High Diastereoselection in the Aldol Reaction of the Bistrimethylsilyl Enol Ether of Methyl Acetoacetate with 2-Benzyloxyhexanal: Synthesis of (−)-Pestalotin

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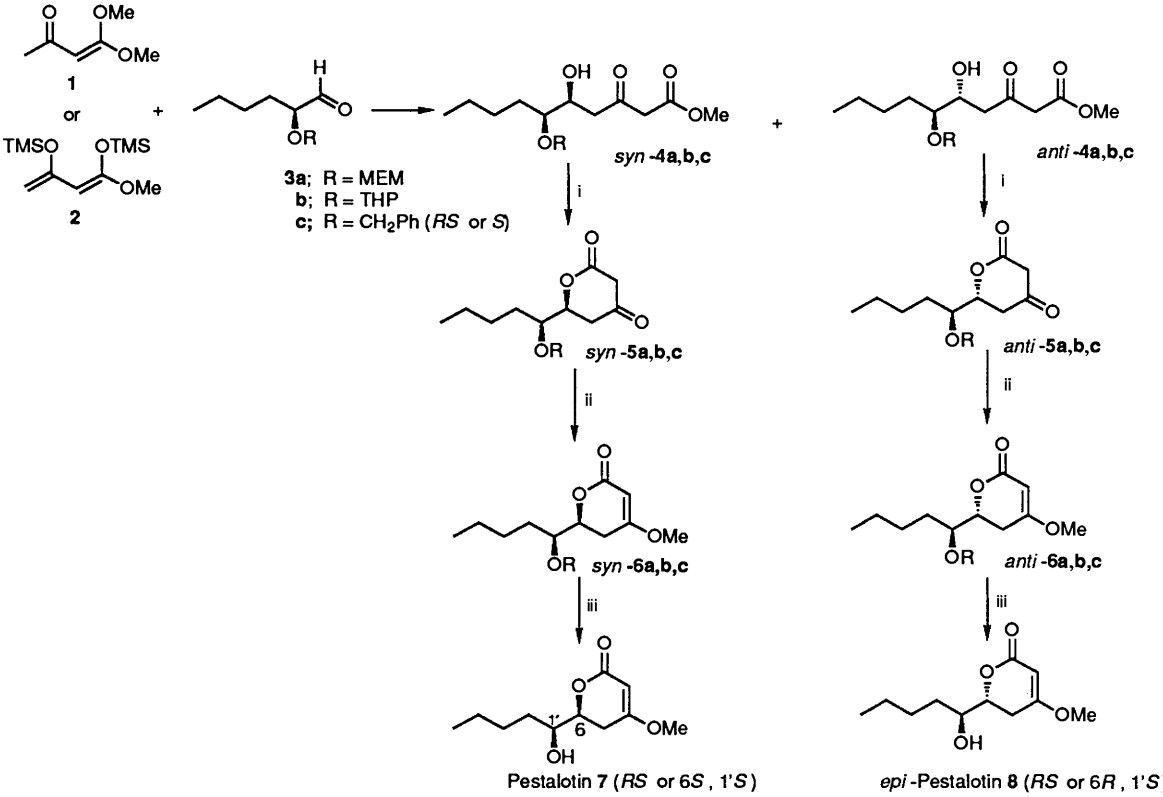
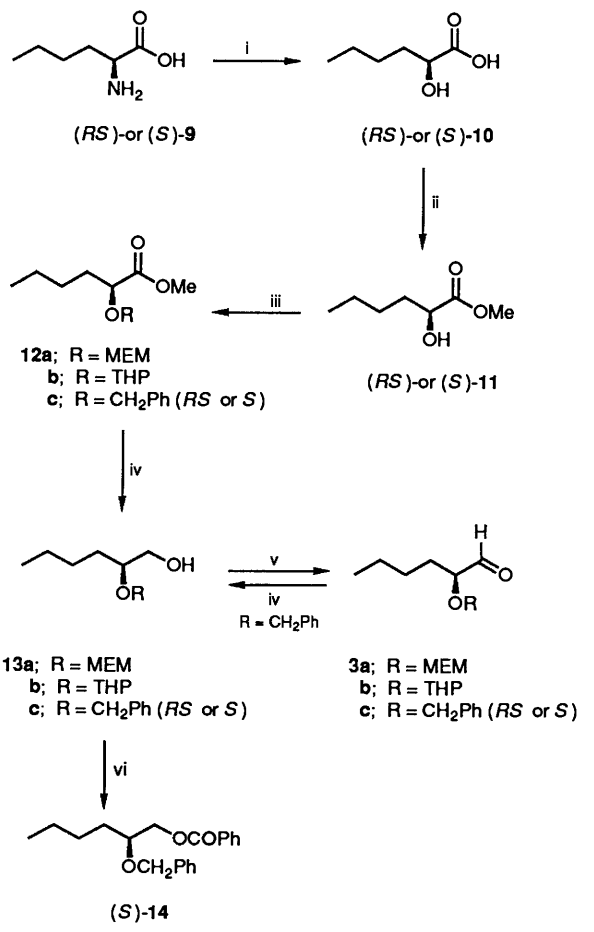
Aldol condensation of the bistrimethylsilyl enol ether of methyl acetoacetate, compound **2**, with 2-benzyloxyhexanal **3c** affords highly selectively (99:1) the *syn*-aldol adduct **4c** in the presence of titanium tetrachloride. The stereocontrolled synthesis of (−)-pestalotin **7** has been achieved.

Strategies for the stereocontrolled construction of polyhydroxylated acyclic molecules have been developed, especially for syntheses of macrolide and polyether antibiotics during the past decade.[1] Among such strategies, nucleophilic addition of enolates or organometallic reagents to alkoxycarbonyl groups were well investigated to construct 1,2- or 1,3-glycols. In order to obtain high diastereofacial selectivity towards addition to carbonyl groups in conformationally non-rigid acyclic compounds, carbonyl components are required to be stereochemically fixed either in the ground and/or in the transition state. The addition of a wide variety of organometallic reagents to alkoxycarbonyl compounds fulfilled high diastereoselectivity taking advantage of conformationally fixed carbonyl groups by intramolecular chelation of a metal cation with the carbonyl groups and the neighbouring alkoxy groups to give *syn*-glycol derivatives,[2] although in most cases only diastereoselectivities were examined, and enantioselectivities were not studied, when employing chiral alkoxy aldehydes. On the other hand, successful examples of the stereocontrolled addition of enolates to alkoxycarbonyl compounds are few, except for the addition of ester enolates having heteroatom substituents at the reacting carbanionic carbon.[3] Selectivity of the addition of the enolates of methyl ketone derivatives are low, probably due to the lack of a directing group at the reacting terminal carbon.[1,3a] As a part of our efforts in designing structural features of natural products by the aldol condensation of 2-alkoxycarbonyl compounds,[4] we delineate herein the highly diastereoselective Lewis acid-mediated aldol condensation of the bistrimethylsilyl enol ether of methyl acetoacetate, compound **2**, with 2-benzyloxyhexanal **3c** under chelation control providing the *syn*-1,2-glycol derivative **4c** and its application to the synthesis of natural (6*S*,1′*S*)-(−)-pestalotin **7**.[5] The cross-aldol condensation products of the acetoacetic ester equivalents with 2-alkoxy aldehydes **3** would be versatile synthetic intermediates in the case where acetoacetic ester is required to add at the methyl ketone terminal to the aldehyde **3**, because the aldol adducts **4** could be transformed into not only the *syn*-1,3,5,6-tetraol system by stereocontrolled reduction of the β-keto ester functionality but also the lactonic portion of an inhibitor of HMG-CoA reductase, mevinic acid,[6] by cyclisation followed by reduction.



