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Stereocontrolled Synthesis of Polyketide Libraries: Boron-Mediated Aldol Reactions with Aldehydes on Solid Support

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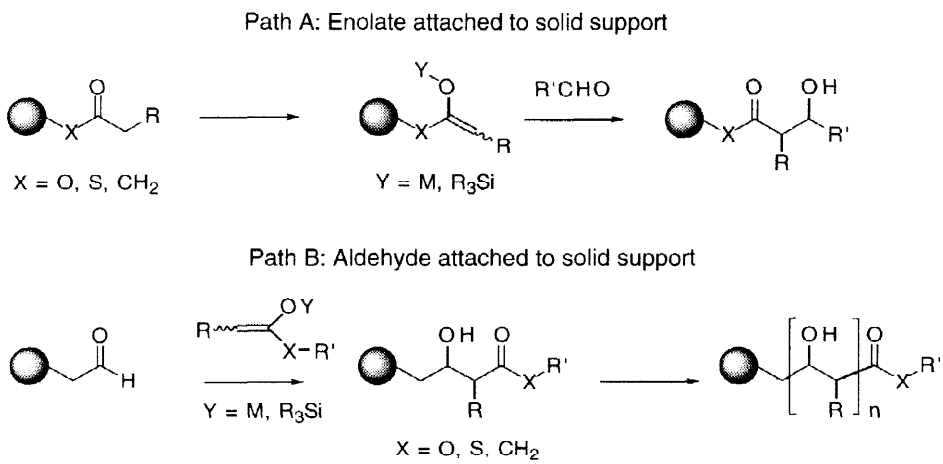
Abstract. Two complementary classes of chiral boron enolates for adaptation to aldol additions to resin-bound aldehydes were studied : (*i*) the thioester-derived enolate **1** bearing chiral ligands on boron, and (*ii*) the chiral ketone-derived enolate **2**. The viability of performing highly enantioselective, boron-mediated, aldol reactions was demonstrated by the preparation of resin-bound adducts **15** (91% ee) and **21** (88% ee). The solid phase aldol reactions of enolate **2** can be combined with an *in situ* reduction of the intermediate aldolate using $LiBH_4$, leading to the controlled introduction of four contiguous stereocentres, as in **33** → **40** (>96% diastereoselectivity). The choice of linker is crucial and the available experimental evidence suggests that trityl and silyl linkers are optimal. This methodology should be amenable to the stereocontrolled synthesis of polyketide libraries.

In the last few years, the study and development of organic synthesis on solid support has seen an enormous surge of interest and activity. Much effort has been expended in the adaptation of a wide variety of organic reactions to the solid phase.[1,2] Solid-supported strategies leading to the iterative synthesis of the most important biopolymers, namely peptides, oligosaccharides and oligonucleotides, are well established and many of these have also been adapted to enable automation. However, an analogous approach to the synthesis of polyketides, a class of biopolymer consisting of a 1,3,5,*n*-polyol chain with defined stereochemistry, is not yet available.



Scheme 1: Alternative synthetic pathways for solid-phase aldol reactions

By using the aldol reaction to mimic the stereoregulated chain growth involved in the biosynthesis of natural polyketides,[3] the combinatorial assembly of libraries of diverse unnatural polyketides can be envisaged. Therefore, we were attracted by the possibility of developing general protocols for performing asymmetric aldol reactions on solid support, which might ultimately be employed in an iterative sense to give polyketide libraries.

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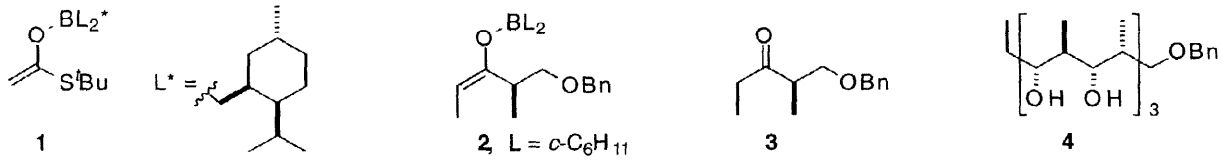
Notably, enormous structural diversification should be possible through variation in the enolate as the nucleophilic building block, the number of chain extensions, the stereochemical information, oxidation state, and the introduction of unsaturation or rings. Some examples of solid phase aldol reactions have recently been reported – with either the enolate (**Scheme 1**, path A)[4,5] or the aldehyde component (path B)[6] linked covalently to the resin support. Provided a suitable conversion to the chain-extended aldehyde can be realised, the latter pathway should allow iteration of the aldol addition step.[7]

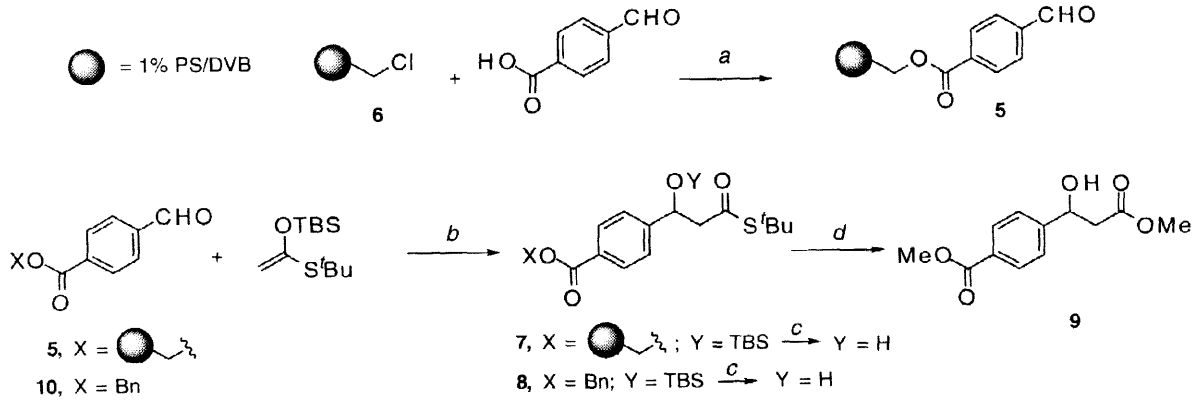


In this initial study towards the stereocontrolled construction of polyketide libraries, we selected two complementary classes of chiral boron enolate for adaptation to aldol additions with resin-bound aldehydes – (*i*) the thioester-derived enolate **1** bearing chiral ligands on boron,[8] and (*ii*) the chiral enolate **2** derived from (*R*)-1-(benzyloxy)-2-methylpentan-3-one (**3**).[9] In the first case, the use of menthone-derived ligands imparts high levels of enantioselectivity in the additions of enolate **1** to prochiral aldehydes and achieves reagent control with chiral aldehydes, as required for introduction of the stereochemistry in the growing polyol chain. Furthermore, the use of a thioester should enable conversion into an aldehyde for further iteration. In the second case, the (*E*)-enol dicyclohexylborinate **2** acts as a versatile dipropionate reagent and undergoes aldol additions to a large variety of aldehydes with high levels of diastereoselectivity. Moreover, this reaction can be combined with an *in situ* reduction step to generate 1,3-diols with defined sequences of four contiguous stereocentres. By using this chemistry in solution phase, the iterative assembly of extended polypropionates, *e.g.* **4**, has recently been demonstrated.[10]

RESULTS AND DISCUSSION

Part 1: Preliminary Work Using Mukaiyama Aldol Reactions

The application of a solid-phase aldol protocol, as depicted in path B of **Scheme 1**, requires the establishment of a temporary bond between the aldehyde and the resin. In addition, this linker should be compatible with the proposed chemistry. In our preliminary studies using Mukaiyama aldol reactions, we opted for the use of an ester linkage in the aldehyde **5** (**Scheme 2**),[11] which was formed by the treatment of Merrifield resin (**6**) with the sodium salt of *p*-carboxybenzaldehyde.

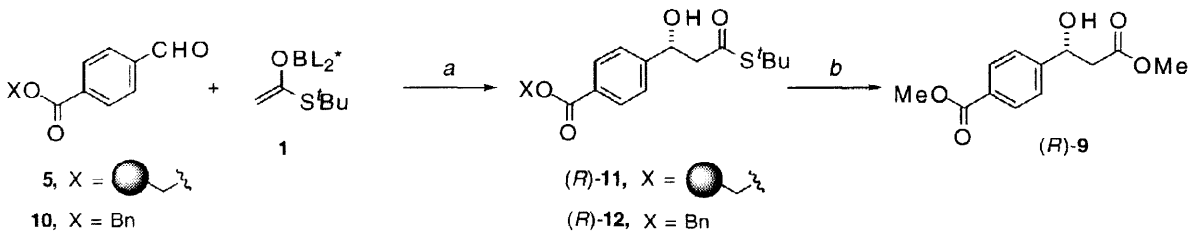


Scheme 2 (a) NaH, $(C_6H_{13})_4NBr$, THF, reflux, 3 d; (b) $BF_3{\bullet}Et_2O$, CH_2Cl_2, -78 °C, 1.5 h; (c) HF, CH_3CN, 20 °C, 7 d; (d) i: Bu_4NOH, THF/MeOH, 70 °C, 24 h; ii: MeI, CH_3CN, 20 °C, 6 h.

The resin-bound aldehyde **5** was then reacted with 2 equivalents of the *t*-butyldimethylsilyl ketene acetal derived from *t*-butyl thioacetate,[12] in the presence of $BF_3 \cdot Et_2O$, leading to the racemic silylated aldol adduct **7** (Y = TBS). The reactions were followed by IR spectroscopy but, since the changes in the C=O stretching frequency were often inconclusive, cleavage of analytical samples of the resin and monitoring the reactions against solution samples were also necessary. Desilylation with HF gave the corresponding aldol product **7** (Y = H), identified by the disappearance of the TBS group (25.8 ppm) in the gel-phase ^{13}C NMR spectrum. A loading of 0.4 mmol/g was determined for the resin **7** (Y = H) by cleavage with tetrabutylammonium hydroxide and formation of the dimethyl ester **9** with methyl iodide in acetonitrile. This corresponds to an overall yield of 36% (*cf.* 56% yield obtained for the analogous solution phase model, as in **10** → **8** → **9**).

Part 2: The Use of Thioester-Derived Boron Enolates

The use of boron enolates **1** bearing chiral ligands were then studied for asymmetric aldol additions with aldehydes on solid support (**Scheme 3**). The resin-bound aldehyde **5** was reacted with the preformed boron enolate **1**, derived from *t*-butyl thioacetate by treatment with the (-)-menthone-derived reagent, L^*_2BBr, in the presence of Et_3N,[8] to give aldol adduct (*R*)-**11**. Cleavage and methylation gave the diester (*R*)-**9** in 18% yield (*cf.* 22% yield obtained for the corresponding solution chemistry, as in **10** → **12** → **9**) – see **Table 1**, entries 1 and 2. These poor yields are ascribed to the reduced reactivity of this type of aldehyde with boron enolates. The enantiomeric excess of the cleaved aldol adduct (*R*)-**9** was determined from an $Eu(hfc)_3$ ^1H NMR study to be 91% (*cf.* 94% ee for (*R*)-**9** obtained from the corresponding solution model **10** *via* **12**).

