences in molecular weight, and there is a linear logarithmic relationship between chain length and retention time. Oligomers up to $B(AB)_3$ (MW 690) were found to give rise to individual signal peaks (using a 50 Å pore column), whilst higher products have been classified into molecular weight ranges by comparison with commercial poly(ethylene glycol) (PEG) standards. A column of 500 Å maximum pore size was used to resolve component ranges above 2000 Daltons. Estimates of the number average and weight average molecular weights, M_n and M_w, were computer generated from PEG calibration and corrected to the known starting material mass. We estimate the confidence band as ± 10%.

In the absence of lipase, adipic acid and butane-1,4-diol gave no detectable reaction in diisopropyl ether at ambient temperature over 24 h. A commercial sample of porcine pancreatic lipase (PPL) showed good initial esterification activity, but was found to be insufficiently resistant to mechanical damage and was completely deactivated after 21 h. Lipozyme IM-20 (a lipase from *Mucor miehei* immobilised on a macroporous anion exchange resin, generously donated by Novo Nordisk Bioindustries UK Ltd.) after 70 h in diisopropyl ether at ambient temperature, produced an oligomeric residue with M_n 527 and M_w 769.

The range of possible solvents was limited by the need for the medium to be both inert to the reaction and sufficiently immiscible with water to prevent dehydration of the enzyme. Hydrocarbons such as hexane or benzene provide a suitable enzyme environment but negligible substrate solubility. We found that dichloromethane suppressed the activity of Lipozyme, whilst the relatively polar solvents tetrahydrofuran (THF) and acetonitrile caused dissociation of lipase protein from the carrier resin, with correspondingly poor catalysis. The best results were obtained using diisopropyl ether, whose physical properties led to good enzyme stability and adequate substrate solubility.

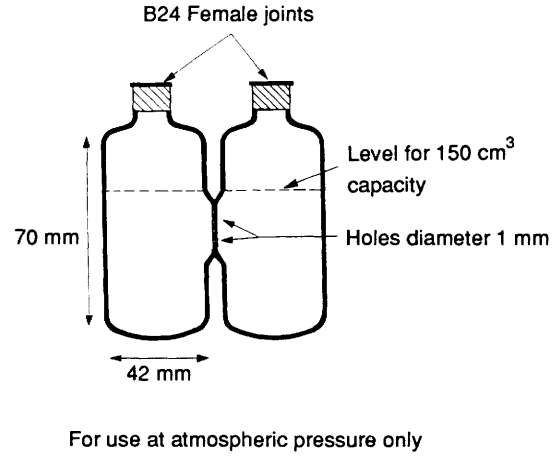


Fig. 1 Horizontal two-chamber reactor

The highest possible substrate concentrations were employed, not only to maximise reaction rates but also to promote linear esterification at the expense of lactonisation. Both the diol and the diacid have low solubility in diisopropyl ether; however, it was found that providing a separate diol phase was a distinct advantage, since polyester chains generated at the enzyme surface were dissolved by the diol, preventing obstruction of the active sites on the protein. Generally, substrate quantities corresponding to 0.4–0.5 mol dm^{-3} were used.

As expected, the rate of polyesterification increased with temperature, but losses of the volatile diisopropyl ether were high above 50 °C, so for this system a working temperature of 40–44 °C was optimal.

The time allowed for reaction is also a determinant of molecular weight average, as progressive condensation of the polyester chains will continue to occur until equilibrium is reached. A polycondensation which was allowed to continue for 30 days generated some components above 4250 Daltons but the weight averages (M_n 1544 and M_w 1975) were substantially lower than those obtained in shorter two-stage reactions (*vide infra*). In general, reactions were terminated after 70 h.

The water liberated by the polycondensation reaction will hydrolyse the product esters in the presence of the lipase, so the reaction will reach equilibrium at less than 70% conversion of starting materials unless some action is taken to prevent the accumulation of water. Since at least a partial monolayer of water molecules is required to maintain the structure of the enzyme, the system cannot be made entirely anhydrous but, nevertheless, the use of a strong desiccant whose affinity for water is greater than that of the anhydrous solvent proved distinctly advantageous. 4 Å Pellet-form molecular sieves were found to be suitable for this purpose and, if present throughout a 70 h reaction, increased the maximum product chain length by a factor of 3 and the weight average molecular weight by a factor of 2. The effect of the sieves diminished with time, and was negligible if they were added 48 h after the start of the condensation. To facilitate use of the sieves a horizontal two-chamber reactor was employed (Fig. 1). This allowed the sieves to be agitated without the risk of abrasive damage to the enzyme.