Scheme 1 *Reagents:* i, NaOH, THF; ii, Me_2SO_4, K_2CO_3, acetone; iii, $TiCl_4$, CH_2Cl_2 for **6a**; PPTS, aq. acetone for **6b**; H_2 5% Pd–C, AcOEt for **6c**



Scheme 2 *Reagents:* i, $NaNO_2$, H_2SO_4; ii, CH_2N_2; iii, Pr^i_2NEt, MEMCl for **12a**; dihydropyran, PPTS, CH_2Cl_2 for **12b**; NaH, $PhCH_2Br$, THF for (*RS*)-**12c**; Ag_2O, $PhCH_2Br$, Et_2O for *S*-**12c**; iv, $LiAlH_4$, Et_2O; v, $(COCl)_2$, Me_2SO, Et_3N, CH_2Cl_2; vi, PhCOCl, Pr^i_2NEt.

Table 1

Entry	Aldehyde	Metal	Solvent	Product ratio *syn*:*anti*	Yield (%)
1	**3a**	Li	THF	45:55	59
2		Zn[a]	THF	46:54	74
3		Zr[b]	THF	35:65	37
4	**3b**	Li	THF	38:62	36
5		Zn[a]	THF	35:65	48
6		Zr[b]	THF	27:73	31
7	**3c**	Li	THF	36:64	43
8		Mg[c]	Et_2O	49:51	25
9[d]		Mg	Pentane–Et_2O	25:75	16
10[e]		Li	THF	32:68	61

[a] A solution of $ZnCl_2$ in THF was added to the lithium enolate of **1** at −80 °C. [b] A solution of $CpZrCl_2$ in THF was added to the lithium enolate of **1** at −80 °C. [c] A solution of $MgBr_2$ in Et_2O was added to the lithium enolate of **1** at −80 °C. [d] A solution of $MgBr_2$ in Et_2O and then compound **3c** were added to the lithium enolate of **1** at −90 °C. [e] The lithium enolate **1** was added to the mixture of $MgBr_2$ and aldehyde **3c**.

Results and Discussion

Cross-Aldol Reaction of 4,4-*Dimethoxybut*-3-*en*-2-*one* **1**.— Initially, the aldol condensation of the enolates of 4,4-dimethoxybut-3-en-2-one **1** with 2-alkoxyhexanals **3** were investigated (Scheme 1), since stereoselectivities are not expected upon aldol condensation of the dianion of acetoacetic ester.[7] Requisite 4,4-dimethylbut-3-en-2-one **1** was prepared according to the known procedure,[8] and racemic 2-alkoxyhexanals **3** were synthesized starting from racemic 2-aminohexanoic acid (norleucine) **9** in the following sequence (Scheme 2). Racemic 2-aminohexanoic acid **9** was treated with sodium nitrite in dil. sulphuric acid to give 2-hydroxyhexanoic acid **10**. After esterification with diazomethane, methyl 2-hydroxyhexanoate **11** was protected as the corresponding (2-methoxyethoxy)methoxy (MEM), tetrahydropyran-2-yl (THP) or benzyl (Bn) ether by conventional routes. The resulting 2-alkoxyhexanoates **12** were reduced with lithium aluminium hydride (LAH) to 2-alkoxyhexanols **13a, b, c** and these were subsequently oxidised by Swern's procedure to give 2-alkoxyhexanals **3a, b, c.**

Table 2

Entry	Lewis acid	Solvent	Product ratio *syn*:*anti*	Yield (%)
1	$TiCl_4$	CH_2Cl_2	99:1	66
2	$SnCl_4$	CH_2Cl_2	89:11	56
3	$BF_3{\cdot}OEt_2$	CH_2Cl_2	71:29	79
4	$EtAlCl_2$	CH_2Cl_2	53:47	42
5[a]	$ZnCl_2$	CH_2Cl_2	86:14	37
6[b]	$TiCl_4$	CH_2Cl_2	54:46	80
7[c]	$TiCl_4$	CH_2Cl_2	83:17	71

[a] A diastereoisomeric mixture of the trimethylsilyl ether **15** and the pyrone **16** was isolated. The yield refers the yields of the trimethylsilyl ether **15** and the product ratio was determined by the procedure indicated in the text after removal of the trimethylsilyl group. [b] $TiCl_4$ was added to the mixture of the bistrimethylsilyl enol ether **2** and the aldehyde **3c**. [c] The bistrimethylsilyl enol ether **2** was added 5 min after mixing of $TiCl_4$ and the aldehyde **3c**.

In aldol reactions, the lithium enolate of 4,4-dimethylbut-3-en-2-one **1** was generated by treatment with lithium diisopropylamide (LDA) at −80 °C. Other metal enolates were prepared by the addition of anhydrous metal halides to the above lithium enolate. To the solutions of these enolates, 2-alkoxyhexanals **3a, b, c** were added at −80 °C.

In order to determine the diastereoselectivity of the aldol reaction and to assign the relative stereochemistry of the aldol adducts **4a, b, c**, the aldol adducts from 2-[(2-methoxyethoxy)-methoxy]hexanal **3a** and 2-benzyloxyhexanal **3c** were transformed into δ-lactones **5** by lactonisation, and this was followed by methylation with dimethyl sulphate to give the lactonic methyl ethers **6a** and **6c** whose diastereoisomeric ratios were determined by preparative medium-pressure liquid chromatography (MPLC), because the diastereoisomers of the aldol products **4a** and **4c** were inseparable by MPLC and were indistinguishable by spectroscopic methods. In the case of the aldol condensation with 2-(tetrahydropyranyloxy)hexanal **3b**, the diastereoisomeric mixture of the lactonic methyl ether **6b** was inseparable by MPLC because of the presence of an extra diastereoisomeric centre of the tetrahydropyranyloxy group. So the diastereoisomeric ratio was determined by MPLC analysis after deprotection of the tetrahydropyranyloxy group. The relative configurations of these lactonic methyl ethers *syn*-**6a, c** and *anti*-**6a, c** were fully assigned according to analyses of the NMR spectra in which the chemical-shift difference of the AB-type quartet ($\Delta\delta_{AB}$ 0.04 ppm) of the benzylic protons in *syn*-**6c** was smaller than that ($\Delta\delta_{AB}$ 0.11 ppm) in *anti*-**6c** as reported by Midland.[9] Finally these lactonic methyl ethers were transformed into (±)-pestalotin **7** and (±)-*epi*-pestalotin **8**, whose NMR spectra were consonant with those of authentic samples. Chemical-shift data of the 1′-proton of pestalotin **7** (δ 3.6) and *epi*-pestalotin **8** (δ 3.93) were diagnostic.

The results of aldol reaction of the enolates from **1** are summarised in Table 1. In contrast to the successful examples of chelation-controlled 1,2-addition of organometallic reagents to

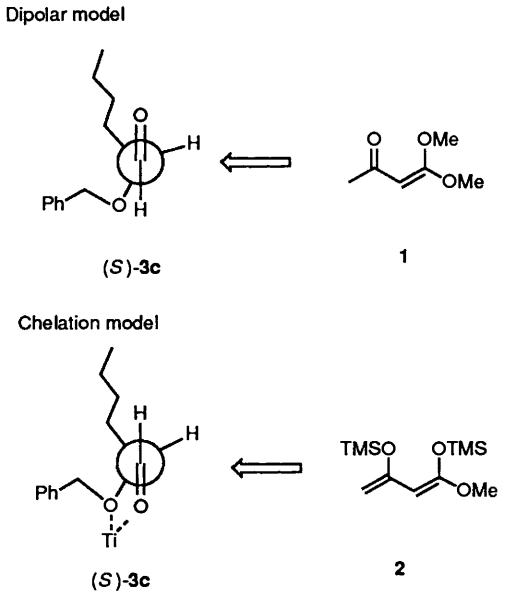
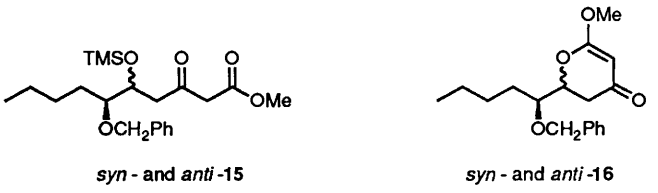


Fig. 1

2-alkoxy aldehydes to afford 1,2-*syn*-glycols,[2] the *anti*-glycol derivatives **4a, b, c** were produced with modest diastereoselectivites which depended neither on the protecting groups at C-2 of the aldehydes **3a, b, c** nor the metal counter-cations of the enolates from **1**. The reaction of 2-benzyloxyhexanal **3c** was carried out in a less polar solvent system in the expectation of stronger chelation with the metal cation, but the diastereoselectivity was not improved (entry 9). Addition of the lithium enolate of **1** to a mixture of magnesium bromide and 2-benzyloxyhexanal **3c** exhibited similar *anti*-selectivity (entry 10). Since a metal cation has the possibility to chelate intramolecularly with the methoxy or trimethylsiloxy group in the enolate of **1**, chelation of the metal cation between the carbonyl and 2-alkoxy groups in 2-alkoxy aldehydes **3** may be prevented. Therefore, the preferential formation of the *anti*-isomers is explicable by assuming that the reaction proceeds mainly through a dipolar model as indicated in Fig. 1.

