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 carrying 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 LiBH4, 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. © 1998 Elsevier Science Ltd. All rights reserved.

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, 7-polyol chain with defined stereochemistry, is not yet available.

Path A: Enolate attached to solid support

\[ R^+\text{CHO} \rightarrow \text{R}^+\text{CHO} \]

Path B: Aldehyde attached to solid support

\[ \text{R}^+\text{CHO} \rightarrow \text{R}^+\text{CHO} \]

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.
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 menthene-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 polyl 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, \textit{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 1](image)

**Scheme 2** (a) \(\text{NaH}\), \((C_6H_{13})_4\text{NBr}\), THF, reflux, 3 d; (b) BF\(_3\)*Et\(_2\)O, CH\(_2\)Cl\(_2\), -78 °C, 1.5 h; (c) HF, CH\(_3\)CN, 20 °C, 7 d; (d) i: Bu\(_4\)NOH, THF/MeOH, 70 °C, 24 h; ii: MeI, CH\(_3\)CN, 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,\(^1\)\(^2\) in the presence of BF\(_3\)Et\(_2\)O, 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 \(^1\)\(^3\)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 \( 10 \rightarrow 8 \rightarrow 9 \)).

**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\(^*\)\(_2\)BBr\(_2\), in the presence of Et\(_3\)N,\(^8\) 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 \( 10 \rightarrow 12 \rightarrow 9 \)) – 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)\(_3\)\(^1\)H NMR study to be 91% (cf. 94% ee for \((R)-\)9 obtained from the corresponding solution model 10 via 12).

![Scheme 3](image)

Scheme 3 (a) i: CH\(_2\)Cl\(_2\)/Et\(_2\)O, -78 °C → -5 °C, 16 h; ii: 30% H\(_2\)O\(_2\), MeOH, pH 7 buffer, 20 °C, 30 min; (b) i: Bu\(_4\)NOH, THF/MeOH, 70 °C, 24 h; ii: Med, CH\(_3\)CN, 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 acid 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.\(^1\)\(^3\)
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.
Table 1. Enantioselective Aldol Reactions of Boron Enolate 1.

<table>
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<th>Entry</th>
<th>Aldehyde</th>
<th>Aldol</th>
<th>Config.</th>
<th>Yield (%)</th>
<th>ee (%) a</th>
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<td>11</td>
<td>R</td>
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<td>91b</td>
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<td>R</td>
<td>77d</td>
<td>80d</td>
</tr>
</tbody>
</table>

(a) Determined by 1H 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. 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 Et2O with the preformed (E)-enol borinate 2 (3 equiv.), derived from treatment of (R)-1-(benzylxyloxy)-2-methylpentan-3-one (3) with c- Hex2BCl in the presence of Et3N, 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 1H NMR).

Scheme 6 (a) DIC, DMAP, HOBt, DMF, 20 °C, 24 h; (b) i: Et2O, -78 °C, 1 h; 0 °C; ii: H2O2, pH 7, 0 °C, 16 h; (c) i: Et2O, -78 °C, 1 h; 0 °C; ii: LiBH4, -78 °C, 4 h; iii: H2O2, 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\textsuperscript{15} in situ with LiBH\textsubscript{4} followed by oxidation with H\textsubscript{2}O\textsubscript{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 \textsuperscript{1}H 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.\textsuperscript{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.\textsuperscript{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 \textsuperscript{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\textsubscript{2}NEt, DMAP, CH\textsubscript{2}Cl\textsubscript{2}, 20 °C, 48 h; (b) i: O\textsubscript{3}, CH\textsubscript{2}Cl\textsubscript{2}; ii: Ph\textsubscript{3}P, 20 °C, 16 h; (c) Et\textsubscript{2}O, -78 °C, 1 h; 0 °C, 16 h; (d) HF, CH\textsubscript{3}CN, 20 °C, 4–16 h; (e) i: Et\textsubscript{2}O, -78 °C, 1 h; 16 h, 0 °C; ii: LiBH\textsubscript{4}, -78 °C, 4 h; iii: H\textsubscript{2}O\textsubscript{2}, pH 7, 0 °C, 16 h; (f) (MeO)\textsubscript{2}CMe\textsubscript{2}, CH\textsubscript{2}Cl\textsubscript{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\textsuperscript{15} in situ with LiBH\textsubscript{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 \textsuperscript{13}C NMR resonances (δ 19.7, 30.1, 97.6).\textsuperscript{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:** \textsuperscript{1}H-NMR and \textsuperscript{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\textsubscript{3} and CD\textsubscript{2}Cl\textsubscript{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; [α]D\textsuperscript{25} values were measured on Perkin Elmer 141 and 241 polarimeters. Chromatographic purifications were performed by “flash chromatography”\textsuperscript{18} using Merck silica gel 270-400 mesh. All organic extracts were dried over Na\textsubscript{2}SO\textsubscript{4} or MgSO\textsubscript{4}. Dry solvents were distilled immediately before use; CH\textsubscript{2}Cl\textsubscript{2} and Et\textsubscript{3}N from CaH\textsubscript{2}, THF and Et\textsubscript{2}O 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.\textsuperscript{16a}