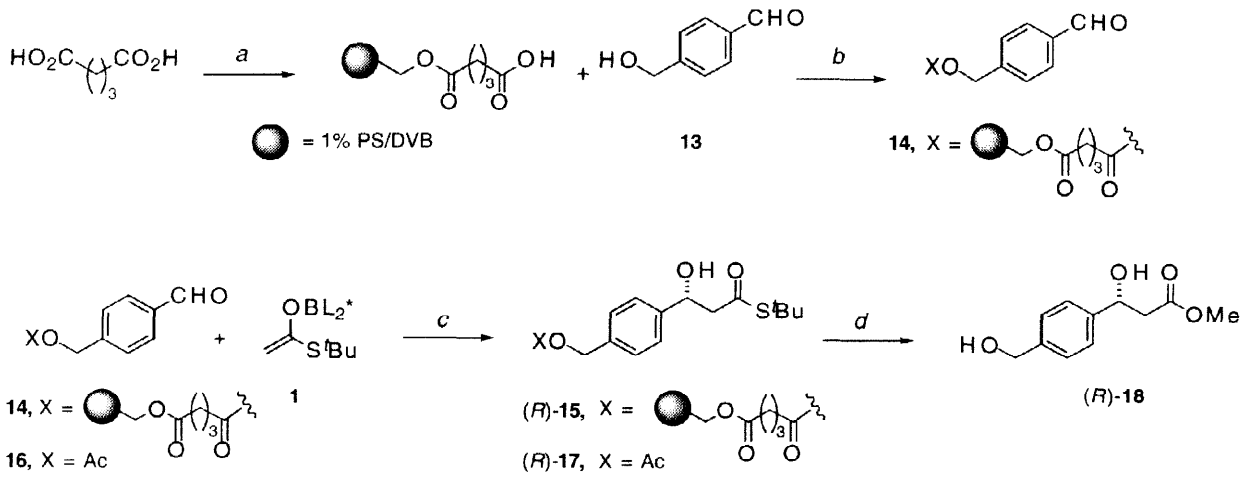


Scheme 3 (a) i: CH_2Cl_2/Et_2O,-78 → -5 °C, 16 h; ii: 30% H_2O_2, MeOH, pH 7 buffer, 20 °C, 30 min; (b) i: Bu_4NOH, THF/MeOH, 70 °C, 24 h; ii: MeI, CH_3CN, 20 °C, 6 h.

These low conversions prompted a reconsideration of the choice of the linker group. We initially decided to maintain the ester linkage though inverting the functionalities on the resin and aldehyde. An aliphatic diacid spacer (glutaric acid) and 4-(hydroxymethyl)benzaldehyde (**13**) were selected on this basis (**Scheme 4**). The attachment of aldehyde **13** was achieved by coupling it, using diisopropylcarbodiimide in the presence of HOBt, with the carboxylic acid derived from reacting sodium glutarate with Merrifield resin (**6**). The loading for the resulting resin-bound aldehyde **14** was determined to be 0.096 mmol/g.

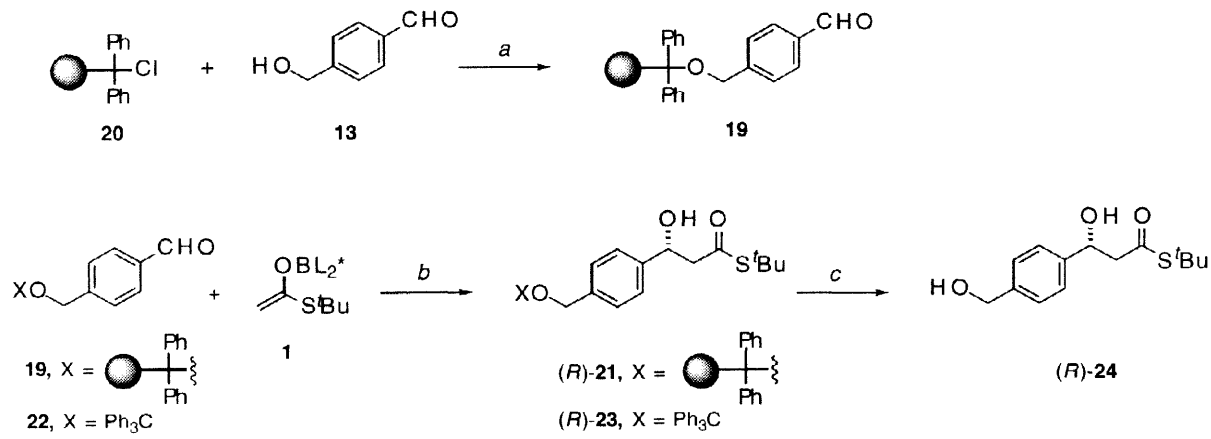
Treatment of resin **14** with the preformed boron enolate **1** led to the formation of the aldol adduct (*R*)-**15**. The same aldol reaction performed on the solution model **16** gave the adduct (*R*)-**17**. After hydrolysis and methylation, in each case, this led to the isolation of ester (*R*)-**18** in 64% (solid phase) and 48% (solution phase) yields – see **Table 1**, entries 3 and 4. The enantiomeric excesses obtained in these reactions were high – both on the resin (91% ee) and in solution (94% ee). Unfortunately, the low loading of the aldehyde on the resin hampered the usefulness of this system.

The preceding results indicated that synthetically useful levels of enantioselectivity could be achieved for solid phase aldol reactions with enolate **1** but the chemical efficiency was poor due to an inappropriate choice of linker. The use of an acid labile ether linker to introduce the aldehyde onto the resin was then considered. The trityl linker was attractive as it had already been employed for the immobilization of alcohols and aldehydes.[13]



Scheme 4 (a) **6**, NaH, $(C_6H_{13})_4NBr$, THF, reflux, 3 d; (b) DIC, DMAP, HOBt, DMF, 20 °C, 24 h; (c) i: CH_2Cl_2/Et_2O, -78 → -5 °C, 16 h; ii: 30% H_2O_2, MeOH, pH 7 buffer, 20 °C, 30 min; (d) i: Bu_4NOH, THF/MeOH, 20 °C, 24 h; ii: MeI, CH_3CN, 20 °C, 6 h.

As shown in **Scheme 5**, the aldehyde **19** was isolated in *ca.* 80% yield by treatment of 4-(hydroxymethyl)benzaldehyde (in the presence of *sym*-collidine and tetrabutylammonium iodide) with commercially available trityl chloride resin **20**. Reaction of this resin-bound aldehyde **19** with the preformed boron enolate **1** led to the isolation, after three reaction cycles, of aldol adduct (*R*)-**21**. The same aldol reaction performed on the solution model **22** gave the adduct (*R*)-**23**. Following cleavage of the aldol product (*R*)-**21** from the resin with *p*-toluenesulfonic acid (0.2 M, THF/MeOH), the *t*-butyl thioester (*R*)-**24** was isolated in 60% overall yield (77% in solution from **23**). In this case, the enantioselectivity of the solid phase process (88% ee for (*R*)-**24**) was better than that achieved for the solution phase reaction (80% ee) – see **Table 1**, entries 5 and 6. This result demonstrated that an acceptable yield and enantioselectivity could be realised with the resin-supported aldehyde **19**. Moreover, the trityl linker should, in principle, be compatible with iterative chemistry.



Scheme 5 (a) *sym*-collidine, Bu_4NI, CH_2Cl_2; (b) i: CH_2Cl_2/Et_2O, from -78 °C to -5 °C, 16 h; ii: 30% H_2O_2, MeOH, pH 7 buffer, 20 °C, 30 min; (c) PTSA, THF/MeOH, 20 °C, 22 h.

Table 1. Enantioselective Aldol Reactions of Boron Enolate **1**.

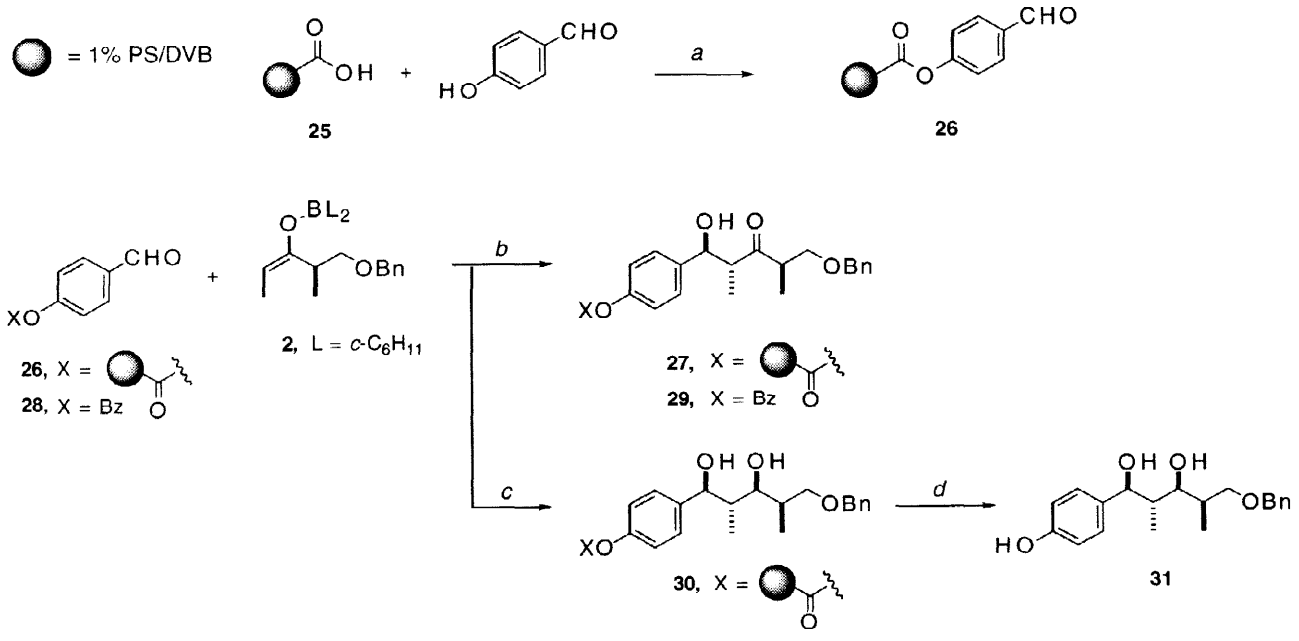
Entry	Aldehyde	Aldol	Config.	Yield (%)	ee (%)[a]
1	**5**	**11**	*R*	18[b]	91[b]
2	**10**	**12**	*R*	22[b]	94[b]
3	**14**	**15**	*R*	64[c]	91[c]
4	**16**	**17**	*R*	48[c]	94[c]
5	**19**	**21**	*R*	60[d]	88[d]
6	**22**	**23**	*R*	77[d]	80[d]

(a) Determined by ^{1}H NMR spectroscopy of the Eu(hfc)$_3$ complexes. (b) Determined after transformation into ester **9**. (c) Determined after transformation into ester **18**. (d) Determined after transformation into thioester **24**.

Part 3: The Use of Ketone-Derived Boron Enolates

While these experiments were underway in Milano, parallel studies on boron-mediated aldol reactions with aldehydes were conducted in Cambridge using the chiral boron enolate **2**. Initially, an ester linkage between the aldehyde and the resin was considered (**Scheme 6**).