Diastereoselective Cross-Aldol Reaction of the Bistrimethylsilyl Enol Ether of Methyl Acetoacetate, Compound **2**.—Since the diastereoselectivity of aldol condensation of the metal enolates of **1** was modest and *anti*-selective, the aldol reaction under Lewis acid-promotion was investigated, using the bistrimethylsilyl enol ether of methyl acetoacetate, compound **2** (Scheme 1), whose utility as a four-carbon addend is now increasing.[6b,10] As an aldol acceptor, 2-benzyloxyhexanal **3c** was employed because of the stability and high affinity of the benzyl protecting group towards Lewis acids. In these aldol reactions, the bistrimethylsilyl enol ether **2** was added at −80 °C to a solution of 2-benzyloxyhexanal **3c** and Lewis acid in dichloromethane instead of an ethereal solvent. The diastereoselectivities of the aldol reaction and the relative stereochemistry of the aldol product **4c** were determined in the same manner as above. The reaction occurred exclusively at the distal carbon atom of the bistrimethylsilyl enol ether **2**. The results are summarised in Table 2.

Among reaction conditions investigated, Mukaiyama-type reaction conditions[11] using titanium tetrachloride was found to give the highest *syn*:*anti* ratio of 99:1 (entry 1). In the case where $TiCl_4$ was added to a solution of the bistrimethylsilyl enol ether **2** and 2-benzyloxyhexanal **3c**, no diastereoselectivity was observed (entry 6). A certain amount of time is required for complete complexation between Ti^{IV} and 2-benzyloxyhexanal **3c**, because the diastereoselectivity decreased when a solution of $TiCl_4$ and 2-benzyloxyhexanal **3c** was stirred for less than 10 min before addition of the bistrimethylsilyl enol ether **2** (entry 7). These results indicate that prior chelation of Ti^{IV} with 2-benzyloxyhexanal **3c** plays an important role in realisation of high diastereoselectivity (Fig. 1). Such chelation between Lewis acid and 2-alkoxy aldehydes was well investigated spectroscopically by Midland using lanthanide shift reagents.[12] When zinc chloride was used, the trimethylsilyl ether of the aldol product, compound **15**, along with the pyrone **16**, a Danishefsky-type hetero-Diels–Alder reaction product,[13] were isolated in 37 and 9% yield, respectively (entry 5).



Synthesis of (−)-*Pestalotin* **7**.—(−)-Pestalotin **7**, a gibberellin synergist, was isolated from the phytopathogenic fungus *Pestalotia cryptomeriaecole*[14] as well as from unidentified *Penicillium* species.[15] The absolute stereostructure of (−)-pestalotin **7** was determined to be (6*S*,1′*S*) by CD spectroscopy.[14–16] There have been four syntheses of racemic pestalotin **7**[7,14b,17] and five syntheses of natural (−)-pestalotin **7**[13b,18] so far. Since the benzyl protecting group in a 2-alkoxy aldehydic component was found to give satisfactorily high diastereoselection in the aldol condensation of bistrimethylsilyl ether **2**, (*S*)-2-benzyloxyhexanal **3c** was employed for the synthesis of natural (−)-pestalotin **7**. The requisite (*S*)-2-benzyloxyhexanal **3c** was prepared starting from (*S*)-(−)-2-aminohexanoic acid (L-norleucine; 97% optically pure) (*S*)-**9** in the same sequence as racemic 2-benzyloxyhexanal **3c**, with some modifications. The benzyl protecting group was introduced to the (*S*)-hydroxy ester (*S*)-**11** in 75% yield by using benzyl bromide (α-bromotoluene) and silver oxide as base to avoid epimerisation at C-2.[3b] After LAH reduction, the resulting (*S*-2-benzyloxyhexan-1-ol (*S*)-**13c** was transformed into (*S*)-2-benzyloxyhexyl benzoate (*S*)-**14** whose enantiomeric excess (e.e.) was determined to be 98% by high-pressure liquid chromatography (HPLC) analysis on a chiral column [Chiralpak OT(+)®] with 95% aq. MeOH, since the 'α-methoxy-α-trifluoromethyl-α-phenylacetic acid' (MTPA) ester of (*S*)-2-benzyloxyhexan-1-ol (*S*)-**13c** did not give any fruitful result in determination of the e.e. either chromatographically or spectroscopically (^{19}F NMR). Therefore, the chirality at C-2 of (*S*)-2-aminohexanoic acid (*S*)-**9** was completely retained in (*S*)-2-hydroxyhexanoic acid (*S*)-**10** *via* intramolecular participation of the carboxy group in the substitution reaction of the diazo group. Swern oxidation of (*S*)-benzyloxyhexanol (*S*)-**13c** led to (*S*)-benzyloxyhexanal (*S*)-**3c** {$[\alpha]_D$ −84.9 10^{-1} deg cm^2 g^{-1} (*c* 1.433, $CHCl_3$)}, which was reduced with LAH back to (*S*)-benzyloxyhexan-1-ol (*S*)-**13c** soon after oxidation. The e.e. of this benzyloxyhexanol **13c** was found to be 98% for its benzoate (*S*)-**14**) by HPLC analysis in the same manner as above. This result indicates that no epimerisation of the 2-benzyloxy group of compound **3c** had occurred during the Swern oxidation.[3b] Then, according to the same procedure as employed for the racemic compound, (6*S*,1′*S*)-(−)-pestalotin **7**, $[\alpha]_D$ −80.3 10^{-1} deg cm^2 g^{-1} (*c* 0.462, MeOH) {lit.,[18c] $[\alpha]_D$ −91.7° (*c* 1.17, MeOH)} was obtained in 31% overall yield from (*S*)-(−)-benzyloxyhexanal (*S*)-**3c**. The diastereoselectivity of the aldol condensation of compound **3c** was 98% d.e. as found by MPLC analysis, similarly observed as for the racemic compound. Decrease in the optical purity (86% e.e.) of (−)-pestalotin **7** indicates that the slight epimerisation (6%)

of (*S*)-benzyloxyhexanal (*S*)-**3c** occurred probably during chelation with titanium(IV). The highest specific rotation of (−)-pestalotin **7** was obtained by three repeated recrystallisations from diethyl ether–hexane {$[\alpha]_D$ −93.7 10^{-1} deg cm^2 g^{-1} (*c* 0.127, MeOH)}.

In summary, highly *syn*-selective aldol condensation of the bistrimethylsilyl enol ether of methyl acetoacetate, compound **2**, with 2-benzyloxyhexanal **3c** has been achieved in the presence of $TiCl_4$. This $TiCl_4$-mediated aldol reaction would extend the validity of stereoselective preparations of not only highly hydroxylated acyclic molecules but also lactonic compounds.