Optimisation of conditions in the above manner and use of molecular sieves to limit the 'back reaction' increases the proportion of higher weight products, leading to a rise in the weight average molecular weight, M_w. However, at the same time the polydispersity of the residue (defined as the ratio M_w/M_n) worsens, because M_n is determined chiefly by the species present in greatest number, namely the starting materials and low-weight esters.

This problem was overcome by a partial separation of the products, exploiting the differences in solubility between the lower and higher components. The starting acid and diol have appreciably greater aqueous solubility than the product esters, and it was found that, by dividing a condensation into two stages and washing the midpoint residue with water, the production of longer chains was enhanced and the overall

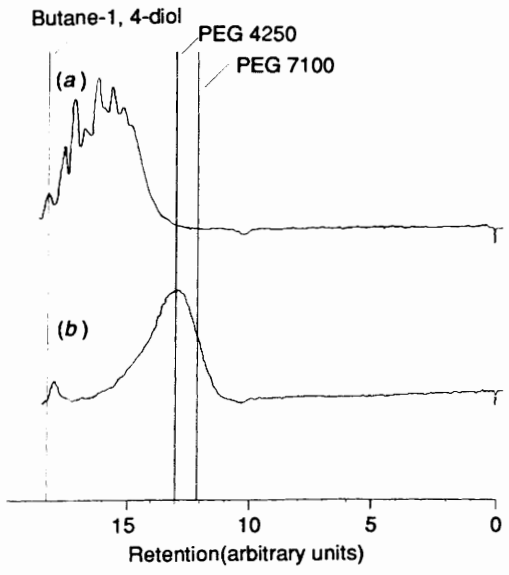


Fig. 2 GPC chromatograms of 2-stage polyesterification reaction residues. (*a*) At end of first stage. (*b*) After second stage and aqueous base wash.

weight average was raised, at some cost in yield. The relatively poor solvating power of the diisopropyl ether is also helpful in this respect. Typically, on removal of the ether, more than 80% of the residue mass remains associated with the enzyme and can be recovered by rinsing with THF. (The remaining 20% is found in the diisopropyl ether; this material can be discarded or recycled, as it comprises mainly starting diol, monoester, and diester, with only negligible amounts of higher esters, none exceeding 200 Daltons). Thus, the polyesters were easily accessible and were found to be of low dispersity. The molecular weight distribution could be narrowed further simply by extraction of residual low molecular weight species into aqueous hydrogen carbonate solution. The residue from a two-stage reaction was decreased in dispersity from 1.26 to 1.11 by utilising the sodium hydrogen carbonate wash, losing 11% of its initial mass in the process and leaving very little material of molecular weight under 600 Daltons (Fig. 2).

The optimal (laboratory scale) technique for the polycondensation of adipic acid with butane-1,4-diol by Lipozyme IM-20 catalysis can therefore be summarised as follows:

Solvent	: Anhydrous diisopropyl ether
Temperature	: 40–44 °C
Substrate/solvent ratio	: 0.4–0.5 mol dm^{-3}/diol and diacid equimolar
Desiccant	: Remote 4 Å molecular sieves employed throughout the reaction
Reaction time	: 70 h per stage
Procedure	: Reaction conducted in two stages with aqueous extraction at the mid point, isolation of the polyester using a THF rinse, and employment of an aqueous base extraction

A typical run under these conditions gave a sample of solid poly(butane-1,4-diyl adipate) in 24% yield (based on total starting material mass). The longest chains detected in the product had masses exceeding 7100 Daltons and thus a degree of polymerisation > 35. The molecular weight averages were M_n 4172 and M_w 4645, giving an average degree of polymerisation of 20 and a dispersity of 1.11. *These appear to be the highest molecular weights yet reported from an enzymic diol/diacid esterification.*

Transesterification performed under equivalent conditions using dimethyl adipate was substantially slower, generating some species over 7100 Daltons but with a lower weight average, M_w 2343.

