Efficient 1,8- and 1,9-asymmetric inductions in the Grignard reaction of δ- and ε-keto esters of 1,1′-binaphthalen-2-ols with an oligoether tether as the 2′-substituent: application to the synthesis of (−)-malyngolide

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Efficient 1,8- and 1,9-asymmetric inductions in the Grignard reaction of podand-type δ- (**3**,**4**) and ε-keto esters (**5**,**6**) are achieved in the presence of $MgBr_2{\cdot}OEt_2$ with up to 97 and 82% optical yields, respectively, by using 2′-[3-(2-methoxyethoxy)propoxy]-1,1′-binaphthalen-2-ol as the chiral auxiliary. The 1,8-asymmetric inductive Grignard reaction has been advantageously utilized in the key step of a synthesis of (−)-malyngolide.

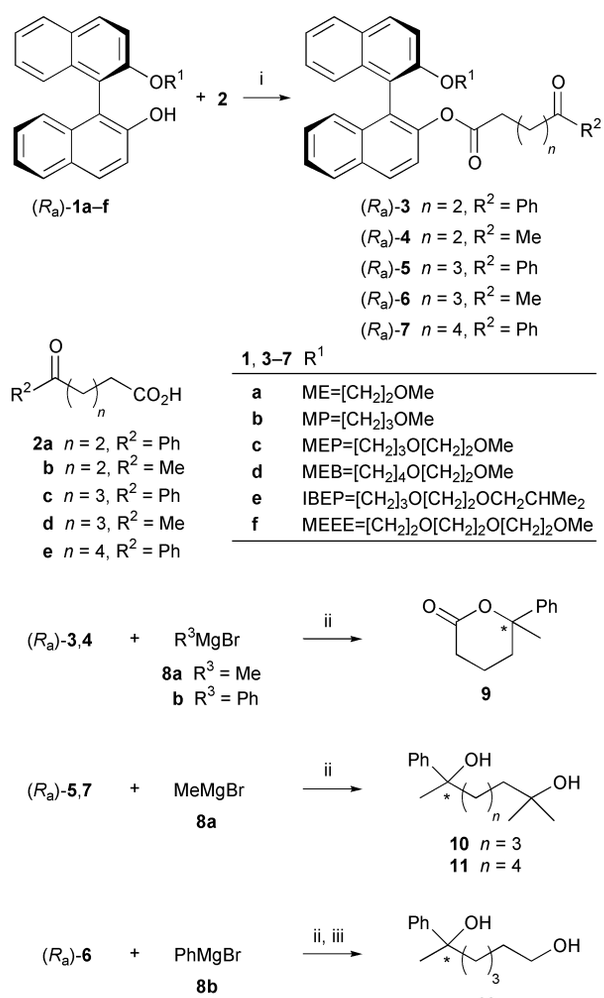
Introduction

Remote asymmetric induction is a challenging subject in the field of asymmetric synthesis,[1] and it has a potential for shortening the synthetic routes to complex chiral molecules. Although several methodologies for highly efficient remote asymmetric induction up to a 1,7-relationship have been developed, little is known about the asymmetric induction beyond a 1,7-relationship.[2] Recently, we have reported that butan-4-olides (γ-lactones) with a quaternary carbon center at the 4-position are synthesized with up to 99% optical yield *via* the diastereoselective Grignard reaction of γ-keto esters of 1,1′-binaphthalen-2-ol derivatives **1** in the presence of an excess of $MgBr_2{\cdot}OEt_2$, followed by a spontaneous lactonization of the resulting hydroxy esters.[3] This highly efficient 1,7-asymmetric induction was attributed to the formation of a pseudo-macrocyclic magnesium chelate composed of the podand-type keto ester and $MgBr_2$ (*e.g.* complex **27**), which would fix the orientation of the keto carbonyl group to make the nucleophile attack preferentially from the outside of the pseudo-macrocycle. Herein, we report the effective extension of the methodology to 1,8- and 1,9-asymmetric inductive Grignard reactions of δ- and ε-keto esters **3**–**6**.[4] Also reported is an advantageous utilization of the 1,8-asymmetric induction protocol in a short-step synthesis of (−)-malyngolide.

Results and discussion

Diastereoselective Grignard reaction of ω-keto esters 3–7

The prerequisite ω-keto esters **3**–**7** were readily prepared by DCC condensation of chiral auxiliaries **1a**–**f** with ω-keto acids **2a**–**e** (Scheme 1). The Grignard reaction was performed as follows: a keto ester **3**–**7** was treated with 3.0 equiv. of $MgBr_2{\cdot}OEt_2$ in dichloromethane at room temperature for 1 h to preorganize the substrate–Lewis acid complex, which was then treated with a diethyl ether solution of an excess of a Grignard reagent **8** at −78 °C until the keto ester had disappeared by monitoring on TLC. In the reaction of δ-keto esters **3** and **4**, the initially produced δ-hydroxy esters spontaneously cyclized during work-up to afford lactone **9** in good yields after purifi-



Scheme 1 *Reagents:* i, DCC, PPy, CH_2Cl_2; ii, $MgBr_2{\cdot}OEt_2$, CH_2Cl_2–Et_2O; iii, LAH, Et_2O.

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Table 1 Grignard reaction of ω-keto esters **3**–**7**

Entry	Substrate	R^1	R^2	R^3	Product	Yield (%)	Ee (%) (Abs. confign.)
1	**3a**	ME	Ph	Me	**9**	73	59(*S*)
2	**3b**	MP	Ph	Me	**9**	56	7 (*S*)
3	**3c**	MEP	Ph	Me	**9**	80	93 (*R*)
4[a]	**3c**	MEP	Ph	Me	**9**	77	85 (*R*)
5[b]	**3c**	MEP	Ph	Me	**9**	85	95 (*R*)
6	**3d**	MEB	Ph	Me	**9**	79	74 (*R*)
7	**3e**	IBEP	Ph	Me	**9**	82	92 (*R*)
8	**3f**	MEEE	Ph	Me	**9**	88	80 (*R*)
9	**4c**	MEP	Me	Ph	**9**	70	92 (*S*)
10	**5c**	MEP	Ph	Me	**10**	90	82 (*S*)
11[a]	**5c**	MEP	Ph	Me	**10**	63	56 (*S*)
12	**5d**	MEB	Ph	Me	**10**	83	41 (*S*)
13[a]	**5d**	MEB	Ph	Me	**10**	75	45 (*S*)
14	**5f**	MEEE	Ph	Me	**10**	75	6 (*S*)
15[a]	**5f**	MEEE	Ph	Me	**10**	87	6 (*S*)
16	**6c**	MEP	Me	Ph	**12**	46	82 (*R*)
17	**7c**	MEP	Ph	Me	**11**	89	4
18	**7d**	MEB	Ph	Me	**11**	96	7
19	**7f**	MEEE	Ph	Me	**11**	96	9

[a] The reaction was conducted in the absence of $MgBr_2 \cdot OEt_2$. [b] $ZnCl_2$ was employed instead of $MgBr_2 \cdot OEt_2$.

cation by preparative TLC (PLC), while the reaction of ε- and ζ-keto esters **5**–**7** gave the diastereomeric hydroxy esters by the same treatment. In order to assess the stereoselectivity of the Grignard addition with care to avoid diastereomeric enrichment, the hydroxy esters obtained from the reaction of benzoyl esters **5**, **7** with methylmagnesium bromide **8a** were methylated *in situ* to diols **10**, **11** by treatment with an additional amount of the Grignard reagent, and the hydroxy ester obtained from acetyl ester **6** and the phenyl Grignard reagent **8b** was reduced to diol **12** by treatment with LAH. The ees of the isolated products **9**–**12** were determined by chiral GLC or HPLC analyses.

Table 1 lists the results of the Grignard reactions. The diastereoselectivity of the reaction between δ-keto esters **3a**–**f** and the methyl Grignard reagent **8a** varied depending on the structure of the 2′-substituent of the chiral auxiliaries (entries 1–3 and 6–8). The keto esters with a mono(alkylene glycol)-type oligoether tether **3a**, **b** showed lower diastereoselectivity and opposite diastereoface selection compared with keto esters with a di- or tri(alkylene glycol)-type substituent **3c**–**f**, though the mono(alkylene glycol)-type chiral auxiliary of ester **3a** gave the highest de in the corresponding Grignard reaction of γ-keto esters.[3] Consideration of the distinct difference in stereoselectivity between the reactions of ester **3b** and ester **3c** (entries 2 and 3) shows that the 3-(2-methoxyethoxy)propoxy (MEP-O) group of keto ester **3c**, which showed the best performance among the chelating groups examined, coordinates to the Lewis acid in a bidentate manner through the terminal ethylenedioxy moiety rather than the internal propylenedioxy moiety. The 4-(2-methoxyethoxy)butoxy (MEB-O) group of keto ester **3d** should also coordinate through the terminal ethylenedioxy moiety (entry 6). These observations may indicate that the optimal chelating group for the remote asymmetric induction varies with the distance between the keto and ester carbonyl groups and that δ-keto esters require a longer oligoether tether to achieve high stereoselectivity than γ-keto esters do. On the other hand, the steric bulk of the terminal alkoxy moiety did not have much effect on the stereoselectivity (compare entry 7 and entry 3).