Experimental

IR spectra were recorded on a JASCO A-3 spectrophotometer for solutions in tetrachloromethane. ^{1}H NMR spectra were obtained for solutions in deuteriochloroform with Bruker CXP-300 (300 MHz) and JEOL PMX-60 (60 MHz) instruments with tetramethylsilane as internal standard. *J*-Values are given in Hz. Mass spectra were run on a JEOL JMS-DX300 spectrometer with a JMA-3500 data system. Optical rotations $[\alpha]_D$ were determined on a JASCO DIP-4S polarimeter. HPLC was performed on a Waters ALC/GPC-244 instrument. MPLC were carried out on a JASCO PRC-50 instrument with a silica gel-packed column. Microanalyses were carried out in the microanalytical laboratory of this Institute. Ether refers to diethyl ether. Anhydrous sodium sulphate was used for drying of organic extracts. Tetrahydrofuran (THF) was distilled from LAH before use. Upon typical work-up, the product was extracted with solvent (2 × 20 cm^3 for 1–10 mmol-scale reaction). The organic layer was washed with water once and brine once. After being dried over sodium sulphate, the solvent was evaporated under reduced pressure.

Methyl 2-Hydroxyhexanoate **11**.—To a stirred solution of racemic 2-aminohexanoic acid **9** (norleucine) (21.04 g, 0.16 mol) in aq. sulphuric acid (350 cm^3, 0.5 mol dm^{-3}) at 0 °C was added aq. sodium nitrite (97 weight %; 17.7 g, 0.256 mol in 50 cm^3). The mixture was stirred at 0 °C for 20 min, and then for a further 18 h at room temperature. Extraction with ether followed by evaporation of the solvent left crystals of 2-hydroxyhexanoic acid **10** (9.28 g, 67%), which was used without purification.

To a stirred solution of the hydroxy acid **10** (7.02 g, 53.2 mmol) in ether (30 cm^3) at 0 °C was added a solution of diazomethane (150 cm^3; ~3.8 mol dm^{-3} solution in ether) until yellow colour of diazomethane persisted. After the mixture had been stirred for 10 min, evaporation of the ether afforded the hydroxy ester **11** (7.6 g, 98%); ν_{max}/cm^{-1} 3550, 1740, 1220, 1140 and 1090; δ(60 MHz) 0.61–2.11 (6 H, m, CH_2), 0.91 (3 H, t, *J* 6.0, Me), 2.93 (1 H, br s, OH), 3.78 (3 H, s, OMe) and 4.19 (1 H, t, *J* 5.5, 2-H).

2-[(2-*Methoxyethoxy*)*methoxy*]*hexanal* **3a**.—To a stirred solution of the hydroxy ester **11** (1.86 g, 14 mmol) in diisopropylethylamine (4.9 cm^3, 28 mmol) at 0 °C was added chloro(methoxyethoxy)methane (3.2 cm^3, 28 mmol). After being stirred for 23 h, the reaction mixture was quenched by the addition of water. Extraction with ether followed by evaporation of the solvents gave methyl 2-[(2-methoxyethoxy)-methoxy]hexanoate **12a** as an oil (2.79 g, 85%).

To a stirred solution of the alkoxy ester **12a** (2.79 g, 11.9 mmol) in anhydrous ether (50 cm^3) at 0 °C was added LAH (0.5 g, 13.1 mmol) portionwise. After the mixture had been stirred for 30 min at that temperature, water was added carefully to the vigorously stirred mixture to precipitate aluminium hydroxide. Filtration, followed by evaporation of the ether, and silica gel column chromatography of the residue afforded the 2-[(2-methoxyethoxy)methoxy]hexan-1-ol **13a** (2.09 g, 72% from **11**).

To a stirred solution of oxalyl dichloride (3.52 cm^3, 40.4 mmol) in anhydrous dichloromethane (10 cm^3) at −60 °C was added a solution of dimethyl sulphoxide (DMSO) (5.73 cm^3, 80.8 mmol) in dichloromethane (5 cm^3) under nitrogen. After the mixture had been stirred for 5 min at that temperature, a solution of the alkoxyhexan-1-ol **13a** (2.09 g, 10.1 mmol) in dichloromethane (10 cm^3) was added and the mixture was stirred for 20 min. Triethylamine (28.2 cm^3, 202 mmol) was added and the resulting slurry was stirred at from −50 to −12 °C for 70 min and then at 0 °C for 1 h. The reaction was quenched by the addition of aq. ammonium chloride and the product was extracted with ether. Evaporation of the ether, followed by silica gel column chromatography, gave the alkoxy aldehyde **3a** (1.81 g, 88%), which was purified by evaporative distillation (bath temperature 85–90 °C at 0.15 mmHg) to afford compound **3a** (1.24 g, 60%); ν_{max}/cm^{-1} 2720, 1735 and 1050; δ(60 MHz) 0.93 (3 H, t, *J* 6, Me), 1.0–1.9 (6 H, m, CH_2), 3.20–4.03 (5 H, m, OCH_2OCH_2 and 2-H), 3.35 (3 H, s, OMe), 4.78 (2 H, s, OCH_2O) and 9.58 (1 H, d, *J* 2.2, CHO).

2-(*Tetrahydropyran-2-yloxy*)*hexanal* **3b**.—A solution of the hydroxy ester **11** (1.37 g, 9.4 mmol) with dihydropyran (1.29 cm^3, 14.1 mmol) and pyridinium toluene-*p*-sulphonate (PPTS) (251 mg, 1.0 mmol) in dichloromethane (5 cm^3) was stirred at room temperature for 19 h. After the addition of aq. sodium hydrogen carbonate, the product was extracted with ether. Evaporation of the ether left methyl 2-(tetrahydropyran-2-yloxy)hexanoate **12b** (2.05 g, 95%).

To a stirred solution of the alkoxy ester **12b** (2.05 g) in anhydrous ether (30 cm^3) at 0 °C was added LAH (391 mg, 10.3 mmol) portionwise. After being stirred for 20 min at 0 °C, the reaction mixture was quenched and worked up as usual. Silica gel column chromatography provided 2-(tetrahydropyran-2-yloxy)hexan-1-ol **13b** (1.657 g, 87% from **11**).

To a stirred solution of oxalyl dichloride (2.86 cm^3, 32.8 mmol) in anhydrous dichloromethane (5 cm^3) was added a solution of DMSO (4.66 cm^3, 65.6 mmol) in dichloromethane (5 cm^3) at −60 °C under nitrogen. After the mixture had been stirred for 5 min at that temperature, a solution of the alkoxyhexanol **13b** (1.66 g, 8.2 mmol) in dichloromethane (10 cm^3) was added and the mixture was stirred for 30 min. Triethylamine (22.9 cm^3, 164 mmol) was added and the resulting slurry was stirred at from −50 to −20 °C for 90 min and then at 0 °C for 1 h. The reaction was quenched by the addition of aq. ammonium chloride and the product was extracted with ether. Evaporation of the ether, followed by silica gel column chromatography, gave the alkoxy aldehyde **3b** (1.372 g, 84%), which was purified by evaporative distillation (bath temperature 70–80 °C at 0.2 mmHg) to afford compound **3b** (1.19 g, 74%); ν_{max}/ cm^{-1} 2730, 1740, 1140, 1085 and 1045; δ(60 MHz) 0.91 (3 H, t, *J* 6, Me), 1.0–2.16 (12 H, m, CH_2), 3.16–4.29 (3 H, m, $OCH_2[CH_2]_3CHO$ and 2-H), 4.46–4.79 (1 H, m, $OCH_2[CH_2]_3CHO$) and 9.63 (1 H, d, *J* 2.5, CHO).

2-*Benzyloxyhexanal* **3c**.—Sodium hydride (50 weight %; 1.47 g, 30.7 mmol) was washed with hexane (10 cm^3 × 3) and dried *in vacuo*. To a stirred slurry of NaH in THF at 0 °C was added a solution of the hydroxy ester **11** (3.74 g, 25.6 mmol) in anhydrous THF (10 cm^3) under nitrogen. After the mixture had been stirred for 2 h at room temperature, a solution of tetrabutylammonium iodide (96 mg, 0.26 mmol) in THF (15 cm^3) and then benzyl bromide (3.25 cm^3, 28.2 mmol) were added successively. After being stirred for 26 h at room temperature, the reaction mixture was quenched by the addition of aq. ammonium chloride. Extraction with ether, followed by evaporation of the ether, and silica gel column chromatography

of the residue afforded methyl 2-benzyloxyhexanoate **12c** (3.04 g, 50%).