**p-Benzoxycarbonyl 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\textsubscript{2}Cl\textsubscript{2} (15 ml), under N\textsubscript{2}, was treated with a solution of DCC (1.5 g, 7.4 mmol) in CH\textsubscript{2}Cl\textsubscript{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\textsubscript{2}Cl\textsubscript{2}. The filtrates were washed with H\textsubscript{2}O, 10% AcOH and H\textsubscript{2}O. The organic phase was dried and evaporated. The residue was purified by flash chromatography (hexanes/CH\textsubscript{2}Cl\textsubscript{2} 1:1) to give 10 as a white solid (1.5 g, 92%): mp: 142-144 °C; IR (nujol) 1716, 1270 cm\textsuperscript{-1}; \textsuperscript{1}H NMR δ (200 MHz, CDCl\textsubscript{3}) 5.42 (2H, s, PhCH\textsubscript{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\textsubscript{15}H\textsubscript{12}O\textsubscript{3}: calc C 74.99, H 5.03; found C 74.98, H 5.07.

**p-Hydroxymethyl benzaldehyde (13).** To a solution of terephthaldehyde (3.0 g, 22 mmol) in THF (44 ml), under N\textsubscript{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\textsubscript{2}O (0.6 ml), 15% NaOH (0.6 ml), H\textsubscript{2}O (1.2 ml) and Na\textsubscript{2}SO\textsubscript{4} (3.9 g). Stirring was maintained for 3-6 h, then the precipitate was separated by filtration and washed with cold Et\textsubscript{2}O. The filtrates were evaporated and the crude product purified by flash chromatography (CH\textsubscript{2}Cl\textsubscript{2}/AcOEt, 75:25) to afford p-hydroxymethyl benzaldehyde (13) as a white solid (1.5 g, 54%): \textsuperscript{1}H NMR δ (200 MHz, CDCl\textsubscript{3}) 2.05 (1H, s, OH), 4.81 (2H, s, CH\textsubscript{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\textsubscript{8}H\textsubscript{8}O\textsubscript{2}: calc C 70.56, H 5.93; found C 70.50, H 5.99.

**p-Acetoxy methyl benzaldehyde (16).** To a solution of p-hydroxymethyl benzaldehyde (35 mg, 0.26 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (0.79 ml), CH\textsubscript{3}CO\textsubscript{2}H (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\textsubscript{2}Cl\textsubscript{2}/hexanes 9:1) to afford 16 as a white solid (37 mg, 80%): IR (nujol) 1728, 1681, 1155 cm\textsuperscript{-1}; \textsuperscript{1}H NMR δ (200 MHz, CDCl\textsubscript{3}) 2.18 (3H, s, CH\textsubscript{3}), 5.22 (2H, s, CH\textsubscript{2}), 7.72 (2H, d, J = 8.3 Hz, Ar), 7.91 (2H, d, J = 8.3 Hz, Ar), 10.05 (1H, s, CHO); C\textsubscript{10}H\textsubscript{10}O\textsubscript{3}: calc C 67.39, H 5.66; found C 67.21, H 5.71.

**p-Trityloxy methyl benzaldehyde (22).** An equimolar (0.5 M) solution of trityl chloride (0.85 g, 3.0 mmol) and Bu\textsubscript{4}NI (1.1 g, 3.0 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (6.0 ml) was added at 25 °C under N\textsubscript{2} to p-hydroxymethyl benzaldehyde (0.25 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\textsubscript{2}O and the two layers were separated. The aqueous phase was extracted twice with CH\textsubscript{2}Cl\textsubscript{2} and the combined organic extracts were washed with H\textsubscript{2}O, saturated NH\textsubscript{4}Cl and H\textsubscript{2}O, 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\textsuperscript{-1}; \textsuperscript{1}H NMR δ (200 MHz, CDCl\textsubscript{3}) 4.30 (2H, s, CH\textsubscript{2}), 7.24-7.60 (17H, m, Ar), 7.88 (2H, d, J = 8.1 Hz, Ar), 10.03 (1H, s, CHO); C\textsubscript{2}H\textsubscript{2}O\textsubscript{2}: calc C 85.68, H 5.86; found C 85.72, H 5.93.