The MEP-O chelating group was also highly effective in the reaction of ε-keto esters **5** with the methyl Grignard reagent **8a** (entries 10, 12 and 14). However, the reaction of ζ-keto esters **7** resulted in low stereoselectivity even using the chelating group varying from MEP-O to a longer oligoether tether (entries 17–19).

The reaction of ω-acetyl esters **4c** and **6c** with the phenyl Grignard reagent **8b** showed almost equal diastereoselectivity with opposite stereochemistry of the adduct to that of the corresponding ω-benzoyl esters **3c** and **5c** with the methyl Grignard reagent **8a**, suggesting that the orientation of the keto carbonyl group in the chelated complex is identical in these reactions (compare entry 9 with entry 3 and entry 16 with entry 10).

In our previous paper,[3] it was shown that the relevant Grignard reaction of γ-keto esters proceeded with fairly good diastereoselectivity even if the preorganization step had been omitted. This was rationalized as ligation of the substrate to $MgBr_2$ present in the reaction mixture by the Schlenk equilibrium prior to the attack of the Grignard reagent. Similar results were obtained in the reaction of δ- and ε-keto esters (entries 4, 11, 13 and 15). The Grignard reaction of ester **3c** with $ZnCl_2$ as the Lewis acid showed almost equal stereoselectivity to that in the presence of $MgBr_2 \cdot OEt_2$ (entry 5). In this case, however, at least 10 equiv. of the Grignard reagent was required to complete the reaction, suggesting the formation of an organozinc reagent from the Grignard reagent and $ZnCl_2$. A control reaction with methylzinc chloride instead of methylmagnesium bromide did not afford lactone **9**. Therefore, it may be concluded that the Grignard reagent, after the consumption of $ZnCl_2$ to form methylzinc chloride, added to the keto ester ligated to $MgBr_2$.

Determination of the absolute configurations of lactone 9 and diols 10, 12

Scheme 2 illustrates the determination of the absolute configurations of lactone **9** and diols **10** and **12**.

Enantiomerically pure lactone (*R*)-(+)-**16** was reduced with LAH to give diol **17**, which was converted into tosylate **21** by the following sequential reactions: initial esterification of the diol **17** with acetic anhydride to hydroxy ester **18**, protection of its hydroxy group as the *tert*-butyldimethylsilyl ether (**19**), reduction of the siloxy ester **19** to alcohol **20**, followed by esterification of the alcohol **20** with toluene-*p*-sulfonyl chloride. Homologation[5] of the tosylate **21** with a Gilman reagent gave (*R*)-2-phenylhexan-2-ol **15**, after removal of the TBDMS-protecting group. On the other hand, lactone (+)-**9** of 90% ee was reduced to give diol **13**, the terminal hydroxy group of which was converted into the tosylate (**14**), and then reduced with LAH to give dextrorotatory alcohol **15**. Comparison of the elution behavior of the sample in HPLC with that of the authentic sample determined the absolute configuration of the alcohol (+)-**15** to be *R*. Thus, the *R* absolute stereochemistry of lactone (+)-**9** was established.

The tosylate (*R*)-**21** was coupled with ethylmagnesium bromide in the presence of Li_2CuCl_4[6] to give authentic (*R*)-2-phenylheptan-2-ol **24**, after removal of the TBDMS-protecting group. On the other hand, a control reaction of the ε-keto ester (R_a)-**5d** with methylmagnesium bromide under the standard conditions (*vide supra*) was quenched to give a diastereomeric mixture of esters **25**, reduction of which with LAH gave levorotatory diol **12** of 43% ee. Tosylation of the diol **12**, followed by LAH reduction of the resulting ester **26** gave levorotatory alcohol **24**. Comparison of the elution behavior of the sample in HPLC with that of the authentic sample determined the absolute configuration of the alcohol (−)-**24**, as well as that of the diol (−)-**12**, to be *S*. This analysis, combined with the result that the diastereomeric mixture of the esters **25** gave levorotatory diol **10**, established that the absolute stereochemistry of the diol **10** should be (*S*)-(−).

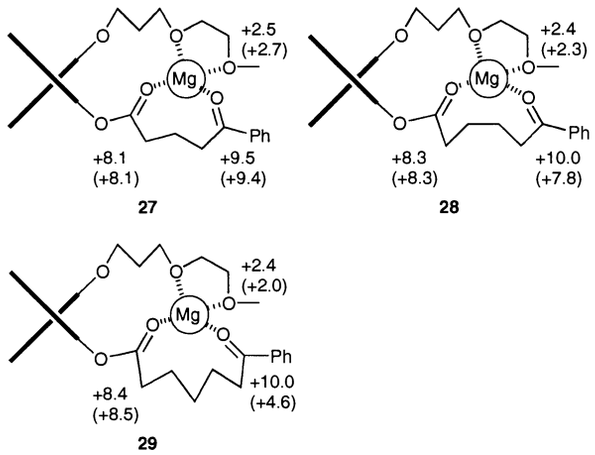
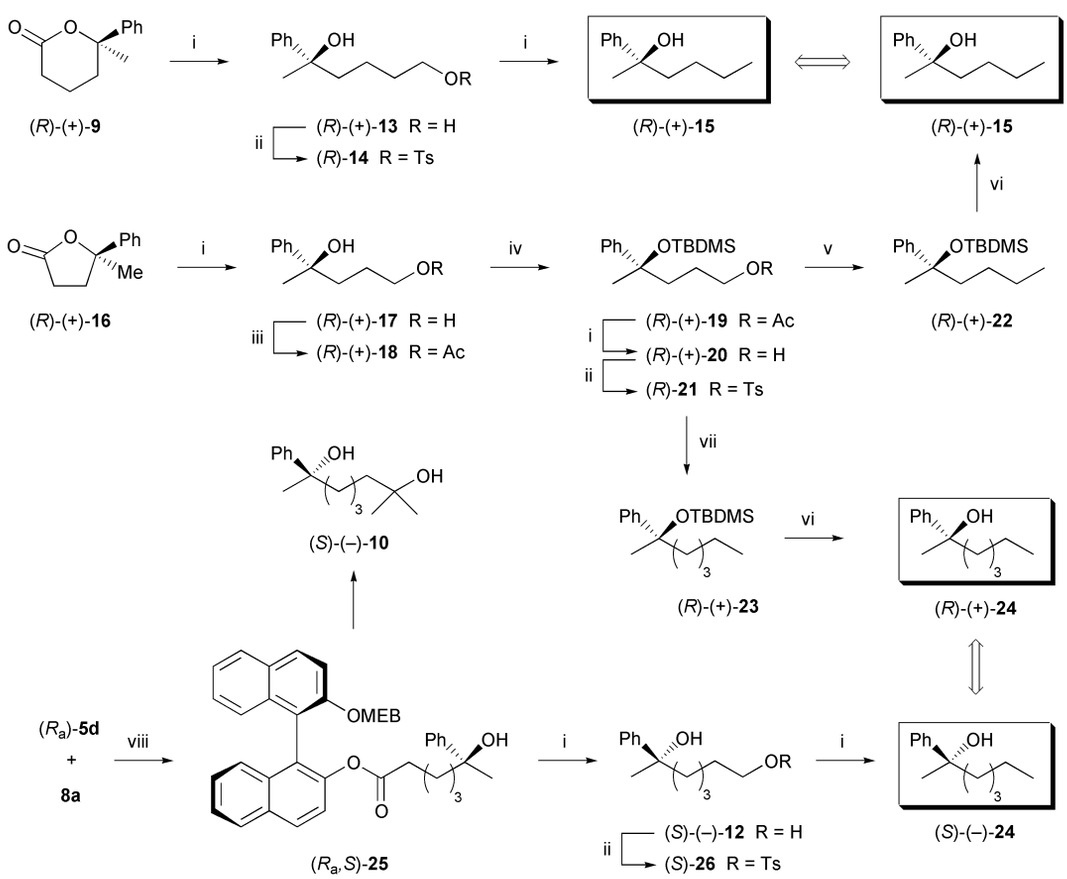


Fig. 1 Downfield shifts in ppm of the ^{13}C NMR signals for keto esters **3c**, **5c** and **7c** upon complexation with $MgBr_2{\cdot}OEt_2$ in [$^2H_2$]dichloromethane. The downfield shifts of the complexes after addition of 7 vol% of diethyl ether are shown in parentheses.