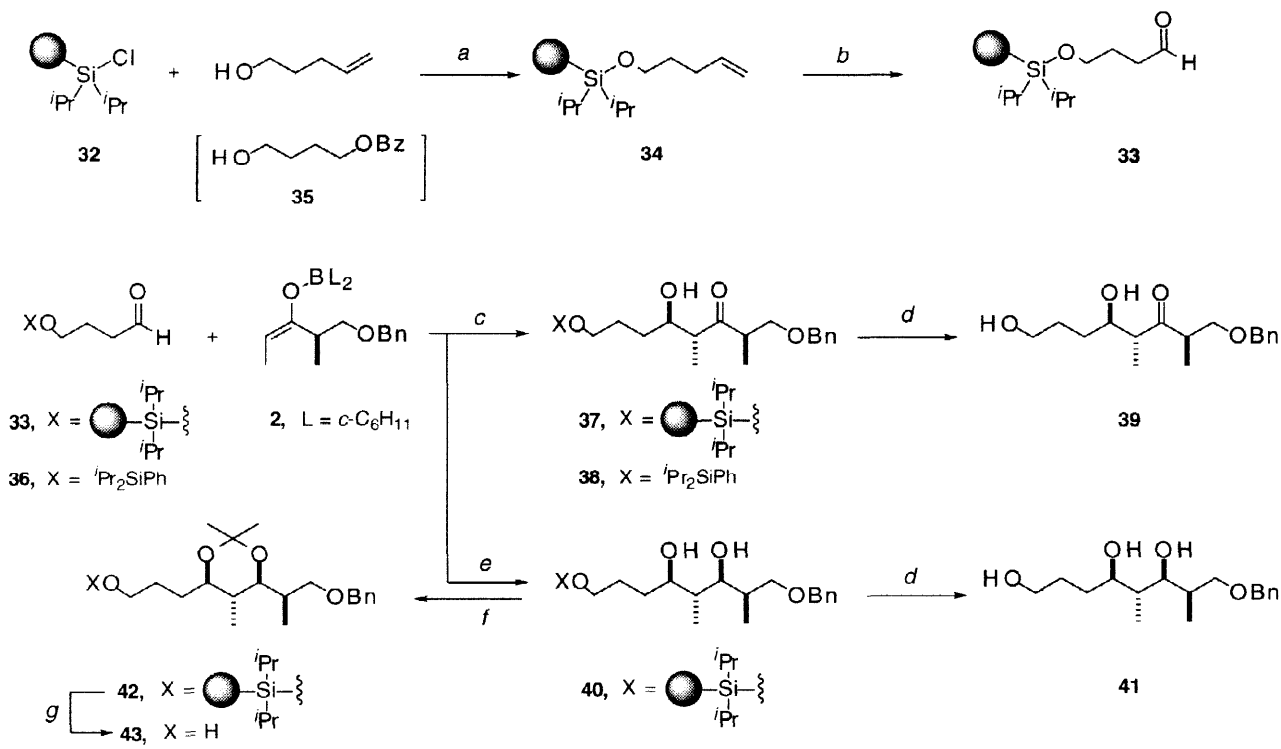
Merrifield resin (**6**) was first converted into carboxypolystyrene **25** by successive oxidations to the aldehyde and then to the acid.[14] 4-Hydroxybenzaldehyde was coupled to resin **25** using 1,3-diisopropylcarbodiimide (cat. DMAP, HOBt) to give aldehyde **26** (the loading was determined to be 0.7 mmol/g by cleavage with NaOH). The resin-bound aldehyde **26** was then reacted at 0 °C in Et_2O with the preformed (*E*)-enol borinate **2** (3 equiv.), derived from treatment of (*R*)-1-(benzyloxy)-2-methylpentan-3-one (**3**) with *c*-Hex_2BCl in the presence of Et_3N,[9] to give, following oxidative work-up, the *anti*-aldol adduct **27**. At this stage, the aldol adduct **27** could not be cleaved cleanly without complications from the retro-aldol reaction. For comparison purposes, the corresponding solution phase reaction of aldehyde **28** with enolate **2** was conducted to give an 86% yield of the *anti*-aldol adduct **29** with >95% diastereoselectivity (500 MHz ^{1}H NMR).



Scheme 6 (a) DIC, DMAP, HOBt, DMF, 20 °C, 24 h; (b) i: Et_2O, -78 °C, 1 h; 0 °C; ii: H_2O_2, pH 7, 0 °C, 16 h; (c) i: Et_2O, -78 °C, 1 h; 0 °C; ii: $LiBH_4$, -78 °C, 4 h; iii: H_2O_2, pH 7, 0 °C, 16 h; (d) NaOH, dioxane, 20 °C, 48 h.

The resin-bound aldehyde **26** was then reacted with the (*E*)-enolate **2** and the resulting boron aldolate reduced[15] *in situ* with $LiBH_4$ followed by oxidation with H_2O_2 at pH 7 to give the *syn* diol **30** (together with the corresponding boronate ester). Cleavage from the resin with NaOH then gave the 1,3-*syn* diol **31** (50%). The diastereoselectivity was determined by 500 MHz ^1H NMR analysis to be greater than 96:4 for the solid phase reaction, which is comparable to that obtained for the corresponding solution phase process.[15]

Due to the incompatibility of the above ester linker with the desired chemistry, a silyl linker was selected at this point (**Scheme 7**). This new linker proved to be beneficial, leading to reproducible results. The required silyl resin **32** was prepared from commercially available polystyrene by lithiation and reaction with dichlorodiisopropylsilane.[16] The aldehyde **33** was obtained by treatment of the silyl resin **32** with 4-penten-1-ol, in the presence of diisopropylethylamine and DMAP, to give the silyl ether **34**, followed by ozonolysis. A non-volatile alcohol **35** was also bound to the silyl resin **32**, which indicated a loading of 0.75 mmol/g on cleavage. The aldehyde **36**, which was intended to serve as a solution model for the chemistry, was prepared by an analogous route. The reactions on solid phase were followed by IR and gel-phase ^{13}C NMR spectroscopy. Spectroscopic characterisation of resin-bound products was possible by comparison with the corresponding model compounds prepared in solution.



Scheme 7 (a) *i*-Pr_2NEt, DMAP, CH_2Cl_2, 20 °C, 48 h; (b) i: O_3, CH_2Cl_2; ii: Ph_3P, 20 °C, 16 h; (c) Et_2O, -78 °C, 1 h; 0 °C, 16 h; (d) HF, CH_3CN, 20 °C, 4–16 h; (e) i: Et_2O, -78 °C, 1 h; 16 h, 0 °C; ii: $LiBH_4$, -78 °C, 4 h; iii: H_2O_2, pH 7, 0 °C, 16 h; (f) $(MeO)_2CMe_2$, CH_2Cl_2, CSA, 20 °C, 24 h, (g) TBAF, THF, 20 °C, 16 h.

The resin-bound aldehyde **33** and its solution model **36** were then reacted separately with the preformed (*E*)-enolate **2** leading to formation of the aldol products **37** and **38**, respectively. At this point, a loading of 0.64 mmol/g was determined for resin **37** by cleavage with HF in acetonitrile to give the *anti*-aldol product **39**, which was obtained with high diastereoselectivity (≥97% ds). This corresponds to an 85% yield for this aldol reaction (*cf.* 78% yield for **36** → **38** in solution), thus demonstrating the viability of this chemistry.

The resin-bound aldehyde **33** was then reacted with the (*E*)-enolate **2** and the resulting boron aldolate reduced[15] *in situ* with $LiBH_4$ to give the *syn* diol **40**. This was then cleaved from the solid support to provide the triol **41**. The overall yield was determined as 71% based on the loading of resin **33** established previously. This reaction proceeded with high diastereoselectivity (>96% ds), where the 1,3-*syn* relationship in the resin-bound diol **40** was determined by forming the corresponding *syn* acetonide **42**, as well as the cleaved alcohol **43**, both of which showed diagnostic ^{13}C NMR resonances (δ 19.7, 30.1, 97.6).[17]

Notably, this last result indicates that highly stereocontrolled aldol/reduction sequences can be performed on solid-supported aldehydes, which should prove amenable to the generation of polyketide libraries. The silyl ether linker employed is compatible with boron aldol chemistry and can be cleaved under controlled conditions to release the required polyketide sequence. Moreover, an iterative aldol sequence should be feasible by conversion of the benzyl ether terminus in resin **42** to an aldehyde.

CONCLUSIONS

The principle of highly stereoselective, boron-mediated, aldol reactions on solid phase has been demonstrated. The choice of linker appears to be crucial and the available experimental evidence is in favour of the trityl and silyl linkers. Further work, which is in progress, is focussed on extending this useful methodology to the synthesis of a variety of polyketide-type compounds.

EXPERIMENTAL SECTION

General: ^1H-NMR and ^{13}C-NMR spectra were recorded on Bruker AC 200, DPX 250, DPX 400 (400 MHz) and DRX 500 (500 MHz) spectrometers at 25 °C using $CDCl_3$ and CD_2Cl_2 as solvent and tetramethylsilane as internal standard. IR spectra were recorded on a JASCO FT-400 IR spectrometer using a nujol mull and on a Perkin-Elmer 1620 FTIR using 5 mm NaCl plates and KBr pellets for the resins; $[\alpha]_D^{25}$ values were measured on Perkin Elmer 141 and 241 polarimeters. Chromatographic purifications were performed by "flash chromatography"[18] using Merck silica gel 270-400 mesh. All organic extracts were dried over Na_2SO_4 or $MgSO_4$. Dry solvents were distilled immediately before use: CH_2Cl_2 and Et_3N from CaH_2, THF and Et_2O from sodium wire.

Resins: Chloromethyl styrene-1% divinylbenzene copolymer (Merrifield resin) **6** (100-200 mesh, 1.0 mmol Cl/g resin) was purchased from Aldrich and used as received. Chlorotrityl styrene-1% divinylbenzene copolymer (trityl chloride resin) **20** (100-200 mesh, 0.4 mmol Cl/g resin) was purchased from Novabiochem and used as received. Styrene-1% divinylbenzene copolymer (200-400 mesh) was purchased from Acros and converted into the silyl resin **32** by the method of Danishefsky *et al.*[16a]

***p*-Benzyloxycarbonyl benzaldehyde (10).** A solution of *p*-carboxybenzaldehyde (1.0 g, 6.7 mmol), benzyl alcohol (0.79 g, 0.76 ml, 7.3 mmol) and DMAP (81 mg, 0.67 mmol) in CH_2Cl_2 (15 ml), under N_2, was treated with a solution of DCC (1.5 g, 7.4 mmol) in CH_2Cl_2 (10 ml). The mixture was stirred at 25 °C for 45 min then cooled to 0 °C. DCU was removed by filtration, and the precipitate washed with cold CH_2Cl_2. The filtrates were washed with H_2O, 10% AcOH and H_2O. The organic phase was dried and evaporated. The residue was purified by flash chromatography (hexanes/CH_2Cl_2 1:1) to give **10** as a white solid (1.5 g, 92%): mp: 142-144 °C; IR (nujol) 1716, 1270 cm^{-1}; ^1H NMR δ (200 MHz, $CDCl_3$) 5.42 (2H, s, PhC$\underline{H_2}$O), 7.39-

7.47 (5H, m, Ph), 7.97 (2H, d, J = 8.4 Hz, Ar), 8.25 (2H, d, J = 8.4 Hz, Ar), 10.12 (1H, s, CHO); $C_{15}H_{12}O_3$: calcd C 74.99, H 5.03; found C 74.98, H 5.07.

***p*-Hydroxymethyl benzaldehyde (13).**[19] To a solution of terephthaldehyde (3.0 g, 22 mmol) in THF (44 ml), under N_2, DIBAL (1.5 M in toluene, 10 ml, 15 mmol) was added dropwise at 0 °C. The reaction mixture was stirred for 30 min at 0 °C, then treated with H_2O (0.6 ml), 15% NaOH (0.6 ml), H_2O (1.2 ml) and Na_2SO_4 (3.9 g). Stirring was maintained for 3-6 h, then the precipitate was separated by filtration and washed with cold Et_2O. The filtrates were evaporated and the crude product purified by flash chromatography (CH_2Cl_2/AcOEt, 75:25) to afford *p*-hydroxymethyl benzaldehyde (**13**) as a white solid (1.5 g, 54%): ^{1}H NMR δ (200 MHz, $CDCl_3$) 2.05 (1H, s, OH), 4.81 (2H, s, CH_2), 7.51 (2H, d, J = 8.1 Hz, Ar), 7.85 (2H, d, J = 8.1 Hz, Ar), 10.03 (1H, s, CHO); $C_8H_8O_2$: calcd C 70.56, H 5.93; found C 70.50, H 5.99.