3-Hydroxy-3-p-benzyloxy carbonyl phenyl propanoic acid tert-butyl thioester (8, Scheme 2). A solution of p-benzyloxy carbonyl benzaldehyde (10) (0.13 g, 0.54 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (1.0 ml) was cooled to -78 °C under N\textsubscript{2} and BF\textsubscript{3}-Et\textsubscript{2}O (77 mg, 0.07 ml, 0.54 mmol) was added dropwise. The mixture was stirred for 10 min then a solution of 1-tert-butythio-1-tert-butyldimethylsilyloxyethylene (prepared according to ref. 12c) (0.20 g, 0.81 mmol) in CH\textsubscript{2}Cl\textsubscript{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\textsuperscript{-1}; \textsuperscript{1}H NMR δ (200 MHz, CDCl\textsubscript{3}) 0.17 (3H, s, SiCH\textsubscript{3}), 0.045 (3H, s, Si(CH\textsubscript{3})\textsubscript{3}), 0.87 (9H, s, Si-r-Bu), 1.46 (9H, s, Si-r-Bu), 2.59 (1H, dd, J = 3.9 Hz, J = 14 Hz, CH\textsubscript{3}COS), 2.89 (1H, dd, J = 8.9 Hz, J = 14 Hz, CHHCO\textsubscript{2}), 5.21 (1H, dd, J = 3.9 Hz, J = 8.9 Hz, CHOTBS), 5.37 (2H, s, PhCH\textsubscript{2}O), 7.38-7.45 (7H, m, Ar), 8.07 (2H, d, J = 8.1 Hz, Ar); \textsuperscript{13}C NMR δ (50.3 MHz, CDCl\textsubscript{3}) 25.7, 29.7, 55.2, 66.7, 71.6, 197.5, 149.5, 129.5, 128.3, 128.6, 125.8; C\textsubscript{27}H\textsubscript{38}O\textsubscript{4}Si: calc 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$_3$CN (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$_2$Cl$_2$ (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$_4$NOH (THF/MeOH) at 70 °C for 24 h, followed by addition of MeI in CH$_3$CN at room temperature, gave compound 9 in quantitative yield.

**Representative Procedure for L$^*$$_2$BBr Promoted Aldol Reactions in Solution.** To a stirred solution of the thioester (0.23 g, 1.7 mmol) in Et$_2$O (4.5 ml) at 0 °C (ice cooling) under an argon atmosphere, a solution of L$^*$$_2$BBr [prepared from (-)-menthone according to ref. 8h] in CH$_2$Cl$_2$ (0.4 M, 6.5 ml, 1.7 mmol) and then Et$_3$N (0.36 ml, 2.6 mmol) were added dropwise. Enolborinate 1 was generated with concurrent formation and precipitation of Et$_3$N-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$_2$O (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$_2$Cl$_2$. 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$_2$O$_2$ 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$_2$Cl$_2$ (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.

**3R)-Hydroxy-3-p-benzylxycarbonylphenylpropanoic acid t-butyli 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%): [α]$^D_{25}$ +29.9 (c 1 in CHCl$_3$); IR (nujol) 3481, 3298, 1727, 1705, 1269 cm$^{-1}$; $^1$H NMR δ (200 MHz, CDCl$_3$) 1.48 (9H, s, CH$_3$), 2.86 (2H, d, J = 5.8 Hz, CH$_2$), 3.33 (1H, d, J = 3.3 Hz, OH), 5.22 (1H, dt, J = 5.8 Hz, J = 3.3 Hz, CHO$_2$), 5.38 (2H, s, PhCH$_2$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, 68.5, 71.8, 117.8, 119.8, 119.9, 121.3, 121.1, 125.9, 135.8, 151.6, 179.05; C$_2$H$_4$O$_4$S: calcd C 67.72, H 6.50; found C 67.88, H 6.65.

**3R)-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$_4$NOH-3H$_2$O (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$_3$CN (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$^{-1}$; $^1$H NMR δ (200 MHz, CDCl$_3$) 2.75 (2H, d, J = 6.4 Hz, CH$_2$), 3.43 (1H, bs, OH), 3.74 (3H, s, OCH$_3$), 3.92 (3H, s, OCH$_3$), 5.20 (1H, bt, J = 6.4 Hz, CHO$_2$), 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.

**3R)-Hydroxy-3-p-acetoxymethylphenylpropanoic acid t-butyli thioester (17, Scheme 4).** Flash chromatography (CH$_2$Cl$_2$/Et$_2$O, 95:5) afforded 17 as a white solid (73 mg, 67%): [α]$^D_{25}$ +19.5 (c 1 in CHCl$_3$); IR (nujol) 3381, 1728, 1674, 1161 cm$^{-1}$; $^1$H NMR δ (200 MHz, CDCl$_3$) 1.49 (9H, s, Sb-Bu), 2.11 (3H, s, CH$_3$), 2.78-2.99 (2H, m, CH$_2$), 3.19 (1H, d, J = 3.0 Hz, OH), 5.10 (2H, s, CH$_2$O), 5.11-5.22 (1H, m, CHO$_2$), 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$_4$: calcd C 61.91, H 7.15; found C 61.78, H 7.35.
(3R)-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 Bu₄NOH·3H₂O (0.20 g, 0.25 mmol) and MeI (0.03 ml, 0.47 mmol). Flash chromatography (CH₂Cl₂/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, CDCl₃) 2.62-2.86 (2H, m, CH₂), 3.29 (1H, bs, OH), 3.73 (3H, s, OCH₃), 4.68 (2H, s, CH₂OH), 5.11-5.21 (1H, m, CH₂O), 7.39 (4H, s, Ar); e.e. [Eu(hfc)₃] = 94%; C₁₁H₁₄O₄: calc'd C 62.83, H 6.72; found C 62.75, H 6.78.