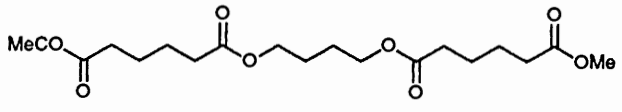
It was interesting to find that all the polyester chains generated in this study were hydroxy-terminated, despite the use of equimolar quantities of starting materials. There was no evidence of acid termination at the higher molecular weights; the only product having a carboxy function that was unambiguously identified in the reaction residues was the monoester AB. This imbalance could not be due to the midpoint aqueous extraction since the aqueous residues contained only short-chain components (typically weight averages in the range 200–250 and no component over 600 Daltons). The aqueous base wash removed residual adipic acid and monoester, but as this was accompanied by a rise in M_w, there could not have been significant loss of acid-terminated polymer.

Under conditions of very low enzyme activity the only product formed is the monoester (AB). If the reaction progresses further, however, this entity soon reaches a limiting concentration and is overtaken by accumulation of the diester BAB and to a lesser extent its homologue $B(AB)_2$, which become the dominant low-weight products. The oligomer $B(AB)_3$ was also identified, and so it appears that addition of the repeat unit AB to hydroxy-terminated oligomers is an important element in the process of chain growth.

The dominance of hydroxy group end-functions is probably a consequence of the very poor solubility of adipic acid in the low-polarity solvent. During much of the reaction the greater part of the acid is undissolved, so there is always a substantial excess of diol at the surface of the catalyst. In this situation rapid conversion of AB into BAB would be expected, making BAB rather than AB the principal active species: it will lose one of its diol moieties on acylating the enzyme, leaving an AB repeat unit bonded at the active site for subsequent transfer to a second BAB molecule.

The use of a 'reservoir' of solid acid allows the continuous production of BAB and hence ongoing chain growth. For industrial purposes this outcome is advantageous, in that hydroxy-terminated polymers are preferred and residual acids can be removed more readily if they are present in solution only as low-weight species.

In our transesterification trials, the relatively good solubility of dimethyl adipate in organic solvents was reflected in an abundance of methoxy-terminated products such as the 'acid diester' EBE **1** and the dimer EBAB, in conjunction with BAB and $B(AB)_2$.



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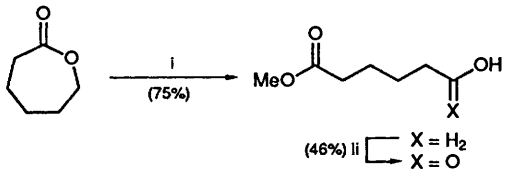
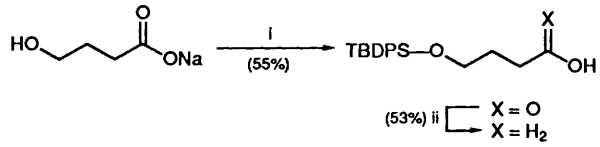
A sample of all-hydroxy terminated polymer (M_n 1109, M_w 1219) reacted with an equimolar quantity of adipic acid to produce a modest rise in weight averages (to M_n 1198, M_w 1370), and a spread of component sizes down to free diol. This suggests that the acid will condense preferentially with smaller chains liberated by destructive hydrolysis, rather than acting to link pre-existing polyester units.

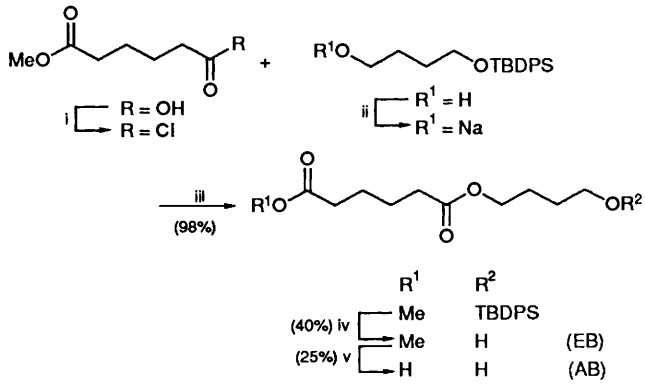
In order to verify the identity and importance of the esters AB and EB in the polymerisation process, both were synthesised from ε-caprolactone and sodium 4-hydroxybutyrate (Schemes 2–4). A sample of the methoxy 'monoester' EB was subjected to lipase catalysis and gave rise to the same condensation products as were obtained in the corresponding diol/dimethyl adipate