Mechanistic consideration of the remote asymmetric induction

In order to gain insight into the mechanism of the remote asymmetric induction, complexation experiments were carried out (Fig. 1). The δ-, ε- and ζ-keto esters with a MEP-O chelating group **3c**, **5c** and **7c** were treated with an excess of $MgBr_2$ in [$^2H_2$]dichloromethane and the resulting complexes were subjected to ^{13}C NMR analyses. The spectra of the $MgBr_2$ chelates **27**–**29** showed considerable downfield shifts of both carbonyl carbons and the terminal carbon of the oligoether tether. The chemical shift values of the complexes **27** and **28** were only slightly changed by the addition of 7 vol% of diethyl ether, the amount of which is almost equal to that in the reaction mixture, while the complex **29** showed considerable decrease in the downfield shifts after the same treatment. These observations indicate that the stability of the magnesium chelates in the presence of diethyl ether changes according to the length of the carbon chain between the two carbonyl groups on the keto acid component. Therefore, it may be concluded that the more stable the pseudo-macrocyclic complex is, the higher the diastereoselectivity obtained by fixing the orientation of the keto carbonyl group and that the carbon chain of the ζ-keto acid moiety in ester **7c** is too long to construct a stable pseudo-macrocyclic chelate with $MgBr_2$.

Detailed CPK and Dreiding molecular model inspections gave the structure of the pseudo-macrocyclic complex **27** of the δ-keto ester **3c** as schematically visualized in Fig. 2. It is of interest to note that the preferred diastereoface of the ε-keto ester **5c** in the Grignard reaction is same as that of the relevant γ-keto ester[3] and is opposite to that of the δ-keto ester **3c**. Although the three-dimensional structure of the pseudo-



Scheme 2 *Reagents:* i, LAH, Et_2O; ii, TsCl, pyridine; iii, Ac_2O, Et_3N, DMAP, Et_2O; iv, TBDMS-OTf, 2,6-lutidine, CH_2Cl_2; v, Me_2CuLi, Et_2O; vi, TBAF, THF; vii, EtMgBr, Li_2CuCl_4, THF; viii, CH_2Cl_2–Et_2O.

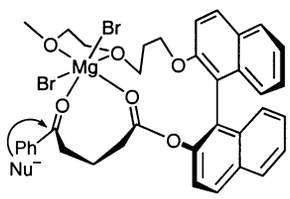


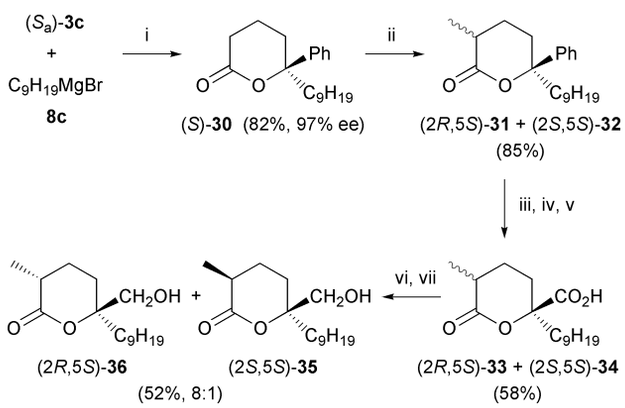
Fig. 2 Schematic view of the pseudo-macrocyclic complex **27** composed of keto ester **3c** and $MgBr_2$.

macrocyclic complex **28** of the ε-keto ester **5c** is unclear at present, the structure seems to be similar to that of the γ-keto ester[3] and different from that of the δ-keto ester. Neither the γ- nor the ε-keto acid component can make a zigzag structure as observed for the δ-keto acid component (**27**), upon ligation to $MgBr_2$. Therefore, although further studies must be done to know the precise origin of the diastereoface selection, the attack of the nucleophile seems to occur preferentially from outside of the pseudo-macrocycles in all these cases to give the observed diastereoselectivity.

Synthesis of (−)-malyngolide

The δ-lactone (−)-malyngolide **36**, an antibiotic discovered from the marine blue-green alga *Lyngbya majuscula*, exhibits significant activity against *Mycobacterium smegmatis* and *Streptococcus pyogenes*.[7] Although a number of papers have dealt with the synthetic strategies, the methods require many steps and/or suffer from low yields.[8]

It occurred to us that the remote asymmetric inductive Grignard reaction of the δ-keto ester **3** could be advantageously utilized for an improved synthesis of malyngolide **36** with a quaternary carbon center (Scheme 3). Our synthetic strategy



Scheme 3 *Reagents:* i, $MgBr_2{\cdot}OEt_2$, CH_2Cl_2–Et_2O; ii, LDA, MeI, THF–HMPA; iii, $HIO_4{\cdot}2H_2O$, $RuCl_3{\cdot}3H_2O$, CCl_4–MeCN–H_2O; iv, CH_2N_2, Et_2O; v, LiI, pyridine; vi, $ClCO_2Et$, Et_3N, Et_2O; vii, $Zn(BH_4)_2$.

started with the reaction of δ-keto ester (S_a)-**3c** with nonylmagnesium bromide **8c**. The Grignard reaction afforded the corresponding δ-lactone **30** of high enantiomeric purity (97% ee), which was methylated by treatment with LDA and iodomethane to give a mixture of epimers **31** and **32**. The RuO_4 oxidation[9] of the mixture gave acids **33** and **34** after chromatographic purification as the methyl esters. The acids were then treated with ethyl chloroformate and the resulting acid anhydrides were reduced with $Zn(BH_4)_2$[10] to give (−)-malyngolide **36** and *epi*-malyngolide **35** in the ratio of 8 : 1. It is well known that these epimers are readily separated by chromatography and that *epi*-malyngolide **35** can be epimerized to malyngolide **36** by treatment with potassium *tert*-butoxide.[11] Therefore, the present method provides an easy access to (−)-malyngolide **36**.

In conclusion, we have shown here that our previously reported methodology to realize the highly efficient 1,7-asymmetric inductive Grignard reaction of γ-keto esters can be successfully extended to the 1,8- and 1,9-asymmetric inductive reactions of δ- and ε-keto esters by changing the 2′-oligoether tether of the chiral auxiliaries and that the former reaction can be advantageously utilized in the synthesis of (−)-malyngolide.

Experimental

Microanalyses were carried out in the Microanalytical Laboratory of the Institute for Chemical Reaction Science, Tohoku University. Optical rotations were measured on a Union Giken PM-101 or JASCO DIP-100 polarimeter and are given in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded on a Shimadzu IR-460 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-250T, DPX-400 or DRX-500 spectrometer using tetramethylsilane as the internal standard and $CDCl_3$ as the solvent unless otherwise noted. *J* Values are given in Hz. Silica gel columns were prepared by use of Nacalai silica gel 60 (70–230 mesh). Merck silica gel $60GF_{254}$ was used for analytical and preparative TLC (PLC). Densities (*d*) are given in units of g cm^{-3}. Na_2SO_4 was employed for the drying of extracts. Water- and air-sensitive reactions were routinely carried out under nitrogen. Diethyl ether and THF were distilled from sodium diphenyl ketyl just before use. Dichloromethane, DMF and pyridine were distilled from CaH_2. Other solvents for experiments requiring anhydrous conditions were purified by usual methods. The complexation experiments were carried out by the same procedure as previously reported.[3] Chiral auxiliaries **1a**–**c**, **e**, **f** were obtained as before.[3]

(R_a)-2′-[4-(2-Methoxyethoxy)butoxy]-1,1′-binaphthalen-2-ol 1d

The starting alcohol, 4-(2-methoxyethoxy)butanol, was prepared according to the method described by Okano *et al.*[12] Thus, 1-chloro-2-methoxyethane (17.6 g, 186 mmol) was added dropwise over a period of 30 min to a boiling solution of butane-1,4-diol (25.0 g, 277 mmol) and NaOH (93%; 11.1 g, 258 mmol) in distilled water (10 cm^3). After being refluxed for 25 h, the mixture was allowed to cool to room temperature and neutralized by addition of conc. HCl. The resulting salt was filtered off and the filtrate was evaporated to leave a pale yellow oil, which was distilled through a Widmer fractionating column. In contrast to the original report, the fractionated distillate (17.6 g; bp 123–124 °C/15 Torr, 1 Torr = 133.3 N m^{-2}) was a mixture of the desired 4-(2-methoxyethoxy)butanol and butane-1,4-diol. Therefore, the mixture was used in the following step without further purification.