(3R)-Hydroxy-3-trityloxyphenylpropanoic 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, CDCl₃) 1.50 (9H, s, St-Bu), 2.86-2.92 (2H, m, CH₂), 3.14 (1H, d, J = 2.8 Hz, OH), 4.17 (2H, s, CH₂O), 5.15-5.23 (1H, m, CH₂O), 7.25-7.55 (19H, m, Tr + Ar); e.e. [Eu(hfc)₃] = 80%; C₃₃H₃₄O₃S: calc'd C 77.61, H 6.72; found C 77.75, H 6.81.

(3R)-Hydroxy-3-p-carboxybenzaldehyde (24, Scheme 5). Compound 23 (41 mg, 0.08 mmol) was treated with a 0.2 M solution of p-TsOH·H₂O in THF/MeOH 1:1 (2.0 ml). The solution was stirred at room temperature for 6 h, then Et₃N was added (40 mg, 0.40 mmol) and the solvent was evaporated. The residue was purified by flash chromatography (CH₂Cl₂/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, CDCl₃) 1.49 (9H, s, St-Bu), 2.84-2.89 (2H, m, CH₂), 3.24 (1H, bs, OH), 4.69 (2H, s, ArCH₂OH), 5.11-5.22 (1H, m, CH₂O), 7.36 (4H, s, Ar); ¹³C NMR δ (50.3 MHz, CDCl₃) 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%; C₁₄H₁₂O₂S: calc'd 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 N₂ for 1 h, then cooled to room temperature and treated with (n-C₆H₁₃)₄NBr (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, H₂O, MeOH, THF and CH₂Cl₂. 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-C₆H₁₃)₄NBr (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, H₂O, 1.0 M HCl in dioxane/H₂O (1:1), H₂O, MeOH, THF and CH₂Cl₂. 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 CH₂Cl₂. 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 Bu₄NOH·3H₂O (0.88 g, 1.1 mmol). The mixture was stirred at 70 °C for 3 d, then filtered, and washed with MeOH and CH₂Cl₂. The combined filtrates were evaporated and the residue purified by flash chromatography (CH₂Cl₂/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 CH₂Cl₂ (10 ml) under N₂ at 25 °C, Bu₄NI (1.2 g, 3.2 mmol) and p-hydroxymethyl benzaldehyde (12) (0.44 g, 3.2 mmol) were added. The mixture was treated with syn-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 CH₂Cl₂ (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·H₂O in THF/MeOH 1:1 (2.0 ml). The mixture was stirred for 17 h, then the resin was filtered and washed with MeOH, Et₂O and CH₂Cl₂. 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 (CH₂Cl₂/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 CH₂Cl₂ (11 ml) under N₂ and cooled to -78 °C. BF₃·Et₂O (0.21 g, 0.18 ml, 1.5 mmol) was added dropwise and the mixture was stirred for 10 min. A solution of 1-tert-butylthio-1-tertiarydimethylsililoxoethylene (prepared according to ref. 12c) (0.49 g, 2.0 mmol) in CH₂Cl₂ (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 CH₂Cl₂ (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 CH₂Cl₂, MeOH, H₂O, MeOH and CH₂Cl₂. The residual solvent was removed in vacuo. Desilylation was performed by treating a suspension of the resin (0.34 g) in CH₃CN (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 Sip-Bu to St-Bu signals in the gel-phase ¹³C NMR spectra: δ 25.77 and 29.74, respectively). The resin was then filtered and washed with CH₃CN and CH₂Cl₂. 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 Bu₄NOH·3H₂O (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*₂BB Br Promoted Aldol Reactions on Solid Phase. To a stirred solution of the thioester (53 mg, 0.40 mmol) in Et₂O (1.5 ml) at 0 °C (ice cooling) under argon atmosphere, a solution of L*₂BB Br [prepared from (-)-menthone according to ref. 8h] in CH₂Cl₂ (0.4 M, 1.5 ml, 0.60 mmol) and then Et₃N (0.09 ml, 0.64 mmol) were added dropwise. Enolborinate 1 was generated with concurrent formation and precipitation of Et₃N·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 Et₂O (0.5 ml). The reaction mixture was stirred at -5 °C for 16 h followed by rinsing and washing with dry CH₂Cl₂. 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 H₂O, MeOH, THF, and CH₂Cl₂. The resin was dried in vacuo, then suspended in MeOH (5 ml), pH7 phosphate buffer (1 ml) and 30% H₂O₂ (1 ml). The mixture was stirred at room temperature for 30 min. This oxidative cycle was repeated twice before washing the resin with H₂O, MeOH and CH₂Cl₂ and drying in vacuo. IR (nujol) 1714, 1675 cm⁻¹.