Scheme 2 Synthesis of methyl adipate. *Reagents and conditions:* i, NaOMe/MeOH, room temp., 2 h; ii, $CrO_3/H_2SO_4/H_2O$/acetone, 0 °C–room temp., 90 min.



Scheme 3 Synthesis of 4-(*tert*-butyldiphenylsiloxy)butan-1-ol. *Reagents and conditions:* i, TBDPSCl/DMF/imidazole (cat.), room temp., 18 h; ii, BH_3·THF/THF, room temp., 19 h.



Scheme 4 Preparation of 4-hydroxybutyl adipate (AB) and the corresponding methyl ester (EB). *Reagents and conditions:* i, $(ClCO)_2/CH_2Cl_2$/DMF (cat.), 0 °C–room temp., 17 h; ii, NaH/THF/imidazole (cat.), room temp., 19 h; iii, THF, reflux, 4 h; iv, TBAF/THF, room temp., 70 h; v, LiI/pyridine, reflux, 20 h.

transesterification, but with higher weight average and maximum chain length. To account for the comparatively high rate of condensation, the 'monoester' itself must be the major incremental unit. Transesterification chain growth probably occurs in the main by the linking of EB molecules into bifunctional $EB(AB)_n$ species, some of which will condense with one another to create the higher esters. Thus, initial reaction of dimethyl adipate with diol generates EB monomer, whereafter the individual substrates are not major participants in the process of polyester formation.

Conclusions

Whilst it seems unlikely that enzymic catalysis can directly generate very high molecular weight commercial polymers, we have shown that intermediate processes such as the production of hydroxy-terminated low polyester in the pre-polymer stage of polyurethane manufacture could certainly benefit from this technology. Useful polycondensation reactions without the need for the synthesis of halogenated derivatives of substrates can be achieved by very simple manipulative techniques which lend themselves to industrial scale-up. The screening of new lipases as they become commercially available should lead to a reduction in process times, and provide a range of catalysts suitable for other diol/diacid combinations.

Experimental

Gel permeation chromatography (GPC) was performed by Baxenden Chemicals Ltd. using Waters 440 series chromatographic equipment. The columns, manufactured by Polymer Laboratories Ltd., had dimensions 600 × 7.5 mm and were packed with PL gel, a highly crosslinked spherical polystyrene/divinylbenzene material of particle size 10 μm and pore size either 50 or 500 Å. The detector was a Waters model 401 differential refractometer, and estimates of molecular weight average were made by a BBC model B microcomputer from a calibration against commercial PEG samples. All molecular weights are expressed in Daltons.

Adipic acid, butane-1,4-diol and dimethyl adipate were obtained commercially, with a stated minimum purity of 99%. For polycondensation experiments, the reactants were held under high vacuum (< 1 mmHg) for a minimum of 2 h immediately before use to remove absorbed air and moisture.

Diisopropyl ether was purchased anhydrous (water content < 0.005%, purity 99%) and handled under nitrogen. Other solvents used as reaction media were dried by standard laboratory methods. Molecular sieves were in pellet form and of 4 Å pore size. They were activated before use by baking at 220 °C under high vacuum for a minimum of 2 h.

Representative Simple Preparation.—Adipic acid (2.09 g, 14.30 mmol) and butane-1,4-diol (1.29 g, 14.30 mmol) in diethyl ether (100 cm^3) were stirred with Lipozyme (0.59 g) under a nitrogen atmosphere at ambient temperature (23–24 °C) for 70 h. Part of the acid failed to dissolve and TLC showed only early-stage products. The enzyme was filtered off and rinsed with THF (5 × 20 cm^3), and the combined filtrates were evaporated to give a moist white solid. GPC analysis: butane-1,4-diol, adipic acid, AB, BAB, 440–600; M_n 147, M_w 291.