To a stirred solution of the alkoxy ester **12c** (2.94 g, 12.5 mmol) in anhydrous ether (50 cm^3) at 0 °C was added LAH (524 mg, 13.5 mmol) portionwise. After the mixture had been stirred for 30 min at 0 °C, water was added cautiously to the vigorously stirred mixture to precipitate aluminium hydroxide. Filtration followed by evaporation of the ether gave 2-benzyloxyhexan-1-ol **13c** (2.59 g, 99%).

To a stirred solution of oxalyl dichloride (4.4 cm^3, 50 mmol) in anhydrous dichloromethane (20 cm^3) at −60 °C was added a solution of DMSO (7.1 cm^3, 100 mmol) in dichloromethane (10 cm^3) under nitrogen. After the mixture had been stirred for 5 min at that temperature, a solution of the alkoxyhexanol **13c** (2.59 g, 12.4 mmol) in dichloromethane (10 cm^3) was added and the mixture was stirred for 30 min. Triethylamine (34.8 cm^3, 250 mmol) was added and the resulting slurry was stirred from −50 to −20 °C for 90 min and then at 0 °C for 40 min. The reaction was quenched by the addition of aq. ammonium chloride and the product was extracted with ether. Evaporation of the ether, followed by silica gel column chromatography, gave the alkoxy aldehyde **3c** (2.14 g, 83%), which was purified by evaporative distillation (bath temperature 95–110 °C at 0.8 mmHg) to afford compound **3c** (1.82 g, 70%). For spectral data, see below.

General Procedure of Aldol Condensation of 2-*Alkoxyhexanal* **3** *with the Metal Enolate of* 4,4-*Dimethoxybut*-3-*en*-2-*one* **1**.—To a stirred solution of diisopropylamine (1.2 mmol) in anhydrous THF (2–3 cm^3) at 0 °C was added BuLi (1.2 mmol; 1.58 mol dm^3 solution in hexane) under nitrogen. After the mixture had been stirred for 10 min, the flask was cooled to −80 °C and a solution of the ketene acetal **1** (1.2 mmol) in THF (3–5 cm^3) was added. Subsequently, a solution of $MgBr_2$ in ether or a solution of Cp_2ZrCl_2 or $ZnCl_2$ in THF was added and the resulting solution was stirred for 30–60 min at −80 to −30 °C to ensure metal exchange with lithium. The solution was cooled again to −80 °C and a solution of 2-alkoxy aldehyde **3** (1 mmol) in THF (3 cm^3) was added. The mixture was stirred for 1 h at −80 to −60 °C and the reaction was quenched by the addition of aq. ammonium chloride and then dil. HCl to make the aqueous layer acidic. The aldol products **4** were isolated by preparative TLC (PLC) [solvent ethyl acetate–hexane (2:1)] separation after extraction with ether.

General Procedure of Aldol Condensation of 2-*Alkoxyhexanal* **3** *with the Bistrimethylsilyl Derivative of Methyl Acetoacetate, Compound* **2**.—To a stirred solution of the 2-alkoxy aldehyde **3** (0.8 mmol) in anhydrous dichloromethane (6 cm^3) was added a solution of Lewis acid (0.8 mmol) at −85 to −75 °C. After the mixture had been stirred for 10 min, a solution of the bistrimethylsilyl enol ether of methyl acetoacetate, compound **2** (1.1 mmol, 1.4 mol equiv.) in dichloromethane (4 cm^3). The mixture was stirred for 60 min at −80 to −60 °C. The reaction was quenched by the addition of water, and the products **4** were extracted with ether and purified by PLC as above. The following spectroscopic data were observed for diastereoisomeric mixtures of the aldol adducts **4**.

Methyl 5-*hydroxy*-6-[(2-*methoxyethoxy*)*methoxy*]-3-*oxodecanoate* **4a**. ν_{max}/cm^{-1} 3480, 1765, 1735, 1130 and 1065; δ(60 MHz) 0.91 (3 H, t, *J* 6, Me), 1.0–1.73 (6 H, m, CH_2), 2.64–2.84 (2 H, m, 4-H_2), 3.31–4.36 (6 H, m, 5- and 6-H, and OCH_2CH_2), 3.38 (3 H, s, OMe), 3.55 (2 H, s, 2-H_2), 3.73 (3 H, s, CO_2Me) and 4.78 (2 H, d, *J* 2, OCH_2O).

Methyl 5-*hydroxy*-3-*oxo*-6-(*tetrahydropyran*-2-*yloxy*)-*decanoate* **4b**. ν_{max}/cm^{-1} 3400, 1745, 1720, 1240, 1140, 1080 and 1030; δ(60 MHz) 0.91 (3 H, t, *J* 6, Me), 1.0–2.05 (12 H, m, CH_2), 2.60–2.88 (2 H, m, 4-H_2), 3.13–4.80 (5 H, m, 5- and 6-H, OCHO and $OCH_2[CH_2]_3CHO$), 3.55 (2 H, d, *J* 2, 2-H_2) and 3.73 (3 H, s, CO_2Me).

Zinc Chloride-mediated Condensation of 2-*Benzyloxyhexanal* **3c** *with the Bistrimethylsilyl Derivative of Methyl Acetoacetate, Compound* **2**.—To a stirred solution of 2-benzyloxyaldehyde **3c** (156 mg, 0.76 mmol) in anhydrous dichloromethane (6 cm^3) at −82 to −78 °C was added a solution of zinc chloride (1 cm^3, 0.76 mmol; 0.7 mol dm^{-3} solution in ether). After the mixture had been stirred for 10 min, a solution of the bistrimethylsily derivative **2** (297 mg, 1.1 mmol) in dichloromethane (3 cm^3) was added. The mixture was stirred for 100 min at −80 to −34 °C. The reaction was quenched by the addition of water, and the product was extracted with ether and purified by PLC on silica gel [solvent ethyl acetate–hexane (2:3)]. The less polar fraction was a diastereoisomeric mixture of methyl 6-benzyloxy-3-oxo-5-(trimethylsiloxy)decanoate **15** (111 mg, 37%); ν_{max}/cm^{-1} 1750, 1720, 1255, 1090, 730 and 700; δ(60 MHz). 0.08 (9 H, s), 0.8–1.93 (6 H, m, CH_2), 0.90 (3 H, t, *J* 6, Me), 2.59–2.88 (2 H, m, 4-H_2), 3.18– 3.59 (1 H, m, 6-H), 3.43 (2 H, s, 2-H_2), 3.71 (3 H, s, CO_2Me), 4.18–4.60 (1 H, m, 5-H), 4.53 (2 H, s, OCH_2Ph) and (5 H, s, Ph).

The more polar fraction was a diastereoisomeric mixture of 2-(1′-benzyloxypentyl)-2,3-dihydro-6-methoxypyran-4-one **16** (22 mg, 9%); ν_{max}/cm^{-1} 1665, 1590, 1230, 1090, 730 and 700; δ(60 MHz) 0.8–1.99 (6 H, m, CH_2), 0.92 (3 H, t, *J* 6, Me), 2.28 and 2.37 (total 1 H, d, *J* 17, B part of AB-type q, 3-CH*H*), 2.59 and 2.82 (total 1 H, d, *J* 17, A part of AB-type q, 3-C*H*H), 3.41–3.74 (1 H, 1′-H), 3.79 (3 H, s, OMe), 4.36–4.61 (1 H, m, 2-H), 4.65 (2 H, s, OCH_2Ph) 4.86 (1 H, s, 5-H) and 7.34 (5 H, s, Ph).