Solid phase bound (3R)-hydroxy-3-p-hydroxymethylphenylpropanoic acid tert-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 Bu₄NOH·30H₂O (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 CH₂Cl₂ and MeOH. The combined filtrates were evaporated, and the residue was dissolved in CH₃CN (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 (3R)-hydroxy-3-p-hydroxymethylphenylpropanoic acid tert-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 (CH₂Cl₂/AcOEt, 8:2) afforded 16 (2.6 mg, 0.06 mmol/g, 64%); e.e. [Eu(hfc)₃] = 91%.

Solid phase bound (3R)-hydroxy-3-p-hydroxymethylphenylpropanoic acid tert-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·H₂O (0.22 g, 1.2 mmol). The mixture was stirred for 22 h, then the resin was filtered and washed with MeOH, MeOH/CH₂Cl₂ 1:1, and CH₂Cl₂. 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 (CH₂Cl₂/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 CH₂Cl₂ (5 ml) was added dry pyridine (0.35 ml, 4.26 mmol) and the resulting mixture was cooled to 0 °C. Benzylo 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 benzylo 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 NaHCO₃ (4 ml), then dried (MgSO₄), filtered and concentrated in vacuo to give the crude product. Flash chromatography (Et₂O/hexanes, 2:8) gave 28 as a colourless solid (0.634 g, 86%); mp = 93-95 °C; IR (CHCl₃) 1741, 1701, 1600 cm⁻¹; ¹H NMR δ (250 MHz, CDCl₃) 7.42 (2H, d, J = 8.6 Hz, ArHOCO), 7.53 (2H, t, J = 7.5 Hz, ArHOCO), 7.67 (1H, tt, J = 7.1, 1.3 Hz, ArHCO₂), 7.97 (2H, d, J = 8.6 Hz, ArHOCO), 8.2 (2H, d, J = 7.5 Hz, ArHCO₂), 10.03 (1H, s, CHO); ¹³C NMR δ (100 MHz, CDCl₃) 122.5, 128.7, 128.9, 130.3, 131.3, 134.0, 155.7, 164.5, 190.9.

(2R,4R,5S)-5-[4’-(Benzoyloxyphenyl)]-1-(benzyl)-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 Et₂O (1.22 ml) was added Et₃N (0.22 ml, 1.55 mmol) at 0 °C. A solution of (R)-1-(benzyl)-2-methylpentan-3-one (3) [prepared according to ref. 9g (61.6 mg, 0.29 mmol) in dry Et₂O (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 CH₂Cl₂/Et₂O (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 Et₂O (3 x 10 ml). The combined organic phases were dried (MgSO₄), 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. H₂O₂ (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 CH₂Cl₂ (3 x 8 ml). The combined organic phases were washed with sat. aqueous NaHCO₃ (8
ml) and brine (8 ml), dried (MgSO₄), filtered and concentrated in vacuo to give an oil. Flash chromatography (EtOAc/hexanes. 25:75) gave 29 as a colourless solid (108 mg, 86%). [α]D₂⁵
-5.3 (c 0.74, CHCl₃); mp = 103-105 °C; IR (CHCl₃) 1734. 1601 cm⁻¹; ¹H NMR δ (500 MHz, CDCl₃) 0.98 (3H, d, J = 7.1, CH₃H), 1.02 (3H, d, J = 7.0, CH₃CH), 3.05 (2H, m, H₄, H₂), 3.15 (1H, d, J = 4.4 Hz, OH), 3.46 (1H, dd, J = 8.8, 4.9 Hz, H₁A), 3.69 (1H, t, J = 8.8 Hz, H₁B), 4.47 (1H, d, J = 12.0 Hz, CH₂Bn), 4.52 (1H, d, J = 12.0 Hz, CH₂Bn), 4.81 (1H, dd, J = 8.1, 4.4 Hz, CHOH), 7.21 (2H, d, J = 8.4 Hz, ArHO-), 7.25-7.35 (5H, m, ArHCH₂), 7.40 (2H, d, J = 8.4 Hz, ArHO-), 7.51 (2H, t, J = 7.7 Hz, ArHCO₂), 7.64 (1H, t, J = 7.4 Hz, ArHCO₂), 8.2 (2H, d, ArHCO₂); ¹³C 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). To carboxy-polystyrene resin 25 [prepared according to ref 14a] (1.5 g, 1.5 mmol) suspended in DMF (10 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 argon atmosphere at room temperature for 24 h. The solvent was filtered and the resin was washed, in sequence, with dioxane, H₂O, dioxane/H₂O 2:1, dioxane, acetone, MeOH, CH₂Cl₂. 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 washed and dried with Et₂O, water, Et₂O, CH₂Cl₂. 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 (MgSO₄), filtered and concentrated in vacuo. The residue was purified by flash chromatography (Et₂O/CH₂Cl₂, 2.8), to afford 4-hydroxybenzaldehyde (0.05 g), corresponding to 0.7 mmol/g of resin (74%).