To a stirred solution of the mixed alcohols (5.03 g) in dry pyridine (40 cm^3) was added toluene-*p*-sulfonyl chloride (14.3 g, 75.0 mmol) at 0 °C and the mixture was stirred at this temperature overnight. The mixture was poured into ice-cold 6 mol dm^{-3} HCl and extracted with dichloromethane. The organic layer was dried and evaporated. The residue was dissolved in the minimum amount of diethyl ether and the solution was cooled in a refrigerator to induce crystallization of butane-1,4-diyl ditosylate, which was removed by filtration. The mother liquid was evaporated and the residue was chromatographed on a silica gel column with hexane–ethyl acetate (3 : 2) as the eluent to give 4-(2-methoxyethoxy)butyl toluene-*p*-sulfonate (5.17 g, 32% based on 1-chloro-2-methoxyethane) as a colorless oil, ν_{max}(neat)/cm^{-1} 1360 (SO_2) and 1173 (SO_2); δ_H(250 MHz) 1.56–2.04 (4 H, m, $TsOCH_2CH_2CH_2$), 2.45 (3 H, s, ArMe), 3.36–3.64 (9 H, m, $CH_2OC_2H_4OMe$), 4.05 (2 H, t, *J* 6.2, $TsOCH_2$), 7.35 (2 H, d, *J* 8.3, ArH) and 7.78 (2 H, d, *J* 8.3, ArH).

To a solution of (*R*)-BINOL (1.56 g, 5.45 mmol) in dry DMF (15 cm^3) was added NaH (60%; 219 mg, 5.48 mmol) portionwise and the mixture was stirred at room temperature for 3 h to give a yellow solution, to which was added a solution of the tosylate (1.66 g, 5.49 mmol) in DMF (15 cm^3) and the mixture was heated at 100 °C for 30 min. The cooled mixture was

poured into 2 mol dm^{-3} HCl and the mixture was extracted with diethyl ether. The extracts were washed successively with saturated aqueous $NaHCO_3$, distilled water and brine, dried and evaporated. The residue was chromatographed on a silica gel column with hexane–ethyl acetate (1 : 2) as the eluent to give auxiliary **1d** (1.71 g, 75%) as a pale yellow oil (Found: C, 77.7; H, 6.6. $C_{27}H_{28}O_4$ requires C, 77.9; H, 6.8%); $[\alpha]_D^{18}$ −12.3 (*c* 1.06 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3330 (OH); δ_H(250 MHz) 1.22–1.60 (4 H, m, $ArOCH_2C_2H_4$), 3.13–3.41 (9 H, m, $CH_2OC_2H_4OMe$), 3.96–4.10 (2 H, m, $ArOCH_2$), 5.25 (1 H, br s, OH) and 7.02–8.02 (12 H, m, ArH).

General procedure for preparation of the δ-, ε- and ζ-keto esters 3–7

Esters **3**–**7** were prepared by DCC condensation of auxiliaries **1a**–**f** with ω-keto acids **2a**–**e** in dichloromethane in the presence of 4-pyrrolidin-1-ylpyridine (PPy), according to the procedure reported before.[3] The eluents for the chromatographic purification, the isolated yields and the physical and spectral characteristics of the esters are given below.

Ester (R_a)-3a. As a colorless oil (88%) (Found: C, 78.93; H, 5.92. $C_{34}H_{30}O_5$ requires C, 78.74; H, 5.83%); $[\alpha]_D^{22}$ −13.4 (*c* 1.41, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1755 (CO) and 1688 (CO); δ_H(250 MHz) 1.35–1.71 (2 H, m, CH_2), 2.00–2.54 (4 H, m, CH_2), 2.98 (3 H, m, OMe), 3.17–3.45 (2 H, m, CH_2), 3.88–4.10 (2 H, m, CH_2) and 7.17–7.99 (17 H, m, ArH).

Ester (R_a)-3b. Benzene–ethyl acetate (8 : 1) as the eluent; a colorless oil (88%) (Found: C, 78.9; H, 6.1. $C_{35}H_{32}O_5$ requires C, 78.9; H, 6.1%); $[\alpha]_D^{16}$ −17.3 (*c* 1.04, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1756 (CO) and 1684 (CO); δ_H(250 MHz) 1.45–1.71 (4 H, m, OCH_2CH_2 and $OCOCH_2CH_2$), 2.16–2.51 (4 H, m, $OCOCH_2CH_2CH_2CH_2$), 2.85–3.02 (5 H, m, CH_2OMe), 3.97–4.11 (2 H, m, $ArOCH_2$) and 7.17–7.99 (17 H, m, ArH).

Ester (R_a)-3c. Benzene–ethyl acetate (4 : 1 to 2 : 1) and then hexane–ethyl acetate (3 : 2); a colorless oil (95%) (Found: C, 77.0; H, 6.4. $C_{37}H_{36}O_6$ requires C, 77.1; H, 6.30%); $[\alpha]_D^{16}$ −21.3 (*c* 1.08, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1756 (CO) and 1684 (CO); δ_H(250 MHz) 1.40–1.55 (4 H, m, $ArOCH_2CH_2$ and $OCOCH_2CH_2$), 2.16–2.52 (4 H, m, $OCOCH_2CH_2CH_2CH_2$), 2.93–3.37 (9 H, m, $CH_2OC_2H_4OMe$), 3.95–4.12 (2 H, m, $ArOCH_2$) and 7.12–8.00 (17 H, m, ArH).

Ester (R_a)-3d. Hexane–ethyl acetate (3 : 2) and then benzene–ethyl acetate (4 : 1) as the eluent; a pale yellow oil (73%) (Found: C, 77.0; H, 6.6. $C_{38}H_{38}O_6$ requires C, 77.3; H, 6.5%); $[\alpha]_D^{18}$ −22.4 (*c* 1.07, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1756 (CO) and 1685 (CO); δ_H(250 MHz) 1.23–1.62 (6 H, m, $ArOCH_2C_2H_4$ and $OCOCH_2CH_2$), 2.13–2.47 (4 H, m, $OCOCH_2CH_2CH_2CH_2$), 3.08–3.15 (2 H, m, $OC_3H_6CH_2$), 3.28–3.44 (7 H, m, C_2H_4OMe), 3.91–4.01 (2 H, m, $ArOCH_2$) and 7.12–7.99 (17 H, m, ArH).

Ester (R_a)-3e. Hexane–ethyl acetate (2 : 1) as the eluent; a colorless oil (85%) (Found: C, 77.9; H, 6.9. $C_{40}H_{42}O_6$ requires C, 77.6; H, 6.8%); $[\alpha]_D^{18}$ −23.0 (*c* 1.00, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1757 (CO) and 1686 (CO); δ_H(250 MHz) 0.81 (6 H, d, *J* 6.7, Me), 1.44–1.85 (5 H, m, $CHMe_2$, $ArOCH_2CH_2$ and $OCOCH_2CH_2$), 2.16–2.43 (4 H, m, $OCOCH_2CH_2CH_2CH_2$), 2.97–3.40 (8 H, m, $CH_2OC_2H_4OCH_2$), 4.00–4.09 (2 H, m, $ArOCH_2$) and 7.16–7.99 (17 H, m, ArH).

Ester (R_a)-3f. Hexane–ethyl acetate (3 : 1) as the eluent; a pale yellow oil (77%) (Found: C, 75.0; H, 6.3. $C_{38}H_{38}O_7$ requires C, 75.2; H, 6.3%); $[\alpha]_D^{16}$ −16.4 (*c* 1.22, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1755 (CO) and 1682 (CO); δ_H(250 MHz) 1.38–1.65 (2 H, m, $OCOCH_2CH_2$), 2.15–2.45 (4 H, m, $OCOCH_2CH_2CH_2CH_2$), 3.09–3.58 (13 H, m, $CH_2OC_2H_4OC_2H_4OMe$), 4.08 (2 H, t, *J* 5.0, $ArOCH_2$) and 7.16–7.97 (17 H, m, ArH).

Ester (R_a)-4c. Hexane–ethyl acetate (1 : 1) as the eluent; a pale yellow oil (87%) (Found: C, 74.6; H, 6.7. $C_{32}H_{34}O_6$ requires C, 74.7; H, 6.7%); $[\alpha]_D^{21}$ −8.2 (*c* 1.06, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1756 (CO) and 1714 (CO); δ_H(250 MHz) 1.25–1.41 (2 H, m, $OCOCH_2CH_2$), 1.72–1.80 (4 H, m, $ArOCH_2CH_2$ and $OCOCH_2$), 1.88 (3 H, s, Ac), 2.04–2.11 (2 H, m, $OCOC_2H_4CH_2$), 2.96–3.41 (9 H, m, $CH_2OC_2H_4OMe$), 4.02–4.14 (2 H, m, $ArOCH_2$), 7.17–7.44 (8 H, m, ArH) and 7.91–7.99 (4 H, m, ArH).

Ester (R_a)-5c. Benzene–ethyl acetate (9 : 1) as the eluent; a pale yellow oil (98%) (Found: C, 77.2; H, 6.5. $C_{38}H_{38}O_6$ requires C, 77.3; H, 6.5%); $[\alpha]_D^{18}$ +19.1 (*c* 1.10, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1757 (CO) and 1687 (CO); δ_H(250 MHz) 0.95–1.48 (4 H, m, $OCOCH_2C_2H_4$), 1.71 (2 H, quint, *J* 6.6, $ArOCH_2CH_2$), 1.99–2.17 (2 H, m, $OCOCH_2$), 2.48–2.72 (2 H, m, CH_2COPh), 2.83–3.49 (6 H, m, $CH_2OC_2H_4O$), 3.30 (3 H, s, OMe), 3.91–4.18 (2 H, m, $ArOCH_2$) and 7.10–8.12 (17 H, m, ArH).