***p*-Acetoxymethyl benzaldehyde (16).** To a solution of *p*-hydroxymethyl benzaldehyde (35 mg, 0.26 mmol) in CH_2Cl_2 (0.79 ml), CH_3CO_2H (0.02 ml, 0.28 mmol), DMAP (3.2 mg, 0.03 mmol) and DCC (59 mg, 0.28 mmol) were added in sequence. After 30 min, the solvent was evaporated and the residue purified by flash chromatography (CH_2Cl_2/hexanes 9:1) to afford **16** as a white solid (37 mg, 80%): IR (nujol) 1728, 1681, 1155 cm^{-1}; ^{1}H NMR δ (200 MHz, $CDCl_3$) 2.18 (3H, s, CH_3), 5.22 (2H, s, CH_2), 7.52 (2H, d, J = 8.3 Hz, Ar), 7.91 (2H, d, J = 8.3 Hz, Ar), 10.05 (1H, s, CHO); $C_{10}H_{10}O_3$: calcd C 67.39, H 5.66; found C 67.21, H 5.71.

***p*-Trityloxymethyl benzaldehyde (22).** An equimolar (0.5 M) solution of trityl chloride (0.85 g, 3.0 mmol) and Bu_4NI (1.1 g, 3.0 mmol) in CH_2Cl_2 (6.0 ml) was added at 25 °C under N_2 to *p*-hydroxymethyl benzaldehyde (0.35 g, 2.6 mmol). The mixture was treated with *sym*-collidine (0.47 g, 0.50 ml, 3.9 mmol) and stirred for 2-3 h at room temperature. The red solution was then diluted with H_2O and the two layers were separated. The aqueous phase was extracted twice with CH_2Cl_2 and the combined organic extracts were washed with H_2O, saturated NH_4Cl and H_2O, then dried and evaporated. The crude product was crystallised from EtOH (40 ml) to give **22** as colourless crystals (0.50 g, 53%): mp: 120-121 °C; IR (nujol) 1671, 1302 cm^{-1}; ^{1}H NMR δ (200 MHz, $CDCl_3$) 4.30 (2H, s, CH_2), 7.24-7.60 (17H, m, Ar), 7.88 (2H, d, J = 8.1 Hz, Ar), 10.03 (1H, s, CHO); $C_{27}H_{22}O_2$: calcd C 85.68, H 5.86; found C 85.72, H 5.93.

3-Hydroxy-3-*p*-benzyloxycarbonylphenylpropanoic acid *tert*-butyl thioester (8, Scheme 2). A solution of *p*-benzyloxycarbonyl benzaldehyde (**10**) (0.13 g, 0.54 mmol) in CH_2Cl_2 (1.0 ml) was cooled to -78 °C under N_2 and BF_3·Et_2O (77 mg, 0.07 ml, 0.54 mmol) was added dropwise. The mixture was stirred for 10 min then a solution of 1-*t*-butylthio-1-*t*-butyldimethylsilyloxyethylene (prepared according to ref. 12c) (0.20 g, 0.81 mmol) in CH_2Cl_2 (2.0 ml) was slowly added. Stirring was maintained at -78 °C for 45 min, then at -40 °C for 30 min. The reaction mixture was quenched by addition of pH 7 phosphate buffer and the two phases were separated after warming to room temperature. The organic phase was washed twice with pH 7 phosphate buffer, dried and evaporated. The crude product was purified by flash chromatography (hexanes/AcOEt 9:1) to give the aldol product **8** (22 mg, 11%) [and the corresponding silylated product as a clear oil (160 mg, 61%)]: IR (nujol) 1725, 1705, 1269 cm^{-1}; ^{1}H NMR δ (200 MHz, $CDCl_3$) -0.17 (3H, s, $SiCH_3$), 0.045 (3H, s, $SiCH_3$), 0.87 (9H, s, Si*t*-Bu), 1.46 (9H, s, S*t*-Bu), 2.59 (1H, dd, J = 3.9 Hz, J = 14 Hz, CHHCOS), 2.89 (1H, dd, J = 8.9 Hz, J = 14 Hz, CHHCOS), 5.21 (1H, dd, J = 3.9 Hz, J = 8.9 Hz, CHOTBS), 5.37 (2H, s, $PhCH_2O$), 7.38-7.45 (7H, m, Ar), 8.07 (2H, d, J = 8.1 Hz, Ar); ^{13}C NMR δ (50.3 MHz, $CDCl_3$) 25.7, 29.7, 55.2, 66.7, 71.6, 197.5, 149.5, 129.5, 128.3, 128.6, 125.8; $C_{27}H_{38}O_4SSi$: calcd C 66.64, H 7.88; found C 66.58, H 7.99.

The silylated aldol product (0.16 g, 0.33 mmol) was dissolved in CH_3CN (0.8 ml) and treated with HF (40%, 0.02 ml, 0.41 mmol). The mixture was stirred at room temperature for 20 h, then the organic solvent was evaporated. The residue was dissolved in CH_2Cl_2 (2.0 ml) and washed thoroughly with water. The organic phase was dried and evaporated, and the crude was purified by flash chromatography (hexanes/AcOEt 9:1) affording **8** (90 mg). The combined yield for **8** was 56%. Treatment with Bu_4NOH (THF/MeOH) at 70 °C for 24 h, followed by addition of MeI in CH_3CN at room temperature, gave compound **9** in quantitative yield.

Representative Procedure for L^*_2BBr Promoted Aldol Reactions in Solution. To a stirred solution of the thioester (0.23 g, 1.7 mmol) in Et_2O (4.5 ml) at 0 °C (ice cooling) under an argon atmosphere, a solution of L^*_2BBr [prepared from (-)-menthone according to ref. 8h] in CH_2Cl_2 (0.4 M, 6.5 ml, 1.7 mmol) and then Et_3N (0.36 ml, 2.6 mmol) were added dropwise. Enolborinate **1** was generated with concurrent formation and precipitation of $Et_3N{\cdot}HBr$. The resulting mixture was stirred at 0 ° C for 2 h followed by cooling to -78 °C upon which a solution of aldehyde (1.3 mmol) in Et_2O (4.5 ml) was added. The reaction mixture was stirred at -20 °C overnight, quenched by addition of pH 7 phosphate buffer (9.0 ml) and allowed to warm to room temperature. The phases were separated and the aqueous phase extracted with CH_2Cl_2. The combined organic phases were dried and evaporated. Oxidation of the crude mixture was achieved by dissolving it in MeOH (30 ml) and treating with an equimolar solution of H_2O_2 and pH 7 phosphate buffer (7.5 ml). After 20 min stirring at room temperature, the mixture was diluted with water and extracted with CH_2Cl_2 (3 x 5 ml). The organic phase was dried and evaporated. The crude product was purified by flash chromatography to give the desired aldol compound.

(3*R*)-Hydroxy-3-*p*-benzyloxycarbonylphenylpropanoic acid *t*-butyl thioester (12, Scheme 3). The crude product was purified by flash chromatography (hexanes/AcOEt, 9:1) to afford **12** as a white solid (11 mg, 22%): $[\alpha]_D^{25}$ +29.9 (c 1 in $CHCl_3$); IR (nujol) 3481, 3298, 1727, 1705, 1269 cm^{-1}; ^1H NMR δ (200 MHz, $CDCl_3$) 1.48 (9H, s, C<u>H</u>$_3$), 2.86 (2H, d, *J* = 5.8 Hz, C<u>H</u>$_2$), 3.33 (1H, d, *J* = 3.3 Hz, O<u>H</u>), 5.22 (1H, dt, *J* = 5.8 Hz, *J* = 3.3 Hz, C<u>H</u>OH), 5.38 (2H, s, PhC<u>H</u>$_2$O), 7.37-7.47 (7H, m, Ph + Ar), 8.07 (2H, d, *J* = 8.3 Hz, Ar); ^{13}C NMR δ (50.3 MHz, $CDCl_3$) 38.0, 54.0, 57.0, 68.3, 71.8, 117.8, 119.8, 119.9, 121.3, 121.1, 125.9, 135.8, 151.6, 179.05; $C_{21}H_{24}O_4S$: calcd C 67.72, H 6.50; found C 67.88, H 6.65.

(3*R*)-Hydroxy-3-*p*-methoxycarbonylphenylpropanoic acid methyl ester (9, Scheme 3). A solution of **12** (67 mg, 0.18 mmol) in MeOH (4.0 ml) was cooled to 0 °C and treated with $Bu_4NOH{\cdot}30H_2O$ (0.30 g, 0.37 mmol). The mixture was stirred at room temperature for 2-4 h, then the solvent was evaporated. The residue was dissolved in CH_3CN (1.0 ml), cooled to 0 °C and treated with MeI (0.15 g, 0.066 ml, 1.0 mmol). The mixture was stirred at 25 °C overnight. The solvent and MeI were removed by evaporation and the residue was purified by flash chromatography (hexanes/AcOEt, 9:1) to afford **9** as a white crystalline solid (37 mg; 100%): mp 55-57 °C; IR (nujol) 3420, 1715, 1690, 1269 cm^{-1}; ^1H NMR δ (200 MHz, $CDCl_3$) 2.75 (2H, d, *J* = 6.4 Hz, C<u>H</u>$_2$), 3.43 (1H, bs, O<u>H</u>), 3.74 (3H, s, OC<u>H</u>$_3$), 3.92 (3H, s, OC<u>H</u>$_3$), 5.20 (1H, bt, *J* = 6.4 Hz, C<u>H</u>OH), 7.46 (2H, d, *J* = 8.3 Hz, Ar), 8.04 (2H, d, *J* = 8.3 Hz, Ar); e.e. [Eu(hfc)$_3$] = 94%; $C_{12}H_{14}O_5$: calcd C 60.48, H 5.93; found C 60.56, H 6.07.

(3*R*)-Hydroxy-3-*p*-acetoxymethylphenylpropanoic acid *t*-butyl thioester (17, Scheme 4). Flash chromatography (CH_2Cl_2/Et_2O, 95:5) afforded **17** as a white solid (73 mg, 67%): $[\alpha]_D^{25}$ +19.5 (c 1 in $CHCl_3$); IR (nujol) 3381, 1728, 1674, 1161 cm^{-1}; ^1H NMR δ (200 MHz, $CDCl_3$) 1.49 (9H, s, S*t*-Bu), 2.11 (3H, s, C<u>H</u>$_3$), 2.78-2.99 (2H, m, C<u>H</u>$_2$), 3.19 (1H, d, *J* = 3.0 Hz, O<u>H</u>), 5.10 (2H, s, C<u>H</u>$_2$O), 5.11-5.22 (1H, m, C<u>H</u>OH), 7.36 (4H, s, Ar); ^{13}C NMR δ (50.3 MHz, $CDCl_3$) 20.9, 29.6, 52.7, 65.9, 70.4, 125.8, 128.3; e.e. [Eu(hfc)$_3$] = 94%; $C_{16}H_{22}O_4S$: calcd C 61.91, H 7.15; found C 61.78, H 7.35.