Solid phase bound (2R,3S,4S,5S)-1-(benzylxoy)-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 Et₂O (5.8 ml) was added Et₃N (0.25 ml, 1.78 mmol) at 0 °C. A solution of (R)-1-(benzylxoy)-2-methylpentan-3-one (3) [prepared according to ref. 9g] (232 mg, 1.11 mmol) in dry Et₂O (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 CH₂Cl₂/Et₂O (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 LiBH₄ (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 NH₄Cl (20 ml) was successively added. The solvent was filtered and the resin washed with water, dioxane, and Et₂O. The resin was then suspended in MeOH (5 ml) and pH 7 buffer (3 ml), cooled to 0 °C and H₂O₂ (30%; 7 ml) was added. The solvent was filtered and the product resin 30 washed, in sequence, with water, dioxane, acetone, MeOH, CH₂Cl₂.

(2R,3S,4S,5S)-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 (0.5 M) (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 Et₂O, water, Et₂O, CH₂Cl₂. 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 (MgSO₄), filtered and concentrated in vacuo to give an oil. The mixture was then suspended in MeOH (0.65 ml) and cooled to 0 °C. H₂O₂ (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 CH₂Cl₂ (3 x 1 ml). The combined organic phases
were washed with sat. aqueous NaHCO₃ (10 ml) and brine (10 ml), dried (MgSO₄), filtered and concentrated in vacuo to give an oil. Flash chromatography (Et₂O/CH₂Cl₂ 3:7) gave 31 as a colourless oil (61.6 mg, 50%), which was unstable. Rf 0.35 (Et₂O/CH₂Cl₂ 3:7); IR (thin film) 3348, 2932, 1614, 1517, 1454 cm⁻¹; ¹H NMR δ (500 MHz, CDCl₃) 0.47 (3H, d, J = 6.8 Hz, CH₃CH), 1.05 (3H, d, J = 7.0 Hz, CH₃CH), 1.83-2.05 (2H, m, H₂, H₄), 3.55-3.65 (2H, m, H₁), 3.93 (1H, dd, J = 9.4, 1.2 Hz, H₃), 4.50 (1H, d, J = 9.0 Hz, H₅), 4.54 (2H, s, OCH₂Ph), 5.15 (1H, s br, OH), 6.67 (2H, d, J = 8.5 Hz, Ar-ΟΗ), 7.12 (2H, d, J = 8.5 Hz, Ar-ΟΗ), 7.2-7.4 (5H, m, ArH).

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 CH₂Cl₂ (1.8 ml) were added diisopropylethylamine (0.31 µl, 1.8 mmol) and chlorodisopropylsilane (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 NaHCO₃ (0.5 ml), the layers separated and the organic phase extracted with CH₂Cl₂ (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, CDCl₃) 1.01 (6H, d, J = 7.3 Hz, CH₃CHSi), 1.1 (6H, d, J = 7.2 Hz, CH₂CHSi), 1.2-1.4 (2H, m, CHSi), 1.7 (2H, m, CH₂), 2.19 (2H, m, CH₂CH), 3.78 (2H, t, J = 6.5 Hz, CH₂OSi), 4.8-5.2 (2H, m, CH=CH₂), 5.85 (1H, ddt, J = 17.1, 10.2, 6.6 Hz, CH=CH₂), 7.2-7.7 (5H, m, ArH); ¹³C NMR δ (50.3 MHz, CDCl₃) 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 C₁₄H₂₄OSi (M-C₇H₇) 233.1363. Found 233.1362.

A solution of the above silyl ether (0.5 g, 1.8 mmol) in dry CH₂Cl₂ (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 CH₂Cl₂. The combined organic layers were dried and evaporated. Flash chromatography (EtOAc/hexanes, 5:95) gave 36 as a pale yellow oil (0.43 g, 86%). Rf 0.17 (EtOAc/hexanes, 5:95); IR (thin film) 2943, 2885, 1726 cm⁻¹; ¹H NMR δ (250 MHz, CDCl₃) 1.0 (12H, m, CH₃CHSi), 1.15-1.4 (2H, m, CHSi), 1.95 (2H, m, CH₂), 2.19 (2H, m, CH₂CH), 2.6 (2H, td, J = 7.2, 1.6 Hz, CH₂CHO), 3.80 (2H, t, J = 6.0 Hz, CH₂OSi), 7.2-7.6 (5H, m, ArH); 9.84 (1H, t, J = 1.6 Hz, CHO); ¹³C NMR δ (50.3 MHz, CDCl₃) 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 C₁₃H₁₉O₂Si (M-C₇H₇) 235.1154. Found 235.1150.