Representative 2-Chamber Preparation.—Adipic acid (9.83 g, 67.28 mmol) and butane-1,4-diol (6.06 g, 67.28 mmol) in diisopropyl ether (150 cm^3) were stirred with Lipozyme (2.94 g) and molecular sieves (dry weight 23.60 g) under a nitrogen atmosphere at 40–42 °C in a horizontal 2-chamber reactor (Fig. 1). The sieves were placed remote from the Lipozyme and stirred. After 70 h the solids were filtered off and rinsed with THF (12 × 25 cm^3), and the combined filtrates were evaporated to give a colourless oil which set to a soft white solid and later partially crystallised. GPC analysis: butane-1,4-diol, adipic acid, AB, BAB, 440–1450, over 1450; M_n 361, M_w 1083. The residue was dissolved in ethyl acetate (200 cm^3) and the solution washed with deionised water (2 × 200 cm^3), dried ($MgSO_4$), filtered and evaporated to give a colourless oil which slowly crystallised. GPC analysis: adipic acid, AB, BAB, 440–1450, over 1450; M_n 477, M_w 1178. The bulk of this residue (8.54 g) was returned to the reactor as before with fresh solvent (140 cm^3), Lipozyme (2.01 g), and molecular sieves (22.86 g), and stirred under nitrogen at 40–42 °C for a further 70 h. The solution was then filtered and evaporated to give a colourless oil (0.84 g) which separated into a clear oil and translucent, semi-solid droplets. GPC analysis: butane-1,4-diol, adipic acid, AB, BAB, 440–1450, over 1450; M_n 260, M_w 555. The Lipozyme and sieves were washed thoroughly with THF (10 × 25 cm^3), and the washings filtered and evaporated to furnish an oil (4.25 g) that crystallised to a dense white solid. GPC analysis (500 Å column): adipic acid, AB, 440–7100, over 7100; M_n 3429, M_w 4316. A sample of this solid (1.72 g) was dissolved in ethyl acetate (100 cm^3) and stirred with saturated aqueous sodium hydrogen carbonate (100 cm^3) for 2 h. The organic phase was washed with equal volumes of deionised water and saturated brine, dried ($MgSO_4$), filtered and evaporated to afford a clear colourless oil which crystallised to a soft white solid (1.54 g). GPC analysis (500 Å column): 600–7100, over 7100; M_n 4172, M_w 4645.

Representative Transesterification/Oligomer Identification.—Dimethyl adipate (2.95 g, 16.94 mmol) and an excess of butane-1,4-diol (1.59 g, 17.66 mmol) in diisopropyl ether (100 cm^3) were stirred with Lipozyme (0.6 g) under a nitrogen atmosphere at ambient temperature (21–23 °C) for 70 h. The solvent was removed and the solid (product + enzyme + support) rinsed with THF (4 × 20 cm^3), the combined filtrates were evaporated to afford a clear oil. GPC analysis: dimethyl adipate, butane-1,4-diol, EB, BAB/EBE, 440–1450; M_n 231, M_w 274. Multistage column chromatography yielded four products. The least polar product was a clear liquid (0.20 g): ν/cm^{-1} 2957 (C–H str), 1739 (C=O str) and 1438 (C–H def); δ_H(100 MHz; $CDCl_3$) 1.68 (8 H, m, β CH_2), 2.34 (5 H, m, OCOCH_2), 3.68 (6 H, s, CH_3) and 4.10 (1 H, m, CH_2O) [Found M^+, 374.1940, $C_{18}H_{30}O_8$ (EBE) requires M^+, 374.1940]. The second component was a clear liquid which set to a white waxy solid (0.06 g): ν/cm^{-1} 3455 (O–H str), 2956 (C–H str) and 1735 (C=O str); δ_H(100 MHz; $CDCl_3$) 1.66 (27 H, m, β CH_2 and OH), 2.34 (10 H, m, OCOCH_2), 3.68 (4 H, t, CH_2OH) and 4.12 (10 H, m, CH_2O) {Found: M^+, 490.2778. $C_{24}H_{42}O_{10}$ [B(AB)$_2$] requires 490.2778}; GPC: BAB, B(AB)$_2$, 600–960; M_n 493, M_w 497. The next component was a clear liquid (0.20 g): ν/cm^{-1} 3439 (O–H str), 2948 (C=H str) and and 1735 (C=O str); δ_H($CDCl_3$) 1.68 (13 H, m, β CH_2), 1.78 (2 H, s, labile, O*H*), 2.34 (4 H, m, OCOCH_2), 3.68 (4 H, t, CH_2OH) and 4.14 (4 H, t, CH_2O) [Found: M^+, 290.1729. $C_{14}H_{26}O_6$ (BAB) requires 290.1729]; GPC: BAB/EBE; M_n 291, M_w 299. The most polar component was a clear liquid (1.36 g): ν/cm^{-1} 3460 (O–H str), 2956 (C–H str), 1728 (C=O str) and 1439 (C–H def); δ_H($CDCl_3$) 1.68 (15 H, m, β CH_2 and O*H*), 2.34 (7 H, m, OCOCH_2), 3.70 (7 H s and m superimposed, CH_3 and CH_2OH) and 4.12 (4 H, t, CH_2O) [Found: (low resolution): M^+, 232 and 432. $C_{11}H_{20}O_5$ (EB) requires 232, $C_{21}H_{36}O_9$ (EBAB) requires 432]; GPC: EB, 440–600, 600–960; M_n 260, M_w 298.