(3*R*)-Hydroxy-3-*p*-hydroxymethylphenylpropanoic acid methyl ester (18, Scheme 4). Saponification and methylation of **17** (37 mg, 0.12 mmol) were carried out as described above (for the synthesis of **8**) with $Bu_4NOH{\cdot}30H_2O$ (0.20 g, 0.25 mmol) and MeI (0.03 ml, 0.47 mmol). Flash chromatography (CH_2Cl_2/AcOEt, 8:2) afforded **18** as a white solid in 71% overall yield: IR (nujol) 3460, 3305, 1715, 1276 cm^{-1}; ^1H NMR δ (200 MHz, $CDCl_3$) 2.62-2.86 (2H, m, C<u>H</u>$_2$), 3.29 (1H, bs, O<u>H</u>), 3.73 (3H, s, OC<u>H</u>$_3$), 4.68 (2H, s, C<u>H</u>$_2$OH), 5.11-5.21 (1H, m, C<u>H</u>OH), 7.39 (4H, s, Ar); e.e. [Eu(hfc)$_3$] = 94%; $C_{11}H_{14}O_4$: calcd C 62.83, H 6.72; found C 62.75, H 6.78.

(3*R*)-Hydroxy-3-*p*-trityloxymethylphenylpropanoic acid *t*-butyl thioester (23, Scheme 5). Flash chromatography (hexanes/acetone, 85:15) afforded **23** as a white solid (0.55 g, 83%): IR (nujol) 3488, 3298, 1725, 1308, 1274 cm^{-1}; ^1H NMR δ (200 MHz, $CDCl_3$) 1.50 (9H, s, S*t*-Bu), 2.86-2.92 (2H, m, C<u>H</u>$_2$), 3.14 (1H, d, *J* = 2.8 Hz, O<u>H</u>), 4.17 (2H, s, C<u>H</u>$_2$O), 5.15-5.23 (1H, m, C<u>H</u>OH), 7.25-7.55 (19H, m, Tr + Ar); e.e. [Eu(hfc)$_3$] = 80%; $C_{33}H_{34}O_3S$: calcd C 77.61, H 6.72; found C 77.75, H 6.81.

(3*R*)-Hydroxy-3-*p*-hydroxymethylphenylpropanoic acid *t*-butyl thioester (24, Scheme 5). Compound **23** (41 mg, 0.08 mmol) was treated with a 0.2 M solution of *p*-TsOH·H_2O in THF/MeOH 1:1 (2.0 ml). The solution was stirred at room temperature for 6 h, then Et_3N was added (40 mg, 0.06 ml, 0.40 mmol) and the solvent was evaporated. The residue was purified by flash chromatography (CH_2Cl_2/AcOEt, 8:2) to give **24** as a white solid (20 mg, 93%): mp 48-51 °C; IR (nujol) 3290, 1680, 1215 cm^{-1}; ^1H NMR δ (200 MHz, $CDCl_3$) 1.49 (9H, s, S*t*-Bu), 2.84-2.89 (2H, m, C<u>H</u>$_2$), 3.24 (1H, bs, O<u>H</u>), 4.69 (2H, s, ArC<u>H</u>$_2$OH), 5.11-5.22 (1H, m, C<u>H</u>OH), 7.36 (4H, s, Ar); ^{13}C NMR δ (50.3 MHz, $CDCl_3$) 29.6, 48.6, 52.6, 64.9, 70.6, 125.8, 127.1, 140.3, 141.7, 199.9; e.e. [Eu(hfc)$_3$] = 80%; $C_{14}H_{20}O_3S$: calcd C 62.66, H 7.52; found C 62.59, H 7.65.

Solid phase bound *p*-carboxybenzaldehyde (5, Schemes 2 and 3). To a suspension of *p*-carboxy benzaldehyde (2.3 g, 15 mmol) in THF (100 ml), NaH (60% in mineral oil, 0.60 g, 15 mmol) was added. The mixture was refluxed under N_2 for 1 h, then cooled to room temperature and treated with (n-C_6H_{13})$_4$NBr (0.26 g, 0.60 mmol) and resin **6** (3.0 g, about 3.0 mmol chloromethyl groups). The suspension was refluxed for 3 d with vigorous stirring, then the resin was filtered and washed in sequence with THF, MeOH, H_2O, MeOH, THF and CH_2Cl_2. The residual solvent was eliminated by vacuum pump. The loading of the aldehyde was assumed to be 1.0 mmol/g (100%): IR (nujol) 1719, 1708 cm^{-1}.

Solid phase bound *p*-hydroxymethylbenzaldehyde (14, Scheme 4). The above procedure was applied to glutaric acid (1.4 g, 10.0 mmol), NaH (60% in mineral oil, 0.40 g, 10 mmol), (n-C_6H_{13})$_4$NBr (0.17 g, 0.40 mmol) and resin **6** (2.0 g, about 2.0 mmol chloromethyl groups). The resin was filtered and washed, in sequence, with THF, MeOH, H_2O, 1.0 M HCl in dioxane/H_2O (1:1), H_2O, MeOH, THF and CH_2Cl_2. IR (nujol) 1740, 1667 cm^{-1}. The resin (2.0 g) was then suspended in DMF (12 ml); DIC (0.96 g, 1.2 ml, 7.6 mmol), DMAP (0.12 g, 0.95 mmol), HOBt (1.0 g, 7.6 mmol) and a solution of *p*-hydroxymethyl benzaldehyde (**12**) (1.0 g, 7.6 mmol) in DMF (2.0 ml) were added. The mixture was stirred at room temperature for 24 h, then the resin was filtered and washed in sequence with DMF, MeOH and CH_2Cl_2. The residual solvent was removed under vacuum. IR (nujol) 1728, 1680 cm^{-1}. To determine the conversion, resin **14** (0.50 g) was suspended in THF/MeOH 1:1 (4.0 ml) and treated with $Bu_4NOH{\cdot}30H_2O$ (0.88 g, 1.1 mmol). The mixture was stirred at 70 °C for 3 d, then filtered, and washed with MeOH and CH_2Cl_2. The combined filtrates were evaporated and the residue purified by flash chromatography (CH_2Cl_2/AcOEt, 8:2) to afford *p*-hydroxymethyl benzaldehyde (6.6 mg, 0.05 mmol), corresponding to 0.096 mmol/g of solid phase bound aldehyde (9.6%).

Solid phase bound *p*-hydroxymethylbenzaldehyde (19, Scheme 5). To a stirred suspension of resin **20** (2.0 g, about 0.80 mmol trityl chloride groups) in CH_2Cl_2 (10 ml) under N_2 at 25 °C, Bu_4NI (1.2 g, 3.2 mmol) and *p*-hydroxymethyl benzaldehyde (**12**) (0.44 g, 3.2 mmol) were added. The mixture was treated with *sym*-collidine (0.58 g, 0.63 ml, 4.8 mmol) and stirred at room temperature for 65 h. The resin was then filtered and washed with dry CH_2Cl_2 (3 x 15 ml) and dry THF (3 x 15 ml). The residual solvent was removed by vacuum pump. To determine the loading, resin **19** (0.20 g) was suspended in a 0.2 M solution of *p*-$TsOH \cdot H_2O$ in THF/MeOH 1:1 (2.0 ml). The mixture was stirred for 17 h, then the resin was filtered and washed with MeOH, Et_2O and CH_2Cl_2. The combined filtrates were treated with triethylamine (0.40 mmol, 40 mg, 0.06 ml) and the solvent was evaporated. The residue was purified by flash chromatography (CH_2Cl_2/AcOEt, 8:2), to afford *p*-hydroxymethylbenzaldehyde (8.0 mg), corresponding to 0.30 mmol/g of solid phase bound aldehyde (73%).

Solid phase bound 3-hydroxy-3-*p*-hydroxymethylphenylpropanoic acid *tert*-butyl thioester (7, Scheme 2). Solid phase bound aldehyde **5** (1.1 g, about 1.1 mmol) was suspended in CH_2Cl_2 (11 ml) under N_2 and cooled to -78 °C. $BF_3 \cdot Et_2O$ (0.21 g, 0.18 ml, 1.5 mmol) was added dropwise and the mixture was stirred for 10 min. A solution of 1-*t*-butylthio-1-*t*-butyldimethylsilyloxyethylene (prepared according to ref. 12c) (0.49 g, 2.0 mmol) in CH_2Cl_2 (2.0 ml) was added *via* cannula. The mixture was stirred at -78 °C for 1.5 h, then the liquid phase was removed by filtration and the resin was washed with cold CH_2Cl_2 (5 x 10 ml). The residual solvent was removed *in vacuo*. This procedure was repeated three times. At the end of the last cycle, the reaction mixture was quenched by addition of phosphate 7 buffer (10 ml). The mixture was warmed to 25 °C, then the resin was filtered and washed in sequence with CH_2Cl_2, MeOH, H_2O, MeOH and CH_2Cl_2. The residual solvent was removed *in vacuo*. Desilylation was performed by treating a suspension of the resin (0.34 g) in CH_3CN (5 ml) with 40% HF (0.07 ml, 1.5 mmol). The mixture was stirred at room temperature for 7 d (the reaction was monitored at intervals by evaluating the ratio of Si*t*-Bu to S*t*-Bu signals in the gel-phase ^{13}C NMR spectra: δ 25.77 and 29.74, respectively). The resin was then filtered and washed with CH_3CN and CH_2Cl_2. To evaluate the conversion, resin **7** (0.11 g) was subjected to saponification and methylation (the same procedure is described below for resin **11, Scheme 3**), with 0.18 g of $Bu_4NOH \cdot 30H_2O$ (0.22 mmol) and 0.06 ml of MeI (1.0 mmol). Flash chromatography (hexanes/AcOEt, 9:1) afforded **9** (9.5 mg, 0.36 mmol/g, 36%).

Representative Procedure for L^*_2BBr Promoted Aldol Reactions on Solid Phase. To a stirred solution of the thioester (53 mg, 0.40 mmol) in Et_2O (1.5 ml) at 0 °C (ice cooling) under argon atmosphere, a solution of L^*_2BBr [prepared from (-)-menthone according to ref. 8h] in CH_2Cl_2 (0.4 M, 1.5 ml, 0.60 mmol) and then Et_3N (0.09 ml, 0.64 mmol) were added dropwise. Enolborinate **1** was generated with concurrent formation and precipitation of $Et_3N \cdot HBr$. The resulting mixture was stirred at 0 °C for 2 h and cooled to -78 °C. This enolate was then transferred *via* cannula into a specially adapted vessel (containing a frit and tap), under argon, charged with a suspension of resin bound aldehyde (about 0.23 mmol) in Et_2O (0.5 ml). The reaction mixture was stirred at -5 °C for 16 h followed by rinsing and washing with dry CH_2Cl_2. The resin was dried under vacuum and the same procedure was repeated for two further reaction cycles. After the third cycle, the resin was quenched with pH7 phosphate buffer (1.5 ml) and washed in sequence with H_2O, MeOH, THF, and CH_2Cl_2. The resin was dried *in vacuo*, then suspended in MeOH (5 ml), pH7 phosphate buffer (1 ml) and 30% H_2O_2 (1 ml). The mixture was stirred at room temperature for 30 min. This oxidative cycle was repeated twice before washing the resin with H_2O, MeOH and CH_2Cl_2 and drying *in vacuo*. IR (nujol) 1714, 1675 cm^{-1}.