(2R,4R,5R)-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 Et₂O (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 H₂O₂ (30%; 0.6 ml) and then stirred at 0 °C for 2 h. The mixture was then partitioned between H₂O (8 ml) and CH₂Cl₂ (10 ml). The aqueous layer was extracted with CH₂Cl₂ (3 x 10 ml) and the organic extracts were dried (MgSO₄) 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); [α]₂⁰⁺ -4.6 (c 1.9, CHCl₃); IR (thin film) 3460, 2940, 2864, 1709, 1613, 1103 cm⁻¹; ¹H NMR δ (500 MHz, CDCl₃) 1.01 (3H, d, J = 7.5 Hz, CH₃), 1.05 (6H, d, J = 7.4 Hz, CH₃), 1.06 (6H, d, J = 7.4 Hz, CH₃), 1.12 (3H, d, J =
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 CH₂Cl₂ (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 CH₂Cl₂ (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 CH₂Cl₂. The resin was re-suspended in a mixture of MeOH, diisopropylethylamine and CH₂Cl₂ (1:1:18) and stirred at room temperature for 1 h, followed by washing, in turn, with CH₂Cl₂, THF, acetone, DMSO, acetone, MeOH, CH₂Cl₂, 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; ¹³C NMR δ (100 MHz, CDCl₃) 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 CH₂Cl₂ (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 1 h under argon. The resin was then transferred to a sintered syringe and filtered with CH₂Cl₂ as eluent. The resin was washed, in turn, with CH₂Cl₂, H₂O, acetone, MeOH, Et₂O, CH₂Cl₂, 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; ¹³C NMR δ (100 MHz, CDCl₃) 12.3, 12.7, 17.1, 17.4, 25.7, 63.0, 202.6.

Solid phase bound (2R,4R,5R)-1-(benzylxoy)-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-(benzylxoy)-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, H₂O₂, ether, MeOH. To the resin was then added (at 0 °C) MeOH (2 ml), pH 7 buffer (2 ml) and H₂O₂ (30%; 6 ml) and the stirring was continued at -26 °C for 16 h. The mixture was then filtered and the resin washed with H₂O, Et₂O, acetone, Et₂O, CH₂Cl₂, 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; ¹³C NMR (100 MHz, CDCl₃) 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.

(2R,4R,5R)-1-(Benzylxoy)-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/CH₃CN (0.5 M; 18 ml) and stirring was continued for 4 h. The reaction mixture was quenched with NaHCO₃ and the resin rinsed and washed with CH₂Cl₂. The organic layer was then extracted with EtOAc (3 x 10 ml), the combined organic extracts were dried (MgSO₄) and
concentrated under reduced pressure. Isolation of the aldon 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); [α]D<sup>25</sup> = -2.9 (c 1.33, CHCl<sub>3</sub>); IR (thin film) 3410, 2936, 1706, 1455 cm<sup>-1</sup>; 1H NMR δ (500 MHz, CDCl<sub>3</sub>) 1.04 (3H, d, J = 7.2 Hz, CH<sub>3</sub>), 1.11 (3H, d, J = 7.2 Hz, CH<sub>3</sub>), 1.38-1.51 (1H, m, CH<sub>2</sub>), 1.70 (3H, m, CH<sub>2</sub>CH<sub>2</sub>), 2.05 (1H, d, J = 9.4 Hz, OH), 2.73 (1H, quint, J = 7.2 Hz, CHCO), 3.05-3.12 (1H, m, CHCO), 3.43 (1H, dd, J = 8.9, 4.8 Hz, CH<sub>2</sub>CH<sub>2</sub>Bn), 3.59-3.66 (2H, m, CH<sub>2</sub>OH), 3.69 (1H, t, J = 8.9 Hz, CH<sub>2</sub>HOBn), 3.75 (1H, td, J = 8.3, 1.8 Hz, CHO), 4.47 (2H, m, OCH<sub>2</sub>Ph), 7.24-7.35 (5H, m, ArH); <sup>13</sup>C NMR δ (50.3 MHz, CDCl<sub>3</sub>) 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 (Cl, NH<sub>3</sub>) 312 (13), 294 (13), 225 (22), 224 (100), 207 (31), 88 (60), 71 (14); HRMS (Cl, NH<sub>3</sub>) calcd for C<sub>17</sub>H<sub>30</sub>N<sub>4</sub>O<sub>4</sub> (M+NH<sub>4</sub><sup>+</sup>) 312.2175. Found 312.2175.