Ester (R_a)-5d. As a colorless oil (76%) (Found: C, 77.7; H, 6.8. $C_{39}H_{40}O_6$ requires C, 77.5; H, 6.7%); $[\alpha]_D^{18}$ +26.9 (*c* 0.97, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1757 (CO) and 1687 (CO); δ_H(250 MHz) 0.95–1.65 (8 H, m, $OCH_2C_2H_4$ and $OCOCH_2C_2H_4$), 2.09 (2 H, t, *J* 7.4, $OCOCH_2$), 2.60 (2 H, t, *J* 7.4, CH_2COPh), 3.00–3.50 (6 H, m, $CH_2OC_2H_4O$), 3.34 (3 H, s, OMe), 3.87–4.08 (2 H, m, $ArOCH_2$) and 7.08–8.08 (17 H, m, ArH).

Ester (R_a)-5f. Benzene–ethyl acetate (7 : 3) as the eluent; a pale yellow oil (66%) (Found: C, 75.5; H, 6.6. $C_{39}H_{40}O_7$ requires C, 75.5; H, 6.5%); $[\alpha]_D^{18}$ +31.8 (*c* 0.98, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1757 (CO) and 1687 (CO); δ_H(250 MHz) 0.96–1.42 (4 H, m, $OCOCH_2C_2H_4$), 2.09 (2 H, t, *J* 7.3, $OCOCH_2$), 2.61 (2 H, t, *J* 7.5, CH_2COPh), 3.33 (3 H, s, OMe), 3.38–3.62 (10 H, m, $CH_2OC_2H_4OC_2H_4O$), 3.97–4.22 (2 H, m, $ArOCH_2$) and 7.10–8.04 (17 H, m, ArH).

Ester (R_a)-6c. Benzene–ethyl acetate (4 : 1) as the eluent; a colorless oil (90%) (Found: C, 74.7; H, 7.0. $C_{33}H_{36}O_6$ requires C, 75.0; H, 6.9%); $[\alpha]_D^{19}$ +21.1 (*c* 1.26, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1754 (CO) and 1714 (CO); δ_H(250 MHz) 0.87–1.28 (4 H, m, $OCOCH_2C_2H_4$), 1.59–1.78 (2 H, m, $ArOCH_2CH_2$), 1.77–2.33 (4 H, m, $OCOCH_2$ and CH_2Ac), 2.00 (3 H, s, Ac), 2.88–3.50 (6 H, m, $CH_2OC_2H_4O$), 3.31 (3 H, s, OMe), 3.92–4.20 (2 H, m, $ArOCH_2$), 7.00–7.60 (8 H, m, ArH) and 7.78–8.10 (4 H, m, ArH).

Ester (R_a)-7c. Hexane–ethyl acetate (1 : 1); a colorless oil (37%) (Found: C, 77.3; H, 6.9. $C_{39}H_{40}O_6$ requires C, 77.5; H, 6.7%); $[\alpha]_D^{15}$ +9.7 (*c* 1.05, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1754 (CO) and 1682 (CO); δ_H(250 MHz) 0.80–1.74 (8 H, m, $ArOCH_2CH_2$ and $OCOCH_2C_3H_6$), 2.07 (2 H, t, *J* 7.2, $OCOCH_2$), 2.62–2.83 (2 H, m, CH_2COPh), 2.88–3.39 (6 H, m, $CH_2OC_2H_4O$), 3.30 (3 H, s, OMe), 3.92–4.22 (2 H, m, $ArOCH_2$), 7.03–7.67 (11 H, m, ArH) and 7.72–8.03 (6 H, m, ArH).

Ester (R_a)-7d. Hexane–ethyl acetate (4 : 1) as the eluent; a colorless oil (46%) (Found: C, 77.55; H, 6.9. $C_{40}H_{42}O_6$ requires C, 77.6; H, 6.8%); $[\alpha]_D^{15}$ +11.0 (*c* 1.00, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1755 (CO) and 1684 (CO); δ_H(250 MHz) 0.78–1.55 (10 H, m, $ArOCH_2C_2H_4$ and $OCOCH_2C_3H_6$), 2.03–2.17 (2 H, m, $OCOCH_2$), 2.62–2.85 (2 H, m, CH_2COPh), 3.03–3.50 (6 H, m, $CH_2OC_2H_4O$), 3.33 (3 H, s, OMe), 3.89–4.07 (2 H, m, $ArOCH_2$), 7.12–7.65 (11 H, m, ArH) and 7.73–8.05 (6 H, m, ArH).

Ester (R_a)-7f. Hexane–ethyl acetate (1 : 2) as the eluent; a colorless oil (53%) (Found: C, 75.6; H, 6.7. $C_{40}H_{42}O_7$ requires C, 75.7; H, 6.7%); $[\alpha]_D^{15}$ +13.6 (*c* 1.05, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1754 (CO) and 1684 (CO); δ_H(250 MHz) 0.80–1.52 (6 H, m, $OCOCH_2C_3H_6$), 2.06 (2 H, t, *J* 7.1, $OCOCH_2$), 2.68–2.82 (2 H, m,

CH_2COPh), 3.04–3.58 (10 H, m, $CH_2OC_2H_4OC_2H_4O$), 3.37 (3 H, s, OMe), 4.05–4.17 (2 H, m, $ArOCH_2$), 7.13–7.68 (11 H, m, ArH) and 7.75–8.04 (6 H, m, ArH).

General procedure for the Grignard reaction of keto esters 3 and 4

To a solution of a keto ester **3** or **4** (100 μmol) in dichloromethane (5.0 cm^3) was added $MgBr_2 \cdot OEt_2$ (300 μmol) and the dispersion was stirred for 1 h and then cooled to −78 °C. After 1 h, 3.0 equiv. of a Grignard reagent **8a** or **b** (1.0 mol dm^{-3} in diethyl ether) was added to the dispersion. The progress of the reaction was monitored by TLC and an additional amount of the Grignard reagent was added to the mixture, if necessary. After the substrate had disappeared on TLC, acetone (1.0 cm^3) was added to the mixture, which was then gradually warmed to room temperature over a period of 1 h. To the mixture was added distilled water and the two layers were separated. The water layer was extracted with chloroform and the combined organic layer was dried and evaporated. The crude product was purified by PLC with hexane–ethyl acetate or benzene–ethyl acetate as the developer to give lactone **9** as colorless crystals (Found: C, 75.75; H, 7.4. $C_{12}H_{14}O_2$ requires C, 75.8; H, 7.4%); ν_{max}(KBr)/cm^{-1} 1717 (CO); δ_H(250 MHz) 1.35–1.78 (2 H, m, CH_2), 1.57 (3 H, s, Me), 1.80–2.04 (1 H, m, CH_2), 2.07–2.52 (3 H, m, CH_2) and 7.24–7.41 (5 H, m, ArH). The enantiomeric excess was determined by GLC analysis on ASTEC Chiraldex G-TA column (0.25 mm id × 20 m) at 150 °C. See Table 1 for the yield and enantiomeric excess of the lactone **9** obtained in each reaction.

General procedure for the Grignard reaction of keto esters 5 and 7

The reaction procedure was the same as that for the Grignard reaction of keto esters **3** and **4**, unless otherwise noted. After the substrate had disappeared by monitoring on TLC (*vide supra*), an additional amount of methylmagnesium bromide **8a** (1.0 mol dm^{-3} in diethyl ether; 1.0 cm^3, 1.0 mmol) was added to the mixture. The resulting mixture was gradually warmed to room temperature before the addition of distilled water. After the work-up, the crude product was purified by PLC with hexane–ethyl acetate or benzene–ethyl acetate as the developer. The ee values of the products were determined by HPLC analyses on a Daicel Chiralcel OB (for diol **10**) or OJ (for diol **11**) column (4.6 mm id × 25 cm) with 10% propan-2-ol in hexane as the eluent. See Table 1 for the yield and enantiomeric excess of the diol **10** or **11** obtained in each reaction. The physical and spectral characteristics of the diols are given below.

Diol 10. As crystals (Found: C, 76.35; H, 10.2. $C_{15}H_{24}O_2$ requires C, 76.2; H, 10.2%); ν_{max}(KBr)/cm^{-1} 3360 (OH); δ_H(250 MHz) 1.16 (6 H, s, Me), 1.05–1.48 (6 H, m, CH_2), 1.56 (3 H, s, Me), 1.68–2.00 (2 H, m, CH_2) and 7.13–7.64 (5 H, m, ArH).