Solid phase bound (3*R*)-hydroxy-3-*p*-hydroxymethylphenylpropanoic acid *t*-butyl thioester (11, Scheme 3). The procedure described above was applied to 0.20 g of resin **5**. To evaluate the

conversion, resin **11** (0.23 g) was suspended in THF/MeOH 1:1 (4.0 ml) and treated with $Bu_4NOH \cdot 30H_2O$ (0.35 g, 0.44 mmol). The mixture was stirred at 70 °C for 24 h, then cooled to room temperature. The resin was filtered and washed with CH_2Cl_2 and MeOH. The combined filtrates were evaporated, and the residue was dissolved in CH_3CN (1.1 ml), cooled to 0 °C and treated with MeI (0.12 ml, 2.0 mmol). Stirring was maintained at room temperature for 6 h, then the solvent and reagent were evaporated. Pure **9** was isolated by flash chromatography (hexanes/AcOEt, 9:1) (9.7 mg, corresponding to 0.18 mmol/g; 18% overall); e.e. $[Eu(hfc)_3] = 91\%$.

Solid phase bound (3*R*)-hydroxy-3-*p*-hydroxymethylphenylpropanoic acid *t*-butyl thioester (13, Scheme 4). The general procedure for aldol condensation was applied to 0.20 g of resin **12**. To evaluate the conversion the cleavage procedure described above was applied to resin **13** (0.20 g). Flash chromatography (CH_2Cl_2/AcOEt, 8:2) afforded **16** (2.6 mg, 0.06 mmol/g, 64%); e.e. $[Eu(hfc)_3] = 91\%$.

Solid phase bound (3*R*)-hydroxy-3-*p*-hydroxymethylphenylpropanoic acid *t*-butyl thioester (21, Scheme 5). The procedure described above was applied to 0.50 g (about 0.15 mmol) of resin **19**. To evaluate the conversion, resin **21** (0.5 g) was suspended in THF/MeOH 1:1 (6 ml) and treated with *p*-TsOH·H_2O (0.22 g, 1.2 mmol). The mixture was stirred for 22 h, then the resin was filtered and washed with MeOH, MeOH/CH_2Cl_2 1:1, and CH_2Cl_2. The combined filtrates were treated with triethylamine (0.12 g, 0.16 ml, 1.2 mmol) and the solvent was evaporated. The crude product was purified by flash chromatography (CH_2Cl_2/AcOEt, 8:2) to afford **24** (24 mg, 0.18 mmol/g, 60%); e.e. $[Eu(hfc)_3] = 88\%$.

4-(Benzoyloxy)benzaldehyde (28, Scheme 6). To a stirred solution of 4-hydroxybenzaldehyde (0.4 g, 3.28 mmol) in CH_2Cl_2 (5 ml) was added dry pyridine (0.35 ml, 4.26 mmol) and the resulting mixture was cooled to 0 °C. Benzoyl chloride (0.53 ml, 4.59 mmol) was then added dropwise. The resulting suspension was stirred at room temperature for 1 h. The reaction mixture was then cooled with ice, and the excess benzoyl chloride was quenched by the addition of *N,N*-dimethylethylenediamine (0.16 ml, 1.45 mmol). After stirring at room temperature for 1 h, the mixture was washed with 3N aqueous hydrochloric acid (3 x 4 ml) and sat. aqueous $NaHCO_3$ (4 ml), then dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product. Flash chromatography (Et_2O/hexanes, 2:8) gave **28** as a colourless solid (0.634 g, 86%): mp = 93-95 °C; IR ($CHCl_3$) 1741, 1701, 1600 cm^{-1}; ^1H NMR δ (250 MHz, $CDCl_3$) 7.42 (2H, d, J = 8.6 Hz, ArHOCO), 7.53 (2H, t, J = 7.5 Hz, $ArHCO_2$), 7.67 (1H, tt, J = 7.1, 1.3 Hz, $ArHCO_2$), 7.97 (2H, d, J = 8.6 Hz, ArHOCO), 8.2 (2H, d, J = 7.5 Hz, $ArHCO_2$), 10.03 (1H, s, CHO); ^{13}C NMR δ (100 MHz, $CDCl_3$) 122.5, 128.7, 128.9, 130.3, 131.3, 134.0, 155.7, 164.5, 190.9.

(2*R*,4*R*,5*S*)-5-[4'-(Benzoyloxyphenyl)]-1-(benzyloxy)-5-hydroxy-2,4-dimethylpentan-3-one (29, Scheme 6). To a stirred solution of dicyclohexylboron chloride (0.09 ml, 0.44 mmol) in dry Et_2O (1.22 ml) was added Et_3N (0.22 ml, 1.55 mmol) at 0 °C. A solution of (*R*)-1-(benzyloxy)-2-methylpentan-3-one (**3**) [prepared according to ref. 9g] (61.6 mg, 0.29 mmol) in dry Et_2O (0.45 ml) was then added *via* cannula and the reaction mixture was stirred at 0 °C for 2 h. A solution of aldehyde **28** (100 mg, 0.44 mmol) in a mixture of CH_2Cl_2/Et_2O (1:2) (2 ml) was then added *via* cannula at -78 °C, and stirring was continued at the same temperature for 2 h. The reaction was then warmed slowly to 0 °C and stirring was continued for 1 h. The reaction mixture was then partitioned between pH 7 buffer (7 ml) and Et_2O (3 x 10 ml). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give an oil. The residue was suspended in MeOH (1.8 ml), pH 7 buffer (1.8 ml) and the mixture was cooled to 0 °C. H_2O_2 (30% aqueous, 0.97 ml) was successively added and stirring continued for 2 h at 0 °C. The reaction mixture was then partitioned between water (10 ml) and CH_2Cl_2 (3 x 8 ml). The combined organic phases were washed with sat. aqueous $NaHCO_3$ (8

ml) and brine (8 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give an oil. Flash chromatography (EtOAc/hexanes, 25:75) gave **29** as a colourless solid (108 mg, 86%): Rf 0.23 (EtOAc/hexanes, 25:75); $[\alpha]_D^{25}$ −5.3 (c 0.74, $CHCl_3$); mp = 103-105 °C; IR ($CHCl_3$) 1734, 1601 cm^{-1}; ^1H NMR δ (500 MHz, $CDCl_3$) 0.98 (3H, d, *J* = 7.1, $C\underline{H}_3CH$), 1.02 (3H, d, *J* = 7.0, $C\underline{H}_3CH$), 3.05 (2H, m, $\underline{H}_4$, $\underline{H}_2$), 3.15 (1H, d, *J* = 4.4 Hz, O$\underline{H}$), 3.46 (1H, dd, *J* = 8.8, 4.9 Hz, $\underline{H}_{1A}$), 3.69 (1H, t, *J* = 8.8 Hz, $\underline{H}_{1B}$), 4.47 (1H, d, *J* = 12.0 Hz, $C\underline{H}_2Bn$), 4.52 (1H, d, *J* = 12.0 Hz, $C\underline{H}_2Bn$), 4.81 (1H, dd, *J* = 8.1, 4.4 Hz, C$\underline{H}$OH), 7.21 (2H, d, *J* = 8.4 Hz, Ar$\underline{H}$O-), 7.25-7.35 (5H, m, Ar$\underline{H}CH_2$), 7.40 (2H, d, *J* = 8.4 Hz, Ar$\underline{H}$O-), 7.51 (2H, t, *J* =7.7 Hz, Ar$\underline{H}CO_2$), 7.64 (1H, t, *J* = 7.4 Hz, Ar$\underline{H}CO_2$), 8.2 (2H, d, Ar$\underline{H}CO_2$); ^{13}C NMR δ (100 MHz, CDCl3) 13.3, 14.0, 46.2, 53.4, 72.1, 73.4, 76.1, 121.7, 127.7, 128.4, 128.6, 129.5, 130.2, 133.6, 139.8, 150.5, 167.8, 217.4.

Solid phase bound 4-hydroxybenzaldehyde (26, Scheme 6).[20] To carboxypolystyrene resin **25** [prepared according to ref 14a] (1.5 g, 1.5 mmol) suspended in DMF (10.0 ml) were added pyridine (0.61 ml, 7.5 mmol), 4-hydroxybenzaldehyde (916 mg, 7.5 mmol), diisopropylcarbodiimide (947 mg, 7.5 mmol), DMAP (31 mg, 0.26 mmol) and HOBt (hydroxybenzotriazole) (30 mg, 0.23 mmol). The stirring was continued under an argon atmosphere at room temperature for 24 h. The solvent was filtered and the resin was washed, in sequence, with dioxane, H_2O, dioxane/H_2O 2:1, dioxane, acetone, MeOH, CH_2Cl_2. The resin **26** was then dried under reduced pressure at 40 °C. IR (KBr) 2744, 1746, 1706 cm^{-1}.
To determine the loading, resin **26** (0.5 g, 0.5 mmol) was suspended in dioxane (5 ml) and NaOH (0.5 M) (10 ml). The mixture was stirred for 48 h, then the resin was filtered and washed with Et_2O, water, Et_2O, CH_2Cl_2. The combined filtrates were neutralized with 1 N aqueous HCl (5 ml) and saturated with NaCl. The organic phases were then extracted with EtOAc (3 x 10 ml), combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (Et_2O/CH_2Cl_2, 2:8), to afford 4-hydroxybenzaldehyde (0.05 g), corresponding to 0.7 mmol/g of resin (74%).

Solid phase bound (2*R*,3*S*,4*S*,5*S*)-1-(benzyloxy)-5-[4'-(hydroxyphenyl)]-2,4-dimethylpentan-3,5-diol (30, Scheme 6). To a stirred solution of dicyclohexylboron chloride (0.36 ml, 1.66 mmol) in dry Et_2O (5.8 ml) was added Et_3N (0.25 ml, 1.78 mmol) at 0 °C. A solution of (*R*)-1-(benzyloxy)-2-methylpentan-3-one (**3**) [prepared according to ref. 9g] (232 mg, 1.11 mmol) in dry Et_2O (1.7 ml) was added *via* cannula and the reaction mixture was stirred at this temperature for 2 h to generate a solution of enolate **2**. The resin (0.5 g, 0.37 mmol) was suspended in a mixture of CH_2Cl_2/Et_2O (1:1), cooled to -78 °C, and the enolate solution was added *via* cannula. Stirring was continued for 1 h at -78 °C, then the mixture was warmed slowly to 0 °C and stirring was continued for 3 h. The reaction mixture was left at 0 °C for 10 h, then cooled to -78 °C and $LiBH_4$ (2M in THF; 2.78 ml, 5.55 mmol) was added. The resulting mixture was stirred for 4 h at the same temperature and sat. aqueous NH_4Cl (20 ml) was successively added. The solvent was filtered and the resin washed with water, dioxane, and Et_2O. The resin was then suspended in MeOH (5 ml) and pH 7 buffer (3 ml), cooled to 0 °C and H_2O_2 (30%; 7 ml) was added. The solvent was filtered and the product resin **30** washed, in sequence, with water, dioxane, acetone, MeOH, CH_2Cl_2.