(6S*,1′S*)-5,6-*Dihydro*-4-*methoxy*-6-{1′-[(2-*methoxyethoxy*)-*pentyl*}*pyran*-2-*one* **6a**.—A solution of the aldol adduct **4a** (80 mg, 0.25 mmol) in THF (3 cm^3) and aq. sodium hydroxide (1 cm^3; 1 mol dm^{-3}) was stirred at room temperature for 30 min. After the addition of aq. ammonium chloride and then dil. HCl, the product was extracted with ethyl acetate to give 5,6-dihydro-6-{1′-[(2-methoxyethoxy)methoxy]pentyl}pyran-2,4-(3*H*)-*dione* **5a** (67 mg), which was used for subsequent reaction without purification.

To a stirred solution of the δ-lactone **5a** (67 mg) and dimethyl sulfate (29 mm^3, 0.31 mmol) in acetone (3 cm^3) was added potassium carbonate (50 mg, 0.36 mmol) under nitrogen. The resulting slurry was stirred at room temperature for 45 h. The reaction was quenched by the addition of water and the products were extracted with ether. MPLC purification (eluent ethyl acetate) afforded the more polar *syn*-isomer **6a** (24 mg) and the less polar *anti*-isomer **6a** (29 mg) (72% in two steps from the aldol adducts **4a**). The spectral data of *syn*-**6a** are as follows; ν_{max}/cm^{-1} 1720, 1630, 1230 and 1040; δ(300 MHz) 0.91 (3 H, t, *J* 6, Me), 1.25–1.82 (6 H, m), 2.29 (1 H, dd, *J* 17 and 3.7, B part of AB-type q, 5-H), 2.71 (1 H, ddd, *J* 17, 13 and 0.5, A part of AB-type q, 5-H), 3.39 (3 H, s, OMe), 3.56 (2 H, t, *J* 4.5, OCH_2CH_2O), 3.73 (2 H, t, *J* 4.5, OCH_2CH_2O), 3.76 (1 H, m, 1′-H), 3.76 (3 H, s), 4.53 (1 H, dt, *J* 13 and 3.7, 6-H), 4.81 (2 H, s, OCH_2OMe) and 5.13 (1 H, d, *J* 0.5, 3-H); *m*/*z* CI (CH_4) 530 (M^+ + 1 + 227, 4%), 529 (M^+ + 227, 14), 391 (M^+ + 89, 23), 343 (M^+ + 41, 8), 331 (M^+ + 29, 23), 303 (M^+ + 1, 100), 227 (48), 197 (10), 183 (11) and 89 (22). The spectral data of *anti*-**6a** are as follows; ν_{max}/cm^{-1} 1720, 1635, 1230 and 1040; δ(60 MHz) 0.92 (3 H, t, *J* 6, Me), 1.0–1.88 (6 H, m, CH_2), 2.28 (1 H, dd, *J* 17 and 4.5, 5-H), 2.53–3.18 (1 H, m, 5-H), 3.38 (3 H, s, OMe), 3.31–4.08 (5 H, m, 1′-H and OCH_2CH_2O), 3.74 (3 H, s, OMe), 4.39 (1 H, dt, *J* 10 and 4.5, 6-H), 4.81 (2 H, s, OCH_2O) and 5.13 (1 H, d, *J* 2, 3-H).

(6S*,1S′*)-5,6-*Dihydro*-4-*methoxy*-6-[1′-(*tetrahydropyran*-2-*yloxy*)*pentyl*]*pyran*-2-*one* **6b**.—A solution of the aldol adduct **4b**

(146 mg, 0.46 mmol) in THF (2 cm^3) and aq. sodium hydroxide (1.5 cm^3; 1 mol dm^{-3}) was stirred at room temperature for 45 min. After the addition of dil. HCl, the product was extracted with ethyl acetate to give 5,6-dihydro-6-[1′-(tetrahydropyran-2-yloxy)pentyl]pyran-2,4(3*H*)-dione **5b** (125 mg), which was used for subsequent reaction without purification.

To a stirred solution of the δ-lactone **5b** (125 mg) and dimethyl sulfate (55 mm^3, 0.58 mmol) in acetone (2.5 cm^3) was added potassium carbonate (92 mg, 0.67 mmol). The resulting slurry was stirred at room temperature for 40 h under nitrogen. The reaction was quenched by the addition of water and the products were extracted with ether to give a diastereoisomeric mixture of the lactonic derivative **6b** (132 mg); ν_{max}/cm^{-1} 1720, 1630, 1225 and 1035; δ(60 MHz) 0.92 (3 H, t, *J* 6, Me), 0.6–1.95 (12 H, m, CH_2), 2.21 (1 H, dd, *J* 17 and 5, 5-H_{eq}) 2.55–3.17 (1 H, m, 5-H_{ax}), 3.33–4.17 (3 H, m, 1′-H and $OCH_2[CH_3]_3CHO$), 3.73 (3 H, s, OMe), 4.45 (1 H, dt, *J* 12 and 5, 6-H), 4.73 (1 H, br s, OCHO) and 5.10 (1 H, d, *J* 2, 3-H). A part of the pure diastereoisomer was isolated by MPLC. The following NMR data indicates that this isomer is *syn*-**6b** because 1′-H appeared at δ 3.8;[9] ν_{max}/cm^{-1} 1720, 1630, 1225 and 1035; δ(300 MHz) 0.91 (3 H, t, *J* 7.1, Me), 1.25–1.92 (12 H, m), 2.27 (1 H, dd, *J* 17 and 3.7, B part of AB-type q, 5-H), 2.70 (1 H, ddd, *J* 17 and 13.1 and 1.0, A part of AB-type q, 5-H), 3.5 (1 H, m, OCH*H*$[CH_2]_3CHO$), 3.75 (3 H, s, OMe), 3.8 (1 H, m, 1′-H), 3.9 (1 H, m, OC*H*H$[CH_2]_3CHO$), 4.46 (1 H, dt, *J* 13.1 and 3.8, 6-H), 4.73 (1 H, br s, OCHO) and 5.14 (1 H, d, *J* 1.0, 3-H); *m/z* CI (CH_4) 598 (2 × M^+ + 2, 26%), 513 (M^+ + 215, 29), 429 (22), 339 (M^+ + 41, 11), 327 (M^+ + 29, 32), 299 (M^+ + 1, 40), 215 (100), 197 (20), 179 (16), 128 (11) and 101 (7) (Found: M^+ + 1, 299.185 82. $C_{16}H_{27}O_5$ requires *m/z*, 299.185 84).

Since the diastereoisomers of the lactonic methyl ether **6b** were inseparable by MPLC, the diastereisomeric ratio was determined after deprotection of the THP derivative. A solution of the lactonic derivative **6b** (132 mg) and PPTS (10 mg, 0.04 mmol) in ethanol (1.5 cm^3) and water (1.5 cm^3) was stirred at 70 °C for 45 min. The resulting solution was poured into brine. Extraction with ether, followed by MPLC separation [eluant ethyl acetate–hexane (3:1)] gave less polar *epi*-pestalotin **8** (38 mg) and more polar pestalotin **7** (14 mg) in 53% yield in three steps from the aldol adduct **4b**.