Methyl 6-Hydroxyhexanoate.—ε-Caprolactone (7.24 g, 63.41 mmol) in methanol (30 cm^3) was stirred with sodium methoxide (7.07 g, 130.78 mmol) at ambient temperature for 2 h. The excess of methoxide formed a white suspension which was cleared by the gradual addition of deionised water. The resulting solution was acidified with 2 mol dm^{-3} HCl (aq) and extracted with diethyl ether (6 × 100 cm^3) and the combined extracts were dried ($MgSO_4$), filtered, and evaporated to yield a clear, colourless oil (6.97 g, 75%): ν/cm^{-1} 3341 (O–H str), 2943 (C–H str) and 1717 (C=O str); δ_H(60 MHz; $CDCl_3$) 1.64 (6 H, m, β CH_2), 2.47 (2 H, m, CH_2CO), 3.76 (2 H, t, CH_2OH), 3.78 (3 H, s, OCH_3) and 4.84 (1 H, s, OH).

Monomethyl Adipate.—Methyl 6-hydroxyhexanoate (6.10 g, 41.73 mmol) in acetone (40 cm^3) at 0 °C was treated with Jones reagent (CrO_3, H_2SO_4 in H_2O/8 mol dm^{-3}), which was added dropwise over 30 min until the orange colour just persisted on stirring. The solution was stirred at ambient temperature for a further 40 min after which the excess of reagent was destroyed by the gradual addition of methanol until no orange colour remained. The solvents were evaporated and the residue dissolved in deionised water (200 cm^3) from which the organic components were extracted into ethyl acetate (3 × 200 cm^3); this was shaken with saturated aqueous sodium hydrogen carbonate until there was no further effervescence, then the aqueous phase was acidified with 2 mol dm^{-3} HCl (aq) and re-extracted into ethyl acetate. The organic phase was dried ($MgSO_4$), filtered and evaporated to yield a partially molten white solid (3.11 g, 46%): ν/cm^{-1} 2200–3600 (O–H str), 2943 (C–H str) and 1688br (C=O str); δ_H(60 MHz; $CDCl_3$) 1.78 (4 H, m, β CH_2), 2.47 (4 H, m, CH_2CO) and 3.77 (3 H, s, OCH_3).