Solid phase bound (2R,3S,4R,5R)-1-(benzylkoxy)-2,4-dimethylotan-3,5,8-trioli (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-(benzylkoxy)-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<sub>4</sub> (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<sub>4</sub>Cl (satd, 20 ml). The resin was then rinsed and washed, in turn, with H<sub>2</sub>O, ether, MeOH. To the resin was then added (at 0 °C) MeOH (9 ml), H<sub>2</sub>O<sub>2</sub> (30%; 5 ml), NaOH (10% aqueous) (3.7 ml), CH<sub>2</sub>Cl<sub>2</sub> (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<sub>2</sub>O, Et<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>, 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<sup>-1</sup>; <sup>13</sup>C NMR δ (100 MHz, CD<sub>2</sub>Cl<sub>2</sub>) 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.

(2R,3S,4R,5R)-1-(Benzylkoxy)-2,4-dimethylotan-3,5,8-trioli (41, Scheme 7). To resin 40 (0.1 g, 0.07 mmol/g) was added a solution of HF/CH<sub>3</sub>CN (0.5 M; 10.5 ml) and stirring was continued for 16 h. The reaction mixture was quenched with sat aqueous NaHCO<sub>3</sub> and the resin rinsed and washed with CH<sub>2</sub>Cl<sub>2</sub>. The aqueous layer was then extracted with EtOAc (3 x 10 ml), the organic extracts were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. Purification by flash chromatography (Et<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub>, 9:1) gave 41 as an opaque oil (15.7 mg, 71%). [α]<sup>D</sup> = +5.9 (c 1.1, CHCl<sub>3</sub>); IR (thin film) 3355, 2923, 1454 cm<sup>-1</sup>; <sup>1</sup>H NMR δ (500 MHz, CDCl<sub>3</sub>) 0.75 (3H, d, J = 6.8 Hz, CH<sub>3</sub>), 1.0 (3H, d, J = 7.1 Hz, CH<sub>3</sub>), 1.53 (1H, m, 1.56-1.81 (4H, m), 1.93 (1H, m, CH<sub>3</sub>), 3.57 (1H, dd, J = 8.9, 4.5 Hz, CH<sub>2</sub>HOBn), 3.63-3.7 (3H, m, CH<sub>2</sub>OH, CH<sub>2</sub>HOBn), 3.7 (1H, td, J = 8.3, 2.2 Hz, CH<sub>2</sub>OH), 3.81 (1H, dd, J = 9.5, 1.5 Hz, CH<sub>2</sub>OH), 4.52 (2H, m, OCH<sub>2</sub>Cl<sub>2</sub>), 7.26-7.38 (5H, m, ArH); <sup>13</sup>C NMR δ (100 MHz, CDCl<sub>3</sub>) 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<sub>17</sub>H<sub>20</sub>O<sub>4</sub>(M+H)<sup>+</sup> 297.0625. Found 297.065.

Solid phase bound (2R,3S,4R,5R)-1-(benzylkoxy)-2,4-dimethyl-3,5-{[(bis-dimethylmethylene)dioxystactan-8-ol (42, Scheme 7). To resin 40 (0.2 g, 0.15 mmol/g), swollen in CH<sub>2</sub>Cl<sub>2</sub> (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<sub>2</sub>Cl<sub>2</sub>, Et<sub>2</sub>O 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\(_2\)Cl\(_2\)) 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.

(2R,3S,4R,5R)-1-(Benzoyloxy)-2,4-dimethyl-3,5-[(bis-dimethyl-methylene)dioxoy]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\(_2\)Cl\(_2\). The combined organic washes were concentrated under reduced pressure. Purification by flash chromatography (CH\(_2\)Cl\(_2\)/Et\(_2\)O, 7:3) gave 43 as an opaque oil (16.6 mg, 45%). \(\alpha\)\(^{25}\)D -1.4 (c 0.52, CHCl\(_3\)); IR (thin film) 3416, 2930, 1454 cm\(^{-1}\), \(^1\)H NMR \(\delta\) (400 MHz, CDCl\(_3\)) 0.75 (3H, d, J = 6.7 Hz, CH\(_3\)), 0.85 (3H, d, J = 6.9 Hz, CH\(_3\)), 1.34 (3H, s, CH\(_3\)), 1.4 (3H, s, CH\(_3\)), 1.45-1.75 (4H, m), 1.83 (1H, m), 2.06 (1H, m), 3.29 (1H, dd, J = 8.7, 6.2 Hz, CH\(_2\)OH), 3.47 (1H, t, J = 8.7 Hz, CH\(_2\)OH), 3.47-3.55 (1H, m, CH\(_2\)OH), 3.63 (2H, t, J = 5.7 Hz, CH\(_2\)OH), 3.72 (1H, dd, J = 10.4, 2.1 Hz, CH\(_2\)OH), 4.46-4.54 (2H, m, OCH\(_2\)Ph), 7.33 (5H, m, ArH); \(^{13}\)C NMR \(\delta\) (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) calecd for C\(_9\)H\(_{29}\)O\(_4\) (M-CH\(_3\)) 321.2066. Found 321.2066.

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REFERENCES AND NOTES