(6S*,1′S*)-6-(1′-*Benzyloxypentyl*)-5,6-*dihydro*-4-*methoxypyran*-2-*one* **6c**.—According to the general procedure, the reaction of the lithium enolate of the ketene acetal **1** (260 mg, 2 mmol) and racemic 2-benzyloxyhexanal **3c** (206 mg, 1 mmol) in THF at from −82 to −70 °C afforded methyl 6-benzyl-5-hydroxy-3-oxodecanoate **4c** (140 mg, 43%), which was treated with sodium hydroxide (1 cm^3; 1 mol dm^{-3}) in THF (3 cm^3) at room temperature for 40 h. Addition of dil. HCl and extraction with ethyl acetate gave 6-(1′-benzyloxypentyl)-5,6-dihydropyran-2,4(3*H*)-dione **5c** (115 mg). A mixture of the δ-lactone **5c** (115 mg), dimethyl sulfate (51 mm^3, 0.54 mmol) and potassium carbonate (82 mg, 0.62 mmol) in acetone (5 cm^3) was stirred at room temperature for 39 h under nitrogen. The reaction was quenched by the addition of water and the product was extracted with ether. After evaporation of the ether, the residue was separated by MPLC [eluent ethyl acetate–hexane 1:1)] to give the less polar *anti*-lactonic derivative **6c** (48 mg) and the more polar *syn*-lactonic derivative **6c** (27 mg) (58% in two steps). The anti-*lactonic* compound **6c** has m.p. 48 °C; ν_{max}/cm^{-1} 1720, 1630, 1225, 1100 and 700; δ(300 MHz) 0.89 (3 H, t, *J* 7, Me), 1.25–1.75 (6 H, m), 2.44 (1 H, dd, *J* 18 and 3.9, B part of AB-type q, 5-H), 2.90 (1 H, ddd, *J* 18, 12.2 and 1.5, A part of AB-type q, 5-H), 3.75 (1 H, m, 1′-H), 3.75 (3 H, s, OMe), 4.4 (1 H, dt, *J* 12.2 and 3.9, 6-H), 4.63 (1 H, d, *J* 11.4, B part of AB-type q, PhCH*H*), 4.74 (1 H, d, *J* 11.4, A part of AB-type q, PhC*H*H), 5.14 (1 H, d, *J* 1.5, 3-H) and 7.3 (5 H, br s, Ph); *m/z* CI (CH_4) 610 (2 × M^+ + 2, 10%), 519 (M^+ + 215, 4), 333 (M^+ + 29, 21), 319 (M^+ + 15, 24), 305 (M^+ + 1, 100), 215 (36), 127 (11), 107 (14) and 91 (18) (Found: C, 70.8; H, 8.2. $C_{18}H_{24}O_4$ requires C, 71.0; H, 8.0%).

For the spectral data of *syn*-**6c**, see below.

(6R*,1′S*)-5,6-*Dihydro*-6-(1′-*hydroxypentyl*)-4-*methoxypyran*-2-*one*, epi-*Pestalotin* **8**.—To a stirred solution of the less polar *anti*-lactonic compound **6a** (122 mg, 0.4 mmol) in dichloromethane (7 cm^3) at −70 °C was added a solution of $TiCl_4$ (2 cm^3, 4 mmol; 2 mol dm^{-3} solution in dichloromethane) under nitrogen. The solution was stirred overnight at between −70 °C and room temperature. The resulting solution was poured into ice–water and the product was extracted with ether. Evaporation of the solvents followed by MPLC purification gave *epi*-pestalotin **8** (53 mg, 50%); mp. 75–76 °C; ν_{max}/cm^{-1} 1745, 1720, 1635, 1240, 1225 and 1050; δ(300 MHz) 0.92 (3 H, t, *J* 7, Me), 1.25–1.6 (6 H, m, CH_2), 2.28 (1 H, dd, *J* 17.2 and 3.7, B part of AB-type q, 5-H*H*), 2.64 (1 H, br s, OH), 2.83 (1 H, ddd, *J* 17.2, 12.8 and 1.5, A part of AB-type q, 5-*H*H), 3.76 (3 H, s, OMe), 3.93 (1 H, m, 1′-H), 4.33 (1 H, dt, *J* 12.8 and 3.7, 6-H) and 5.14 (1 H, d, *J* 1.5, 3-H); *m/z* 127 (100%), 99 (18), 95 (9), 67 (12) and 41 (12) (Found: C, 61.7; H, 8.5. Calc. for $C_{11}H_{18}O_4$ requires C, 61.7; H, 8.5%).

Methyl (S)-(+)-2-*Hydroxyhexanoate* **11**.—To a stirred solution of (*S*)-2-aminohexanoic acid **9** [(*S*)-norleucine] {4.36 g, 33 mmol, $[\alpha]_D$ +22.7 10^{-1} deg cm^2 g^{-1} (*c* 0.365, 5 mol dm^{-3} HCl), 97% optically pure} in aq. sulfuric acid (70 cm^3; 0.5 mol dm^{-3}) was added a solution of sodium nitrite (3.77 g, 53 mmol) in water (15 cm^3) at ice-bath temperature. The mixture was stirred at that temperature for 1 h and then for a further 23 h at room tempeature. Addition of brine followed by extraction (ether) provided the (*S*)-2-hydroxyhexanoic acid **10** (3.09 g, 71%). Diazomethane esterification of acid **10** (2.54 g, 19.3 mmol) in ether gave methyl (*S*)-2-hydroxyhexanoate **11** (2.82 g, 100%).

(S)-(+)-2-*Benzyloxyhexan*-1-*ol* **13c**.—To a stirred solution of methyl (*S*)-2-hydroxyhexanoate **11** (2.668 g, 18.2 mmol) and benzyl bromide (3.3 cm^3, 27.3 mmol) in anhydrous ether (10 cm^3) was added a slurry of freshly prepared silver oxide (9.3 g, 40 mmol) in anhydrous ether (10 cm^3) under nitrogen, and the mixture was heated under reflux for 30 min. Filtration and evaporation of the ether left methyl (*S*)-2-benzyloxyhexanoate **12c** (3.23 g, 75%).

To a stirred solution of the benzyl ether **12c** (3.23 g, 13.7 mmol) in anhydrous ether (30 cm^3) at ice-bath temperature was added LAH (760 mg, 20 mmol) portionwise. After being stirred for 30 min at ice-bath temperature, the reaction mixture was quenched by the addition of water. Filtration, evaporation, and silica gel column chromatography afforded (S)-2-*benzyloxyhexan*-1-*ol* **13c** (2.79 g, 75%); $[\alpha]_D$ +22.3 10^{-1} deg cm^2 g^{-1} (*c* 1.134, $CHCl_3$); ν_{max}/cm^{-1} 3480, 1100, 1075, 730 and 700; δ(60 MHz), 0.91 (3 H, t, *J* 5.5, Me), 1.0–1.98 (6 H, m, CH_2), 2.12 (1 H, br, OH), 3.32–3.90 (m, 3 H, 1-H_2 and 2-H), 4.58 (2 H, s, PhCH_2) and 7.32 (5 H, s, Ph); *m/z* 208 (M^+, 0.7%), 177 (13), 92 (19) and 91 (100) (Found: M^+, 208.146 32; C, 74.7; H, 9.8%. $C_{13}H_{20}O_2$ requires M, 208.146 32; C, 75.0; H, 9.7%).

(S)-2-*Benzyloxyhexyl Benzoate* **14**.—To a stirred solution of (*S*)-(+)-2-benzyloxyhexan-1-ol **13c** (72 mg, 0.35 mmol) in diisopropylethylamine (0.5 cm^3) at ice-bath temperature was added benzoyl chloride (62 mm^3, 0.53 mmol). After being stirred at room temperature for 18 h, the reaction mixture was quenched by the addition of water. Extraction with ether, followed by MPLC separation, provided benzyloxyhexyl benzoate **14** (75 mg, 69%); ν_{max}/cm^{-1} 1730, 1270, 1120, 1100,

720 and 700; δ(60 MHz) 0.92 (3 H, s, Me), 1.0–1.93 (6 H, m, CH_2), 3.52–4.05 (1 H, m, 2-H), 4.42 (2 H, m, 1-H_2), 4.67 (2 H, s, PhCH_2) and 7.13–7.30 (10 H, m, Ph); *m/z* 177 (4%), 123 (19), 107 (41), 105 (64) and 91 (100).

The racemic benzoate **14** prepared by the same procedure was analysed by HPLC on a chiral column [chiral pack OT(+)®] at 15 °C with 95% aq. MeOH, giving two peaks of equal area at 10.4 and 12.2 min. Baseline separation of two peaks were observed.

Under the same conditions, the optically active benzoate **14** was analysed to give 98.0% e.e.

The benzoate **14** prepared from (*S*)-(−)-2-benzyloxyhexanal **3c** by reduction and benzoylation showed 97.8% e.e. by this analysis.