(2*R*,3*S*,4*S*,5*S*)-1-(Benzyloxy)-5-[4'-(hydroxyphenyl)]-2,4-dimethylpentan-3,5-diol (31, Scheme 6). The resin **30** (0.5 g, 0.37 mmol) was suspended in dioxane (10 ml), NaOH (0.5M) (7.4 ml, 3.7 mmol) was added and stirring continued for 48 h at room temperature. The solvent was filtered and the resin was washed with Et_2O, water, Et_2O, CH_2Cl_2. The aqueous phases were neutralized with 1N aqueous HCl (3 ml) and saturated with NaCl. The organic phases were then extracted with EtOAc (5 x 10 ml), combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give an oil. The mixture was then suspended in MeOH (0.65 ml) and cooled to 0 °C. H_2O_2 (30%; 0.36 ml) and NaOH (10%; 0.27 ml) were added and stirring was continued for 1 h. The reaction mixture was then partitioned between water (2 ml) and CH_2Cl_2 (3 x 1 ml). The combined organic phases

were washed with sat. aqueous $NaHCO_3$ (10 ml) and brine (10 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give an oil. Flash chromatography (Et_2O/CH_2Cl_2, 3:7) gave **31** as a colourless oil (61.6 mg, 50%), which was unstable. Rf 0.35 (Et_2O/CH_2Cl_2, 3:7); IR (thin film) 3348, 2932, 1614, 1517, 1454 cm^{-1}; ^1H NMR δ (500 MHz, $CDCl_3$) 0.47 (3H, d, *J* = 6.8 Hz, $C\underline{H}_3CH$), 1.05 (3H, d, *J* = 7.0 Hz, $C\underline{H}_3CH$), 1.83-2.05 (2H, m, $\underline{H}_2$, $\underline{H}_4$), 3.55-3.65 (2H, m, $\underline{H}_1$), 3.93 (1H, dd, *J* = 9.4, 1.2 Hz, $\underline{H}_3$), 4.50 (1H, d, *J* = 9.0 Hz, $\underline{H}_5$), 4.54 (2H, s, $OC\underline{H}_2Ph$), 5.15 (1H, s br, O$\underline{H}$), 6.67 (2H, d, *J* = 8.5 Hz, Ar$\underline{H}$OH), 7.12 (2H, d, *J* = 8.5 Hz, Ar$\underline{H}$OH), 7.2-7.4 (5H, m, Ar$\underline{H}$).

4-(Diisopropylphenylsilyloxy)butanal (36, Scheme 7). To a solution of 4-penten-1-ol (0.16 g, 1.8 mmol) and DMAP (5 mg) in CH_2Cl_2 (1.8 ml) were added diisopropylethylamine (0.31 μl, 1.8 mmol) and chlorodiisopropylphenylsilane (0.5 g, 2.2 mmol) at 0 °C under argon. The reaction mixture was then warmed to room temperature and stirred for 1 h. The reaction was then quenched by the addition of saturated aqueous $NaHCO_3$ (0.5 ml), the layers separated and the organic phase extracted with CH_2Cl_2 (3 x 4 ml). The combined organic extracts were evaporated *in vacuo*. Flash chromatography (EtOAc/hexanes, 1:9) gave the silyl ether as a colourless oil (0.46 g, 92%). Rf 0.26 (hexanes); IR (thin film) 2941, 2865, 1641 cm^{-1}; ^1H NMR δ (250 MHz, $CDCl_3$) 1.01 (6H, d, *J* = 7.3 Hz, $C\underline{H}_3CHSi$), 1.1 (6H, d, *J* = 7.2 Hz, $C\underline{H}_3CHSi$), 1.2-1.4 (2H, m, $C\underline{H}Si$), 1.7 (2H, m, $C\underline{H}_2$), 2.19 (2H, m, $C\underline{H}_2CH$), 3.78 (2H, t, *J* = 6.5 Hz, $C\underline{H}_2OSi$), 4.8-5.1 (2H, m, $CH=C\underline{H}_2$), 5.85 (1H, ddt, *J* = 17.1, 10.2, 6.6 Hz, $C\underline{H}=CH_2$), 7.2-7.7 (5H, m, Ar$\underline{H}$); ^{13}C NMR δ (50.3 MHz; $CDCl_3$) 12.1, 17.4, 17.3, 30.0, 32.1, 63.2, 114.5, 127.2, 134.7, 138.5; m/z (EI) 233 (100), 191 (50), 149 (24), 137 (62), 121 (26); HRMS (EI) calcd for $C_{14}H_{21}OSi$ ($M-C_3H_7$) 233.1363. Found 233.1362.

A solution of the above silyl ether (0.5 g, 1.8 mmol) in dry CH_2Cl_2 (70 ml) was ozonolysed at -78 °C until the solution turned bright blue. Oxygen was then bubbled through the reaction mixture until it became colourless and then triphenylphosphine (0.95 g, 3.6 mmol) was added at -78 °C. After stirring for 3 h under argon, the reaction mixture was quenched by the addition of water, the phases were separated and the aqueous layers extracted with CH_2Cl_2. The combined organic layers were dried and evaporated. Flash chromatography (Et_2O/hexanes, 5:95) gave **36** as a pale yellow oil (0.43 g, 86%). Rf 0.17 (Et_2O/hexanes, 5:95); IR (thin film) 2943, 2885, 1726 cm^{-1}; ^1H NMR δ (250 MHz, $CDCl_3$) 1.0 (12H, m, $C\underline{H}_3CHSi$), 1.15-1.4 (2H, m, $C\underline{H}Si$), 1.95 (2H, m, $C\underline{H}_2$), 2.19 (2H, m, $C\underline{H}_2CH$), 2.6 (2H, td, *J* = 7.2, 1.6 Hz, $C\underline{H}_2CHO$), 3.80 (2H, t, *J* = 6.0 Hz, $C\underline{H}_2OSi$), 7.2-7.6 (5H, m, Ar$\underline{H}$), 9.84 (1H, t, *J* = 1.6 Hz, C$\underline{H}$O); ^{13}C NMR δ (50.3 MHz, $CDCl_3$) 12.0, 17.4, 17.3, 25.5, 40.7, 62.7, 127.6, 129.3, 134.3, 134.5, 202.5; m/z (EI) 235 (46), 193 (33), 173 (55), 137 (100), 105 (18), 77 (15), 45 (15); HRMS (EI) calcd for $C_{13}H_{19}O_2Si$ ($M-C_3H_7$) 235.1154. Found 235.1150.

(2*R*,4*R*,5*R*)-1-(Benzyloxy)-5-hydroxy-2,4-dimethyl-8 (diisopropylphenylsilyloxy)octan-3-one (38, Scheme 7). To a cooled solution (0 °C) of dicyclohexylboron chloride (0.05 ml, 0.25 mmol) in dry ether (0.69 ml) under argon was added triethylamine (0.04 ml, 0.27 mmol) and the mixture stirred for 10 min. A solution of (*R*)-1-(benzyloxy)-2-methylpentan-3-one (**3**) [prepared according to ref. 9g] (35 mg) in ether (0.26 ml) was added *via* cannula and the reaction mixture was stirred at 0 °C for 2 h, before cooling to -78 °C. Aldehyde **36** (70 mg, 0.25 mmol) was then added and stirring was continued for 1 h at -78 °C and 2 h at 0 °C. The reaction mixture was then partitioned between pH 7 buffer (1.6 ml) and Et_2O (3 x 2.4 ml). The organic extracts were concentrated *in vacuo*. The residue was suspended in MeOH (1 ml), pH 7 buffer (1 ml) and H_2O_2 (30%; 0.6 ml) and then stirred at 0 °C for 2 h. The mixture was then partitioned between H_2O (8 ml) and CH_2Cl_2 (10 ml). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 ml) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Isolation of the aldol adduct was achieved by flash chromatography (EtOAc/hexanes 1:9) to give **38** as an opaque oil (62 mg, 78%). Rf 0.22 (EtOAc/hexanes, 1:9); $[\alpha]_D^{25}$ –4.6 (c 1.9, $CHCl_3$); IR (thin film) 3460, 2940, 2864, 1709, 1613, 1103 cm^{-1}; ^1H NMR δ (500 MHz, $CDCl_3$) 1.01 (3H, d, *J* = 7.5 Hz, $C\underline{H}_3$), 1.05 (6H, d, *J* = 7.4 Hz, $C\underline{H}_3$), 1.06 (6H, d, *J* = 7.4 Hz, $C\underline{H}_3$), 1.12 (3H, d, *J* =

7.1 Hz, C<u>H</u>$_3$), 1.27 (2H, m, C<u>H</u>Si), 1.45 (1H, m), 1.65-1.85 (3H, m), 2.75 (1H, quint, J = 7.1 Hz, C<u>H</u>CO), 3.09 (1H, tq, J = 1.7, 6.9 Hz, C<u>H</u>CO), 3.14 (1H, d J = 5.8 Hz, O<u>H</u>), 3.44 (1H, dd, J = 5.0, 8.8 Hz, C<u>H</u>$_2$OBn), 3.69 (1H, t, J = 8.8 Hz, C<u>H</u>$_2$OBn), 3.74-3.84 (3H, m), 4.44-4.53 (2H, m, OC<u>H</u>$_2$Ph), 7.23-7.41 (8H, m, Ar<u>H</u>), 7.54 (2H, m, Ar<u>H</u>); ^{13}C NMR δ (50.3 MHz, $CDCl_3$) 12.1, 13.4, 13.6, 17.3, 17.5, 29.0, 31.3, 45.7, 52.0, 63.8, 72.3, 73.4, 73.4, 127.6, 127.7, 128.4, 129.2, 134.4, 134.6, 137.9, 217.8; m/z (CI, NH_3) 296 (12), 280 (14), 279 (60), 225 (13), 224 (100), 208 (9), 207 (25), 108 (9); HRMS (CI, NH_3) calcd for $C_{29}H_{45}O_4Si$ ($M+H^+$) 485.3087. Found 485.3087.

Solid phase bound 4-penten-1-ol (34, Scheme 7). The resin **32** [prepared according to ref. 16a] (1.6 g) was swollen in dry CH_2Cl_2 (10 ml) and dimethylaminopyridine (6 mg, 0.05 mmol) was added at room temperature. A solution of 4-penten-1-ol (2.96 ml, 24.7 mmol) in CH_2Cl_2 (20 ml) containing diisopropylethylamine (4.26 ml, 24.5 mmol) was added *via* cannula to the resin. The reaction mixture was then stirred for 48 h at room temperature under argon. The resin was then vacuum filtered and rinsed with anhydrous CH_2Cl_2. The resin was re-suspended in a mixture of MeOH, diisopropylethylamine and CH_2Cl_2 (1:1:18) and stirred at room temperature for 1 h, followed by washing, in turn, with CH_2Cl_2, THF, acetone, DMSO, acetone, MeOH, CH_2Cl_2, and MeOH, then dried under reduced pressure at 50 °C for 3 h. This gave **34** as a pale yellowish-brown resin (1 g). IR (KBr) 1640, 1104 cm^{-1}; ^{13}C NMR δ (100 MHz, CD_2Cl_2) 12.9, 18.2, 30.0, 32.9, 63.4, 115.3, 139.1.

Solid phase bound 4-hydroxybutanal (33, Scheme 7). The resin **34** (0.96 g, maximum loading 0.75 mmol/g) was swollen in dry CH_2Cl_2 (70 ml) and ozonolysed at -78 °C until the solution turned bright blue. Oxygen was then bubbled through the reaction mixture until it became colourless and then triphenylphosphine (2.3 g, 9.0 mmol) was added at -78 °C. The reaction was then warmed to room temperature and stirred for 16 h under argon. The resin was then transferred to a sintered syringe and filtered with CH_2Cl_2 as eluent. The resin was washed, in turn, with CH_2Cl_2, H_2O, acetone, MeOH, Et_2O, CH_2Cl_2, and MeOH, followed by drying under reduced pressure at 50 °C for 3 h. This gave **33** as a pale yellow resin (970 mg). IR (KBr) 1724, 1114 cm^{-1}; ^{13}C NMR δ (100 MHz, CD_2Cl_2) 12.3, 12.7, 17.1, 17.4, 25.7, 63.0, 202.6.