Diol 11. As crystals (Found: C, 76.9; H, 10.5. $C_{16}H_{26}O_2$ requires C, 76.8; H, 10.5%); ν_{max}(KBr)/cm^{-1} 3400 (OH); δ_H(250 MHz) 1.17 (6 H, s, Me), 1.21–1.47 (8 H, m, CH_2), 1.55 (3 H, s, Me), 1.70–1.95 (2 H, m, CH_2) and 7.20–7.50 (5 H, m, ArH).

Reaction of keto ester 6c with the Grignard reagent 8b

The reaction procedure was the same as that for the Grignard reaction of keto esters **3** and **4**, unless otherwise noted. After the substrate had disappeared by monitoring on TLC (*vide supra*), the reaction mixture was quenched with distilled water and worked up. The crude product was purified by PLC with hexane–ethyl acetate (1 : 1) as the developer to give the corresponding hydroxy ester, which was dissolved in diethyl ether (1.0 cm^3) and treated with a large excess of LAH at 0 °C for 1 h. The reaction was quenched by successive addition of crushed ice and 2 mol dm^{-3} HCl and the mixture was extracted with chloroform. The extracts were washed with brine, dried and evaporated. The residue was purified by PLC with benzene–ethyl acetate (1 : 1) as the developer to give diol **12** (9.6 mg, 46%) as a colorless oil (Found: C, 74.8; H, 9.75. $C_{13}H_{20}O_2$ requires C, 75.0; H, 9.7%); ν_{max}(neat)/cm^{-1} 3355 (OH); δ_H(250 MHz) 1.00–2.23 (8 H, m, CH_2), 1.55 (3 H, s, Me), 3.57 (2 H, t, *J* 6.5, CH_2OH) and 7.12–7.69 (5 H, m, ArH). The enantiomeric excess of the diol **12** was determined to be 82% by HPLC analysis on a Daicel Chiralcel OB column (4.6 mm id × 25 cm) with 5% propan-2-ol in hexane as the eluent.

Determination of the absolute configuration of lactone 9

Conversion of lactone 9 into alcohol 15. To a solution of the lactone (+)-**9** of 90% ee { $[\alpha]_D^{12}$ +39.8 (*c* 1.01, $CHCl_3$); 34.7 mg, 182 μmol} in diethyl ether (9.0 cm^3) was added LAH (23.0 mg, 606 μmol) and the mixture was stirred at room temperature for 15 min. The mixture was cooled in an ice bath and quenched by successive addition of crushed ice and 2 mol dm^{-3} HCl. The mixture was extracted with chloroform and the extracts were dried and evaporated. The residue was purified by PLC with benzene–ethyl acetate (1 : 1) as the eluent to give diol **13** (31.1 mg, 88%) as a colorless oil (Found: C, 74.3; H, 9.3. $C_{12}H_{18}O_2$ requires C, 74.2; H, 9.3%); $[\alpha]_D^{23}$ +15.6 (*c* 1.04, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3355 (OH); δ_H(250 MHz) 1.10–2.03 (7 H, m, CH_2 and OH), 1.53 (3 H, s, Me), 2.10 (1 H, br s, OH), 3.57 (2 H, t, *J* 6.8, CH_2OH) and 7.16–7.53 (5 H, m, ArH).

To a solution of the diol **13** (24.0 mg, 124 μmol) in pyridine (1.2 cm^3) was added toluene-*p*-sulfonyl chloride (45.3 mg, 238 μmol) at 0 °C and the mixture was stirred at this temperature overnight. The reaction was quenched with ice-cold 6 mol dm^{-3} HCl and the resulting mixture was extracted with chloroform. The extracts were washed successively with 2 mol dm^{-3} HCl, water and brine, dried and evaporated to give tosylate **14**, which was used in the next step without further purification.

To a solution of the tosylate in diethyl ether (2.0 cm^3) was added LAH (18.0 mg, 474 μmol) at 0 °C and the mixture was stirred at this temperature for 1 h. The reaction was quenched by successive addition of ethyl acetate, distilled water and 2 mol dm^{-3} HCl. The mixture was extracted with chloroform and the extracts were dried and evaporated. The residue was purified by PLC with benzene–ethyl acetate (7 : 1) as the eluent to give dextrorotatory alcohol **15** (10.3 mg, 47%) as a colorless oil (Found: C, 80.7; H, 10.1. $C_{12}H_{18}O$ requires C, 80.9; H, 10.2%); $[\alpha]_D^{19}$ +10.3 (*c* 0.53, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3415 (OH); δ_H(250 MHz) 0.91 (3 H, t, *J* 6.7, C_3H_6*Me*), 1.04–1.49 (4 H, m, CH_2), 1.62 (3 H, s, Me), 1.74–2.00 (3 H, m, CH_2 and OH) and 7.20–7.63 (5 H, m, ArH).

Conversion of lactone 16 into alcohol 15. To a solution of lactone (*R*)-(+)-**16**[13] of 99% ee (267 mg, 1.52 mmol) in diethyl ether (16 cm^3) was added LAH (124 mg, 3.27 mmol) at 0 °C and the mixture was stirred at this temperature for 30 min. The reaction was quenched with 2 mol dm^{-3} HCl and the mixture was extracted with chloroform. The extracts were washed successively with saturated aqueous $NaHCO_3$ and brine, dried, and evaporated. The residue was purified by column chromatography on a silica gel column with hexane–ethyl acetate (1 : 2 to 4 : 1) as the eluent to give diol **17** (257 mg, 94%) as a colorless oil (Found: C, 73.3; H, 9.2. $C_{11}H_{16}O_2$ requires C, 73.3; H, 9.0%); $[\alpha]_D^{20}$ +21 (*c* 0.74, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3340 (OH); δ_H(250 MHz) 1.32–1.63 (2 H, m, CH_2), 1.57 (3 H, s, Me), 1.80–2.10 (2 H, m, CH_2), 2.09 (1 H, br s, OH), 2.89 (1 H, br s, OH), 3.60 (2 H, t, *J* 5.8, CH_2OH) and 7.08–7.53 (5 H, m, ArH).

To an ice-cold solution of the diol **17** (257 mg, 1.43 mmol) in diethyl ether (7.0 cm^3) was added acetic anhydride (*d* 1.08; 175 mm^3, 1.85 mmol), triethylamine (*d* 0.726; 250 mm^3, 1.79 mmol) and DMAP (47.1 mg, 386 μmol) and the mixture was stirred at room temperature for 10 min. The reaction was quenched by

addition of 2 mol dm^{-3} HCl dropwise at 0 °C and the mixture was extracted with chloroform. The extracts were washed successively with saturated aqueous $NaHCO_3$ and brine, dried and evaporated. The residue was purified by column chromatography on a silica gel column with ethyl acetate as the eluent to give acetate **18** (294 mg, 93%) as a colorless oil (Found: C, 70.2; H, 8.2. $C_{13}H_{18}O_3$ requires C, 70.2; H, 8.2%); $[\alpha]_D^{19}$ +3.6 (*c* 1.67, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3475 (OH) and 1734 (CO); δ_H(250 MHz) 1.32–1.74 (2 H, m, CH_2), 1.61 (3 H, s, Me), 1.74–1.93 (2 H, m, CH_2), 2.00 (3 H, s, Ac), 2.05 (1 H, br s, OH), 3.99 (2 H, t, *J* 6.6, C*H*$_2$OAc) and 7.12–7.53 (5 H, m, ArH).

To an ice-cold solution of the acetate **18** (260 mg, 1.17 mmol) in dichloromethane (1.2 cm^3) was added 2,6-lutidine (*d* 0.920; 275 mm^3, 2.36 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (*d* 1.15; 400 mm^3, 1.74 mmol) and the mixture was stirred at 0 °C for 20 min. The reaction was quenched with 2 mol dm^{-3} HCl and the mixture was extracted with chloroform. The extracts were washed successively with 2 mol dm^{-3} HCl, saturated aqueous $NaHCO_3$ and brine and dried. The solvents were evaporated and the residue was chromatographed on a silica gel column with hexane–benzene–ethyl acetate (15 : 1 : 1) as the eluent to give a mixture (304 mg) of silyl ether **19** and a by-product, a small portion of which was purified by PLC with hexane–benzene as the developer to give analytically pure ether **19** as a colorless oil (Found: C, 67.9; H, 9.6. $C_{19}H_{32}O_3Si$ requires C, 67.8; H, 9.6%); $[\alpha]_D^{20}$ +6.6 (*c* 1.23, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1742 (CO); δ_H(250 MHz) 0.08 (3 H, s, SiMe), 0.19 (3 H, s, SiMe), 1.03 (9 H, s, Bu^t), 1.24–1.52 (1 H, m, CH_2), 1.69 (3 H, s, Me), 1.59–2.00 (3 H, m, CH_2), 2.06 (3 H, s, Ac), 4.00 (2 H, t, *J* 6.6, C*H*$_2$OAc) and 7.17–7.58 (5 H, m, ArH). To an ice-cold solution of the mixture (269 mg) in diethyl ether (9.0 cm^3) was added LAH (88.5 mg, 2.33 mmol) and the mixture was stirred at 0 °C for 10 min. The reaction was quenched with 2 mol dm^{-3} HCl and the mixture was extracted with chloroform. The extracts were washed successively with saturated aqueous $NaHCO_3$ and brine, dried and evaporated. The residue was chromatographed on a silica gel column with hexane–ethyl acetate (6 : 1 to 5 : 1) as the eluent to give alcohol **20** (200 mg, 66% based on acetate **18**) as a colorless oil (Found: C, 69.3; H, 10.2. $C_{17}H_{30}O_2Si$ requires C, 69.3; H, 10.3%); $[\alpha]_D^{19}$ +19.0 (*c* 0.87, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3350 (OH); δ_H(250 MHz) 0.06 (3 H, s, SiMe), 0.18 (3 H, s, SiMe), 1.02 (9 H, s, Bu^t), 1.21–2.07 (4 H, m, CH_2), 1.69 (3 H, s, Me), 3.57 (2 H, t, *J* 6.5, C*H*$_2$OH) and 7.14–7.57 (5 H, m, ArH).