4-(tert-*Butyldiphenylsiloxy)butyric Acid.*—Sodium 4-hydroxybutyrate (3.27 g, 25.97 mmol), imidazole (3.90 g, 57.21 mmol), dry DMF (20 cm^3) and *tert*-butylchlorodiphenylsilane (7.5 cm^3, 7.9 g, 29 mmol) were stirred together under a nitrogen atmosphere at ambient temperature for 18 h. The mixture was poured into ice–water (100 cm^3), acidified with 2 mol dm^{-3} HCl (aq) and extracted into hexane (3 × 400 cm^3). The combined extracts were then evaporated to 50 cm^3 and shaken with saturated aqueous sodium hydrogen carbonate until no further effervescence occurred. After addition of water to the solution to redissolve a fluffy white precipitate, it was acidified with 2 mol dm^{-3} HCl (aq) and extracted into hexane (3 × 300 cm^3). The combined extracts were then dried ($MgSO_4$) and evaporated to yield a colourless, viscous oil (4.86 g, 55%): ν/cm^{-1} 2200–3600 (O–H str), 3074 (phenyl C–H str), 2932 (alkyl C–H str), 1887 (C=O str), 1107 (diethyl ether C–O str) and 701 (phenyl C–H def); δ_H(60 MHz; $CDCl_3$) 1.24 (9 H, s, Bu^t), 2.08 (2 H, m, β CH_2), 2.63 (2 H, m, CH_2CO), 3.83 (2 H, m, OCH_2), 7.53 (6 H, m, ArH), 7.75 (4 H, m, ArH) and 9.42 (1 H, s, br, CO_2H).

4-(tert-*Butyldiphenylsiloxy)butan-1-ol.*—4-(*tert*-Butyldiphenylsiloxy)butyric acid (4.68 g, 13.67 mmol) in THF (7 cm^3) was stirred under a nitrogen atmosphere at ambient temperature and a solution of borane (1 mol dm^{-3} in THF) injected dropwise over 20 min. Addition was continued until no further effervescence resulted, to a total volume of 20 cm^3 (20 mmol). The mixture was stirred for 19 h and the excess of borane destroyed by the gradual addition of cold deionised water (50 cm^3). The organic compounds were extracted into diethyl ether (3 × 80 cm^3) and the combined extracts were thoroughly shaken with saturated aqueous sodium hydrogen carbonate, washed with deionised water (2 × 100 cm^3), dried ($MgSO_4$), filtered and evaporated to provide a yellowish oil (3.61 g) containing both alcohol and acid. Column chromatography on silica gel yielded pure monoprotected diol (2.40 g, 53%) as a colourless oil: ν/cm^{-1} 3352 (O–H str), 3073 (phenyl C–H str), 2934 (alkyl C–H str), 1107 (ether C–O str) and 701 (phenyl C–H def); δ_H(60 MHz; $CDCl_3$) 1.23 (9 H, s, Bu^t), 1.80 (4 H, m, β CH_2), 2.22 (1 H, s, OH), 3.80 (4 H, m, OCH_2), 7.49 (6 H, m, ArH) and 7.73 (4 H, m, ArH).

4-*Hydroxybutyl Adipate* (*AB*) *and the Corresponding Methyl Ester* (*EB*).—Sodium hydride/mineral oil composite (0.32 g, 0.19 g NaH, 7.9 mmol) was stirred with THF (15 cm^3). After settling, the supernatant liquid was drawn off and the procedure repeated. THF (15 cm^3) and imidazole (one crystal) were added to the mixture which was then stirred under a nitrogen atmosphere at 0 °C. A solution of 4-(*tert*-butyldiphenylsiloxy)-butan-1-ol (2.36 g, 7.17 mmol) in THF (35 cm^3) was injected slowly over several minutes and stirring continued at ambient temperature for 19 h to form a solution of sodium 4-(*tert*-butyldiphenylsiloxy)butoxide. Monomethyl adipate (3.00 g, 18.70 mmol) in dry CH_2Cl_2 (50 cm^3) was stirred under a nitrogen atmosphere at 0 °C and oxalyl chloride (2.0 cm^3, 2.9 g, 23 mmol) was injected dropwise. After 5 min, one drop of DMF was added. The mixture was allowed to reach ambient temperature and stirred for 17 h; the volatile components were then evaporated to leave a clear oil. This oil was dissolved in dry THF (20 cm^3) and added to the crude solution of sodium 4-(*tert*-butyldiphenylsiloxy)butoxide. The mixture was heated under reflux for 4 h after which residual NaH and acyl chloride were destroyed by the gradual addition of deionised water (10 cm^3), followed by further water (90 cm^3) to redissolve the resulting precipitate. The organic solvent was evaporated and the organic components were extracted into ethyl acetate. The extract was stirred with saturated aqueous sodium hydrogen carbonate, washed with saturated brine, dried ($MgSO_4$), filtered and evaporated to yield 4-(*tert*-butyldiphenylsiloxy)butyl methyl