Solid phase bound (2*R*,4*R*,5*R*)-1-(benzyloxy)-5,8-dihydroxy-2,4-dimethyloctan-3-one (37, Scheme 7). To a cooled solution (-78 °C) of dicyclohexylboron chloride (0.80 ml, 3.73 mmol) in dry ether (10 ml) under argon was added triethylamine (0.55 ml, 3.98 mmol) and the mixture stirred for 10 min. A solution of (*R*)-1-(benzyloxy)-2-methylpentan-3-one (**3**) [prepared according to ref. 9g] (0.52 g, 2.49 mmol) in ether was added *via* cannula and the reaction mixture was warmed to 0 °C and stirred for 2 h. The resulting enolate solution was then added *via* cannula to aldehyde **33** (278 mg, 0.21 mmol) cooled at -78 °C and the stirring was continued for 1 h before storing in the freezer (-26 °C) for 16 h. The enolate solution was then filtered off and the resin was washed with pH 7 buffer, H_2O, ether, MeOH. To the resin was then added (at 0 °C) MeOH (2 ml), pH 7 buffer (2 ml) and H_2O_2 (30%; 6 ml) and the stirring was continued at -26 °C for 16 h. The mixture was then filtered and the resin washed with H_2O, Et_2O, acetone, Et_2O, CH_2Cl_2, and MeOH. The resin was then dried under reduced pressure at 50 °C for 3 h. This gave **37** as a pale yellow resin (282 mg). IR (KBr) 3446, 1706, 1098 cm^{-1}; ^{13}C NMR (100 MHz, CD_2Cl_2) 12.3, 12.7, 13.5, 13.6, 17.1, 17.5, 29.2, 31.5, 45.9, 52.2, 64.1, 72.6, 73.4, 127.8, 128.2, 217.7.

(2*R*,4*R*,5*R*)-1-(Benzyloxy)-5,8-dihydroxy-2,4-dimethyloctan-3-one (39, Scheme 7). To resin **37** (0.28 g, 0.21 mmol/g) was added a solution of HF/CH_3CN (0.5 M; 18 ml) and stirring was continued for 4 h. The reaction mixture was quenched with $NaHCO_3$ and the resin rinsed and washed with CH_2Cl_2. The organic layer was then extracted with EtOAc (3 x 10 ml), the combined organic extracts were dried ($MgSO_4$) and

concentrated under reduced pressure. Isolation of the aldol adduct was achieved by flash chromatography (EtOAc/hexanes, 8:2) to give **39** as an opaque oil (53 mg, 85%). Rf 0.43 (EtOAc/hexanes 8:2); $[\alpha]_D^{25}$ –2.9 (c 1.33, $CHCl_3$); IR (thin film) 3410, 2936, 1706, 1455 cm^{-1}; ^1H NMR δ (500 MHz, $CDCl_3$) 1.04 (3H, d, *J* = 7.2 Hz, $C\underline{H}_3$), 1.11 (3H, d, *J* = 7.2 Hz, $C\underline{H}_3$), 1.38-1.51 (1H, m, $C\underline{H}_2$), 1.70 (3H, m, $C\underline{H}_2C\underline{H}_2$), 2.05 (1H, d, *J* = 9.4 Hz, O<u>H</u>), 2.73 (1H, quint, *J* = 7.2 Hz, C<u>H</u>CO), 3.05-3.12 (1H, m, C<u>H</u>CO), 3.43 (1H, dd, *J* = 8.9, 4.8 Hz, $C\underline{H}_AH_BBn$), 3.59-3.66 (2H, m, $C\underline{H}_2OH$), 3.69 (1H, t, *J* = 8.9 Hz, $CH_A\underline{H}_BOBn$), 3.75 (1H, td, *J* = 8.3, 1.8 Hz, C<u>H</u>OH), 4.47 (2H, m, $OC\underline{H}_2Ph$), 7.24-7.35 (5H, m, Ar<u>H</u>); ^{13}C NMR δ (50.3 MHz, $CDCl_3$) 13.5, 13.8, 29.1, 31.4, 45.3, 52.1, 62.7, 72.3, 73.4, 127.7, 127.7, 128.4, 137.7, 217.8; m/z (CI, NH_3) 312 (13), 294 (13), 225 (22), 224 (100), 207 (31), 88 (60), 71 (14); HRMS (CI, NH_3) calcd for $C_{17}H_{30}NO_4$ ($M+NH_4^+$) 312.2175. Found 312.2175.

Solid phase bound (2*R*,3*S*,4*R*,5*R*)-1-(benzyloxy)-2,4-dimethyloctan-3,5,8-triol (40, Scheme 7). To a cooled solution (-78 °C) of dicyclohexylboron chloride (1.32 ml, 6.21 mmol) in dry ether (17 ml) under argon was added triethylamine (0.92 ml, 6.62 mmol) and the mixture was stirred for 10 min. A solution of (*R*)-1-(benzyloxy)-2-methylpentan-3-one (**3**) [prepared according to ref. 9g] (0.86 g, 4.14 mmol) in ether was added *via* cannula and the reaction mixture was warmed to 0 °C and stirred for 2 h. The resulting solution of enolate **2** was then added *via* cannula to the aldehyde **33** (0.46 g, 0.35 mmol) cooled to -78 °C. Stirring was continued for 1 h before storing in the freezer (-26 °C) for 16 h. The reaction mixture was then re-cooled to -78 °C, a solution of $LiBH_4$ (2M in THF; 6.9 ml, 13.8 mmol) was added and stirring was continued at -78 °C for 4 h. The reaction mixture was quenched by addition of aqueous NH_4Cl (satd, 20 ml). The resin was then rinsed and washed, in turn, with H_2O, ether, MeOH. To the resin was then added (at 0 °C) MeOH (9 ml), H_2O_2 (30%; 5 ml), NaOH (10% aqueous) (3.7 ml), CH_2Cl_2 (2 ml) and stirring was continued at room temperature for 16 h. The mixture was then filtered and the resin was washed, in turn, with H_2O, Et_2O, CH_2Cl_2, and MeOH. The resulting resin was then dried under reduced pressure at 50 °C for 3 h. This gave **40** as a white resin (480 mg). IR (KBr) 3628, 3445, 1113 cm^{-1}; ^{13}C NMR δ (100 MHz, CD_2Cl_2) 9.4, 12.4, 12.7, 13.0, 17.2, 17.5, 28.8, 30.0, 31.7, 53.5, 64.5, 73.6, 75.6, 76.6, 76.7, 127.9, 128.6.

(2*R*,3*S*,4*R*,5*R*)-1-(Benzyloxy)-2,4-dimethyloctan-3,5,8-triol (41, Scheme 7). To resin **40** (0.1 g, 0.07 mmol/g) was added a solution of HF/CH_3CN (0.5 M; 10.5 ml) and stirring was continued for 16 h. The reaction mixture was quenched with sat aqueous $NaHCO_3$ and the resin rinsed and washed with CH_2Cl_2. The aqueous layer was then extracted with EtOAc (3 x 10 ml), the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash chromatography (Et_2O/CH_2Cl_2, 9:1) gave **41** as an opaque oil (15.7 mg, 71%). $[\alpha]_D^{25}$ +5.9 (c 1.1, $CHCl_3$); IR (thin film) 3355, 2923, 1454 cm^{-1}; ^1H NMR δ (500 MHz, $CDCl_3$) 0.75 (3H, d, *J* = 6.8 Hz, $C\underline{H}_3$), 1.0 (3H, d,*J* = 7.1 Hz, $C\underline{H}_3$), 1.53 (1H, m), 1.56-1.81 (4H, m), 1.93 (1H, m, $C\underline{H}CH_3$), 3.57 (1H, dd, *J* = 8.9, 4.5 Hz, $C\underline{H}_AH_BOBn$), 3.63-3.7 (3H, m, $C\underline{H}_2OH$, $CH_A\underline{H}_BOBn$), 3.7 (1H, td, *J* = 8.3, 2.2 Hz, C<u>H</u>OH), 3.81 (1H, dd, *J* = 9.5, 1.5 Hz, C<u>H</u>OH), 4.52 (2H, m, $OC\underline{H}_2Bn$), 7.26-7.38 (5H, m, Ar<u>H</u>); ^{13}C NMR δ (100 MHz, $CDCl_3$) 9.3, 12.9, 28.4, 31.73, 34.9, 40.2, 63.0, 73.5, 75.8, 76.0, 79.8, 127.6, 127.6, 127.8, 128.5, 137.7; m/z (EI) 297 (82), 129 (60), 108 (68), 91 (100), 82 (63), 71 (78); HRMS (EI) calcd for $C_{17}H_{29}O_4$ ($M+H^+$) 297.2065. Found 297.2065.

Solid phase bound (2*R*,3*S*,4*R*,5*R*)-1-(benzyloxy)-2,4-dimethyl-3,5-[(*bis*-dimethylmethylene)dioxy]octan-8-ol (42, Scheme 7). To resin **40** (0.2 g, 0.15 mmol/g), swollen in CH_2Cl_2 (2 ml), was added dimethoxypropane (2.95 ml, 24 mmol) and camphorsulfonic acid (0.01 g, 0.05 mmol). The reaction mixture was stirred under argon at room temperature for 24 h . The resin was then rinsed and washed, in turn, with CH_2Cl_2, Et_2O and MeOH, followed by drying under reduced pressure at 50 °C for 3 h. This gave **42**

as a pale yellow resin (200 mg): IR (KBr) 1097 cm^{-1}; ^{13}C NMR (100 MHz; CD_2Cl_2) 9.6, 11.7, 12.2, 12.6, 17.1, 17.4, 19.7, 28.7, 29.6, 30.1, 34.2, 35.4, 40.7, 63.5, 73.3, 73.4, 74.4, 97.6, 127.8, 128.4.

(2*R*,3*S*,4*R*,5*R*)-1-(Benzyloxy)-2,4-dimethyl-3,5-[(*bis*-dimethyl-methylene)dioxy]octan-8-ol (43, Scheme 7). To resin **42** (0.19 g, 0.11 mmol/g), swollen in THF (4 ml), was added TBAF (1 M in THF; 4.0 ml). The reaction mixture was stirred under argon at room temperature for 16 h. The resin was rinsed and washed with CH_2Cl_2. The combined organic washes were concentrated under reduced pressure. Purification by flash chromatography (CH_2Cl_2/Et_2O, 7:3) gave **43** as an opaque oil (16.6 mg, 45%). $[\alpha]_D^{25}$ -1.4 (c 0.52, $CHCl_3$); IR (thin film) 3416, 2930, 1454 cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 0.75 (3H, d, *J* = 6.7 Hz, C<u>H</u>$_3$), 0.85 (3H, d,*J* = 6.9 Hz, C<u>H</u>$_3$), 1.34 (3H, s, C<u>H</u>$_3$), 1.4 (3H, s, C<u>H</u>$_3$), 1.45-1.75 (4H, m), 1.83 (1H, m), 2.06 (1H, m), 3.29 (1H, dd, *J* = 8.7, 6.2 Hz, C<u>H</u>$_2$OBn), 3.47 (1H, t, *J* = 8.7 Hz, C<u>H</u>$_2$OBn), 3.47-3.55 (1H, m, C<u>H</u>OH), 3.63 (2H, t, *J* = 5.7 Hz, C<u>H</u>$_2$OH), 3.72 (1H, dd, *J* = 10.4, 2.1 Hz, C<u>H</u>OH), 4.46-4.54 (2H, m, OC<u>H</u>$_2$Ph), 7.33 (5H, m, Ar<u>H</u>); ^{13}C NMR δ (100 MHz, $CDCl_3$) 9.5, 11.7, 19.6, 28.7, 29.9, 30.0, 33.9, 34.6, 62.9, 72.8, 73.0, 73.1, 74.8, 97.9, 127.5, 127.6, 128.3, 138.7; m/z (EI) 321 (90), 260 (21), 231 (21), 190 (36), 179 (26), 153 (22), 91 (100), 71 (28), 59 (26); HRMS (EI) calcd for $C_{19}H_{29}O_4$ (M-CH_3) 321.2066. Found 321.2066.

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