To an ice-cold solution of the alcohol **20** (153 mg, 520 μmol) in pyridine (5.0 cm^3) was added toluene-*p*-sulfonyl chloride (210 mg, 1.10 mmol) portionwise and the mixture was stirred at 0 °C overnight. The reaction was quenched with ice-cold 4 mol dm^{-3} HCl and the mixture was extracted with chloroform. The extracts were washed successively with 4 mol dm^{-3} HCl, saturated aqueous $NaHCO_3$ and brine, dried, and evaporated. The residue was purified by column chromatography on silica gel with hexane–benzene (1 : 1) as the eluent to give spectrometrically pure tosylate **21** (190 mg, 82%) as a colorless oil, δ_H(250 MHz) 0.02 (3 H, s, SiMe), 0.12 (3 H, s, SiMe), 0.97 (9 H, s, Bu^t), 1.24–1.50 (1 H, m, CH_2), 1.63 (3 H, s, Me), 1.68–1.95 (3 H, m, CH_2), 2.49 (3 H, s, ArMe), 3.94 (2 H, t, *J* 6.4, C*H*$_2$OTs), 7.20–7.50 (7 H, m, ArH) and 7.71–7.88 (2 H, m, ArH).

The Gilman reagent was prepared by addition of methyllithium (1.5 mol dm^{-3} in diethyl ether; 5.6 cm^3, 8.4 mmol) to an ice-cold suspension of CuI (802 mg, 4.21 mmol) in diethyl ether (2.0 cm^3). To the cold solution was added a solution of the tosylate **21** (190 mg, 423 μmol) in diethyl ether (4 cm^3) over a period of 5 min and the mixture was stirred at 0 °C for 30 min. The reaction was quenched with saturated aqueous NH_4Cl and the mixture was extracted with chloroform. The extracts were washed with water and then brine, dried and evaporated. The residue was purified by column chromatography on silica gel with hexane as the eluent to give compound **22** (105 mg, 85%) as a colorless oil (Found: C, 73.4; H, 11.3. $C_{18}H_{32}OSi$ requires C, 73.9; H, 11.0%); $[\alpha]_D^{19}$ +16.0 (*c* 1.25, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2940, 1492, 1470, 1446, 1374, 1254, 1171, 1130, 1071, 995, 772 and 698; δ_H(250 MHz) 0.06 (3 H, s, SiMe), 0.17 (3 H, s, SiMe), 0.87 (3 H, t, *J* 6.9, C_3H_6*Me*), 1.02 (9 H, s, Bu^t), 1.07–1.44 (4 H, m, CH_2), 1.65 (3 H, s, Me), 1.66–1.94 (2 H, m, CH_2) and 7.17–7.51 (5 H, m, ArH).

To an ice-cold solution of the silyl ether **22** (75.8 mg, 259 μmol) in THF (1.5 cm^3) was added TBAF (1.0 mol dm^{-3} in THF; 1.28 cm^3, 1.3 mmol) and the mixture was stirred at room temperature for 66 h. The reaction was quenched by successive addition of crushed ice and 2 mol dm^{-3} HCl and the mixture was extracted with chloroform. The extracts were washed successively with saturated aqueous $NaHCO_3$ and brine, dried and evaporated. The residue was chromatographed on a silica gel column with hexane–ethyl acetate (4 : 1) as the eluent to give authentic alcohol (*R*)-**15** (24.5 mg, 53%).

The elution behavior of the sample in HPLC on a Daicel Chiralcel OB with 1% propan-2-ol in hexane as the eluent was identical with that of the slower running major isomer of the alcohol **15** derived from the lactone (+)-**9** of 90% ee, which determined the absolute configuration of the alcohol (+)-**15** to be *R*. Thus, the *R* absolute stereochemistry of the lactone (+)-**9** was established.

Determination of the absolute configurations of diols 10 and 12

Conversion of tosylate 21 into alcohol 24. The tosylate (*R*)-**21** (69.2 mg, 154 μmol) derived from lactone (*R*)-**16** of 99% ee was dissolved in THF (340 mm^3) and the solution was cooled to 0 °C. To the solution was added ethylmagnesium bromide (1.0 mol dm^{-3} in THF; 300 mm^3, 300 μmol) and Li_2CuCl_4 (1.0 mol dm^{-3} in THF; 100 mm^3, 100 μmol) at once and the mixture was stirred at this temperature for 3 h. The reaction was quenched by successive addition of crushed ice and 2 mol dm^{-3} HCl and the mixture was extracted with chloroform. The extracts were washed with saturated aqueous $NaHCO_3$ and then brine, dried and evaporated. The residue was purified by column chromatography on silica gel eluting with hexane to give silyl ether **23** (42.0 mg, 89%) as a colorless oil (Found: C, 74.2; H, 11.5. $C_{19}H_{34}OSi$ requires C, 74.4; H, 11.2%); $[\alpha]_D^{20}$ +15.7 (*c* 0.65, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2935, 1492, 1462, 1254, 1169, 1086, 1003, 833, 771 and 698; δ_H(250 MHz) 0.04 (3 H, s, SiMe), 0.16 (3 H, s, SiMe), 0.86 (3 H, t, *J* 7.0, C_4H_6*Me*), 1.01 (9 H, s, Bu^t), 1.12–1.42 (6 H, m, CH_2), 1.64 (3 H, s, Me), 1.70–1.96 (2 H, m, CH_2) and 7.12–7.62 (5 H, m, ArH).

A mixture of the silyl ether **23** (21.5 mg, 70.1 μmol) and TBAF (1.0 mol dm^{-3} in THF; 210 mm^3, 210 μmol) was stirred at room temperature for 21 h. The reaction was quenched by successive addition of crushed ice and 2 mol dm^{-3} HCl and the mixture was extracted with chloroform. The extracts were washed successively with saturated aqueous $NaHCO_3$ and brine, dried and evaporated. The residue was purified by PLC with hexane–ethyl acetate (4 : 1) as the developer to give authentic alcohol (*R*)-**24** (6.1 mg, 45%) as a colorless oil. The spectral data were identical with those of alcohol **24** obtained from ester (R_a)-**5d** (*vide infra*).

Conversion of ester 5d into alcohol 24. To a solution of the keto ester (R_a)-**5d** (350 mg, 579 μmol) in dichloromethane (29 cm^3) was added dropwise an excess of methylmagnesium bromide (0.88 mol dm^{-3} in diethyl ether; 2.6 cm^3, 2.3 mmol) at −78 °C and the mixture was stirred at this temperature for 5 h. After the reaction had been quenched with distilled water, the mixture was extracted with chloroform and the extracts were dried and evaporated. The crude product was purified by column chromatography on silica gel with benzene–ethyl acetate (4 : 1 to 2 : 1) as the eluent to give hydroxyester **25** (305 mg, 85%) as a colorless oil (Found: C, 77.15; H, 7.0. $C_{40}H_{44}O_6$ requires C, 77.4; H, 7.1%); ν_{max}(neat)/cm^{-1} 3460 (OH) and 1757 (CO); δ_H(250 MHz) 0.69–1.63 (10 H, m, $OCH_2C_2H_4$ and OCO-

$CH_2C_3H_6$), 1.45 (3 H, s, Me), 1.94 (2 H, t, *J* 7.0, $OCOCH_2$), 2.98–3.50 (6 H, m, $CH_2OC_2H_4O$), 3.32 (3 H, s, OMe), 3.83–4.06 (2 H, m, $ArOCH_2$), 7.05–7.58 (13 H, m, ArH) and 7.78–8.10 (4 H, m, ArH).