(S)-(−)-2-*Benzyloxyhexanal* (**3c**).—To a stirred solution of oxalyl dichloride (1.21 cm^3, 13.9 mmol) in dichloromethane (5 cm^3) at −60 °C was added a solution of DMSO (1.97 cm^3, 27.8 mmol) in dichloromethane (3 cm^3) under nitrogen. After the mixture had been stirred for 5 min, a solution of (*S*)-2-benzyloxyhexan-1-ol **13c** (723 mg, 3.48 mmol) in dichloromethane (3 cm^3) was added, and the mixture was stirred for 30 min at −60 to −50 °C. Addition of triethylamine (9.7 cm^3, 69.5 mmol) gave white precipitates, and the mixture was stirred for 75 min at from −50 °C to ice-bath temperature. The reaction was quenched by the addition of water. Extractive work-up with ether, followed by MPLC purification, afforded (*S*)-2-benzyloxyhexanal **3c** (314 mg, 44%); $[\alpha]_D$ −86.1 10^{-1} deg cm^2 g^{-1} (*c* 0.977, $CHCl_3$); ν_{max}/cm^{-1} 2710, 1735, 1100, 730 and 700; δ(60 MHz) 0.88 (3 H, br t, Me), 1.05–2.03 (6 H, CH_2), 3.72 (1 H, td, *J* 6 and 3, 1-H), 4.52 (1 H, d, *J* 12, B part of AB-type q, PhCH*H*), 4.64 (1 H, d, *J* 12, A part of AB-type q, PhC*H*H), 7.31 (5 H, s, Ph) and 9.57 (1 H, d, *J* 3, CHO).

(+)-*Methyl* (5S,6S)-6-*Benzyloxy*-5-*hydroxy*-3-*oxodecanoate* **4c**.—To a stirred solution of (*S*)-(−)-2-benzyloxyhexanal **3c** (286 mg, 1.39 mmol, used soon after Swern oxidation) in dichloromethane (11 cm^3) at −90 °C was added titanium tetrachloride (1.39 cm^3; 1 mol dm^{-3} solution in dichloromethane) under nitrogen. After the mixture had been stirred for 20 min, a solution of the bistrimethylsilyl compound **2** (560 mg, 2.15 mmol) in dichloromethane (5 cm^3) was added dropwise to the reaction mixture cooled to −90 °C. After being stirred for 20 min at −90 °C, the reaction mixture was quenched by the addition of water. Extraction with ether, followed by MPLC purification [eluent ethyl acetate–hexane (1:1)], gave the *aldol product* **4c** (313 mg, 71%); $[\alpha]_D$ +1.2 10^{-1} deg cm^2 g^{-1} (*c* 1.00, $CHCl_3$); ν_{max}/cm^{-1} 3560, 1745, 1720, 1245, 1075, 730 and 700; δ(300 MHz) 0.9 (3 H, br t, Me), 1.2–1.7 (6 H, m, 7-, 8- and 9-H_2), 2.7 (2 H, m, 4-H_2), 3.35 (1 H, q, *J* 5.3, 6-H), 3.48 and 3.5 (each 1 H, s, 2-H_2), 4.16 (1 H, br s, 5-H) and 7.3 (5 H, br s, Ph); *m/z* 197 (2%), 177 (8), 145 (23) 113 (17), 92 (28) and 91 (100) (Found: C, 66.9; H, 8.5. $C_{18}H_{26}O_5$ requires C, 67.1; H, 8.1%).

(6S,1′S)-(−)-6-(1′-*Benzyloxypentyl*)-5,6-*dihydro*-4-*methoxypyran*-2-*one* **6c**.—A solution of the aldol adduct **4c** (313 mg, 0.97 mmol) in THF (4 cm^3) and aq. sodium hydroxide (1 cm^3) was stirred at room temperature for 30 min. After the addition of dil. HCl, the product was extracted with ether to give (6*S*,1′*S*)-6-(1′-benzyloxypentyl)-5,6-dihydropyran-2,4(3*H*)-dione **5c** (367 mg), which was used for subsequent reaction without purification.

To a stirred solution of the δ-lactone **5c** (367 mg) and dimethyl sulfate (0.11 cm^3, 1.21 mmol) in acetone (5 cm^3) was added potassium carbonate (195 mg, 1.41 mmol). The resulting slurry was stirred at room temperature for 36 h under nitrogen. The reaction was quenched by the addition of water and the products were extracted with ether. The diastereoisomeric ratio of the aldol products were determined to be *syn*:*anti* 98.5:1.5 by MPLC purification which afforded the syn-*isomer* **6c** [248 mg, 85% from the (*S*)-aldehyde **3c** through 3 steps] along with the *anti*-isomer (trace); $[\alpha]_D$ −99.1 10^{-1} deg cm^2 g^{-1} (*c* 0.903, $CHCl_3$); m.p. 77 °C; ν_{max}/cm^{-1} 1720, 1630, 1230, 1080 and 700; δ(300 MHz) 0.89 (3 H, t, *J* 7, Me), 1.2–1.8 (6 H, m), 2.27 (1 H, dd, *J* 17.1 and 3.7, B part of AB-type q, 5-H), 2.70 (1 H, ddd, *J* 17.1, 13.1 and 1.4, A part of AB-type q, 5-H), 3.6 (1 H, m, 1′-H), 3.74 (3 H, s, OMe), 4.55 (1 H, dt, *J* 13.1 and 3.8, 6-H), 4.63 (1 H, d, *J* 11.3, B part of AB-type q, PhCH*H*), 4.67 (1 H, d, *J* 11.3, A part of AB-type q, PhC*H*H), 5.14 (1 H, d, *J* 1.4, 3-H) and 7.3 (5 H, br s, Ph); *m/z* CI (CH_4) 610 (2 × M^+ + 2, 24%), 609 (2 × M^+ + 1, 56), 396 (13), 395 (M^+ + 91, 44), 333 (M^+ + 29, 21), 306 (M^+ + 2, 24), 305 (M^+ + 1, 100), 287 (11) and 91 (11) (Found: C, 70.9; H, 8.0. $C_{18}H_{24}O_4$ requires C, 71.0; H, 8.0%).

(6S,1′S)-(−)-5,6-*Dihydro*-6-(1′-*hydroxypentyl*)-4-*methoxypyran*-2-*one*, (−)-*Pestalotin* **7**.—A solution of the lactonic compound **6c** (248 mg, 0.82 mmol) in ethyl acetate (20 cm^3) was hydrogenated over palladium–charcoal (5%; 200 mg) at room temperature for 46 h. Removal of the catalyst by filtration through a silica gel short column, followed by PLC purification gave (−)-pestalotin **7** (107 mg, 66%); $[\alpha]_D$ −80.3 10^{-1} deg cm^2 g^{-1} (*c* 0.462, MeOH) {lit.,[18c] $[\alpha]_D$ −91.7° [*c* 1.17, MeOH)}; $[\alpha]_D$ −93.7 10^{-1} deg cm^2 g^{-1} (*c* 0.127, MeOH, after three recrystallisations from ether–hexane); m.p. 84–85 °C; ν_{max}/cm^{-1} 1745, 1725, 1635, 1240, 1255 and 1050; δ(300 MHz) 0.92 (3 H, t, *J* 7, 5′-Me), 1.0–1.8 (6 H, m), 2.1 (1 H, br, OH), 2.25 (1 H, dd, *J* 17.1 and 3.7, B part of AB-type q, 5-H), 2.8 (1 H, ddd, *J* 17.1, 13 and 1.6, A part of AB-type q, 5-H), 3.6 (1 H, m, 1′-H), 3.76 (3 H, s, OMe), 4.3 (1 H, ddd, *J* 13, 4.1 and 3.7, 6-H) and 5.14 (1 H, d, *J* 1.6, 3-H); *m/z* 215 (M^+ + 1, 1%), 214 (M^+, 0.7) 128 (67), 127 (100), 99 (13) and 67 (11) (Found: M^+, 214.1205. Calc. for $C_{11}H_{18}O_4$: M, 214.1205).

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