adipate (3.32 g, 98%): ν/cm^{-1} 3073 (phenyl C–H str), 2956 (alkyl C–H str), 1732 (C=O str), 1107 (ether C–O str) and 704 (phenyl C–H def); δ_H(60 MHz; $CDCl_3$) 1.05 (9 H, s, Bu^t), 1.64 (8 H, m, β CH_2), 2.30 (4 H, m, CH_2CO), 3.62 (3 H, s, OCH_3), 3.65 (2 H, t, OCH_2), 4.04 (2 H, t, CH_2OCO), 7.37 (6 H, m, ArH) and 7.63 (4 H, m, ArH). 4-(*tert*-Butyldiphenylsiloxy)butyl methyl adipate (1.78 g, 3.78 mmol) in THF (20 cm^3) was stirred under a nitrogen atmosphere at ambient temperature with tetrabutylammonium fluoride (1 mol dm^{-3} solution in THF; 8.0 cm^3). After 70 h the THF was evaporated and the residue dissolved in deionised water (50 cm^3). The solution was extracted into dichloromethane (4 × 100 cm^3) and the combined extracts were washed with saturated brine (100 cm^3), dried ($MgSO_4$), filtered and evaporated to yield a brown oil. This was chromatographed on silica gel to give a clear oil characterised as 4-hydroxybutyl methyl adipate (EB) (0.3517 g, 40%): ν/cm^{-1} 3454 (OH str), 2953 (CH str) and 1734 (C=O str); δ_H(250 MHz; $CDCl_3$) 1.75 (1 H, s, OH), 1.68 (8 H, m, β CH_2), 2.34 (4 H, m, CH_2CO), 3.68 (2 H, t, CH_2OCO), 3.68 (3 H, s, OCH_3) and 4.12 (2 H, t, CH_2LH) [Found: M$^+$, 232.13 108, $C_{11}H_{20}O_6$ (EB) requires 232.13 108]. 4-Hydroxybutyl methyl adipate (0.16 g, 0.69 mmol) in pyridine (3.2 cm^3) was protected from light and refluxed under a nitrogen atmosphere with anhydrous lithium iodide (0.37 g, 2.8 mmol) for 20 h. The pyridine was evaporated and the residue dissolved in water (5 cm^3) and the solution acidified with 2 mol dm^{-3} HCl (aq). It was then extracted into ethyl acetate (4 × 40 cm^3) and the combined extracts were washed with aqueous sodium thiosulfate (2 × 100 cm^3) to remove iodine. The organic phase was vigorously stirred with an equal volume of saturated aqueous sodium hydrogen carbonate, after which the aqueous phase was acidified and re-extracted into ethyl acetate (3 × 50 cm^3). The combined extracts were washed with deionised water (150 cm^3) and saturated brine (150 cm^3), dried ($MgSO_4$), filtered and evaporated to yield the carboxylic acid (AB) (0.04 g): ν/cm^{-1} 2400–3600 (OH str), 2947 (CH str) and 1717br (C=O str); δ_H(250 MHz; $CDCl_3$) 1.66 (8 H, m, β CH_2), 2.33 (4 H, m, CH_2CO), 3.66 (2 H, t, CH_2OCO), 4.10 (2 H, m, CH_2OH) and 7.00 (2 H, s br, OH and COOH) [Found: M$^+$, 218.1154, $C_{10}H_{18}O_5$ (AB) requires 218.1154].

Acknowledgements

We should like to thank Mr. Paul Dunnings of Baxenden Chemicals Ltd. for the provision of GPC data and Dr. Julia Dickinson and Dr. Martin McClinton at Exeter University for helpful advice.

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Paper 3/00160A
Received 11*th January* 1993
Accepted 22*nd January* 1993