To an ice-cold solution of **25** (274 mg, 441 μmol) in diethyl ether (9.0 cm^3) was added LAH (44.3 mg, 1.17 mmol) portionwise and the mixture was stirred at 0 °C for 30 min before being quenched with 2 mol dm^{-3} HCl. The mixture was extracted with chloroform and the extracts were dried and evaporated. The residue was purified by column chromatography on silica gel with chloroform–ethyl acetate (5 : 1 to 1 : 1) as the eluent to give levorotatory diol **12** (82.4 mg, 90%), $[a]_D^{18}$ −5.3 (*c* 0.91, $CHCl_3$), 43% ee. To a stirred solution of the diol **12** (53.9 mg, 259 μmol) in pyridine (2.6 cm^3) was added toluene-*p*-sulfonyl chloride (148 mg, 776 μmol) at 0 °C and the mixture was stirred overnight. The reaction was quenched with ice-cold 6 mol dm^{-3} HCl and the resulting mixture was extracted with chloroform. The extracts were washed successively with 2 mol dm^{-3} HCl, water and brine, dried and evaporated to give tosylate **26**, which was used without further purification in the next step.

To a solution of the tosylate **26** in diethyl ether (4.0 cm^3) was added LAH (33.6 mg, 885 μmol) portionwise at 0 °C and the mixture was stirred at this temperature for 1 h. The reaction was quenched by successive addition of ethyl acetate, distilled water and 2 mol dm^{-3} HCl. The mixture was extracted with chloroform and the extracts were dried and evaporated. The residue was purified by PLC with benzene–ethyl acetate (8 : 1) as the developer to give alcohol **24** (35.9 mg, 72% based on diol **12**) as a colorless oil (Found: C, 81.2; H, 10.5. $C_{13}H_{20}O$ requires C, 81.2; H, 10.5%); $[a]_D^{19}$ −2.4 (*c* 1.18, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3415 (OH); δ_H(250 MHz) 0.90 (3 H, t, *J* 6.7, C_4H_8*Me*), 1.05–1.47 (6 H, m, CH_2), 1.62 (3 H, s, Me), 1.71–2.04 (2 H, m, CH_2) and 7.11–7.76 (5 H, m, ArH).

Comparison of the elution behavior of the sample in HPLC on a Chiralcel OB column with 1% propan-2-ol in hexane as the eluent with that of the authentic alcohol (*R*)-**24** derived from tosylate (*R*)-**21** determined the absolute configuration of the major isomer running faster than the minor to be *S*, which established the absolute configuration of the diol **12** as (*S*)-(−). On the other hand, the reaction of the ester (R_a)-**5d** with the Grignard reagent **8a** under the conditions of entry 10 in Table 1 gave levorotatory diol **10** of 82% ee, $[a]_D^{18}$ −5.5 (*c* 1.11, $CHCl_3$). These results determine the absolute configuration of the diol (−)-**10** to be *S*.

Synthesis of (−)-malyngolide

The antipode of the keto ester (R_a)-**3c** was obtained as above by the DCC condensation of chiral auxiliary (S_a)-**1c** with 5-oxo-5-phenylpentanoic acid. To a solution of the keto ester (S_a)-**3c** (450 mg, 780 μmol) in dichloromethane (40 cm^3) was added $MgBr_2{\cdot}OEt_2$ (609 mg, 2.36 mmol) and the mixture was stirred at room temperature for 1 h and then cooled to −78 °C. After 1 h, a quarter aliquot (900 mm^3) of a solution of the Grignard reagent **8c** (1.05 mol dm^{-3} in diethyl ether; 3.60 cm^3, 3.78 mmol) was added dropwise to the mixture. The reaction was monitored by TLC and 900 mm^3 each of the Grignard solution was added to the mixture after 6, 12 and 24 h. The mixture was stirred for a further 6 h before addition of acetone (2.0 cm^3). The mixture was allowed to warm to room temperature, stirred for 2 h and then cooled in an ice bath. To the mixture was added 2 mol dm^{-3} HCl and the resulting mixture was extracted with chloroform. The extracts were dried and evaporated and the residue was chromatographed on a silica gel column eluting with hexane–chloroform (1 : 3) to give lactone **30** (193 mg, 82%) as a colorless oil (Found: C, 79.2; H, 9.9. $C_{20}H_{30}O_2$ requires C, 79.4; H, 10.0%); $[a]_D^{22}$ −27.8 (*c* 0.81, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1736 (CO); δ_H(400 MHz) 0.86 (3 H, t, *J* 6.9, C_8H_{16}*Me*), 1.00–1.13 (1 H, m, CH_2), 1.15–1.32 (12 H, m, CH_2), 1.35–1.46 (1 H, m, CH_2), 1.48–1.65 (1 H, m, CH_2), 1.70–1.80 (1 H, m, CH_2), 1.82–1.94 (2 H, m, CH_2), 1.96–2.08 (1 H, m, CH_2), 2.24–2.33 (1 H, m, CH_2), 2.35–2.50 (2 H, m, $COCH_2$), 7.25–7.32 (3 H, m, ArH) and 7.32–7.41 (2 H, m, ArH). The enantiomeric excess of the lactone **30** was determined to be 97% ee by HPLC analysis on a Daicel Chiralpak AD column (4.6 mm id × 25 cm) with 3% propan-2-ol in hexane as the eluent. On the other hand, by the same procedure as used for the transformation of lactone **31** into malyngolide **36** (*vide infra*), a portion of the sample was transformed into (*S*)-5-hydroxymethyltetradecan-5-olide, $[a]_D^{20}$ −2.2 (*c* 0.51, $CHCl_3$) {lit.,[14] $[a]_D^{19}$ −2.37 (*c* 1.10, $CHCl_3$) for (*S*)-isomer of 100% ee}. This determined the absolute configuration of the lactone (−)-**30** to be *S*.

To a solution of LDA, which had been prepared from diisopropylamine (*d* 0.722; 70 mm^3, 499 μmol) and butyllithium (1.62 mol dm^{-3} in hexane; 310 mm^3, 502 μmol) in THF (500 μm^3), was added a solution of lactone **30** (102 mg, 337 μmol) in THF (2.0 cm^3) at −78 °C and the mixture was stirred for 1 h. To the mixture was added iodomethane (*d* 2.28; 90 mm^3, 1.45 mmol) and HMPA (90 mm^3). After 2 h, the mixture was warmed to −45 °C, stirred overnight and then quenched with saturated aqueous NH_4Cl. The mixture was extracted with diethyl ether and the extracts were dried and evaporated. The residue was purified by column chromatography on silica gel eluting with hexane–chloroform (1 : 1) to give a mixture of epimers **31** and **32** (90.6 mg, 85%) as a colorless oil (Found: C, 79.4; H, 10.4. $C_{21}H_{32}O_2$ requires C, 79.7; H, 10.2%); ν_{max}(neat)/cm^{-1} 1732 (CO); δ_H(400 MHz) 0.86 (3 H, t, *J* 6.9, C_8H_{16}*Me*), 0.98–1.14 (1 H, m, CH_2), 1.15–1.39 (16 H, m, CH_2 and Me), 1.48–1.59 (1 H, m, CH_2), 1.77–1.97 (3 H, m, CH_2), 2.07–2.18 (1 H, m, CH_2), 2.22–2.37 (2 H, m, CH_2 and CH) and 7.24–7.40 (5 H, m, ArH).

The mixture of epimers **31** and **32** (51.6 mg, 163 μmol) were mixed with tetrachloromethane (2.0 cm^3), acetonitrile (2.0 cm^3), distilled water (3.0 cm^3) and $HIO_4{\cdot}2H_2O$ (500 mg, 2.19 mmol) to give a biphasic solution, to which was added $RuCl_3{\cdot}3H_2O$ (7.0 mg, 27 μmol) and the mixture was stirred at 35 °C for 1 d. The cooled mixture was extracted with diethyl ether and the extracts were washed with brine, dried and evaporated. The residue was treated with an excess of diazomethane in diethyl ether at room temperature to give, after purification by PLC with hexane–dichloromethane (1 : 1) as the developer, a mixture of the methyl esters of **33** and **34**. This mixture was boiled with LiI (92.2 mg, 689 μmol) in pyridine (1.0 cm^3) for 8 h. To the cooled mixture was added water and the mixture was acidified by addition of 2 mol dm^3 HCl. The mixture was extracted with diethyl ether and the extracts were washed with water, dried and evaporated. The residue was passed through a silica gel plug with ethyl acetate as the eluent to give a mixture of acids **33** and **34** (27.0 mg, 58% based on the mixture of **31** and **32**) as a colorless oil, δ_H(500 MHz) 0.88 (3 H, t, *J* 6.9, C_8H_{16}*Me*), 1.17–1.34 (15 H, m, CH_2 and Me), 1.52–1.68 (2 H, m, CH_2), 1.75–2.07 (4 H, m, CH_2), 2.18–2.28 (1 H, m, CH_2), 2.43–2.67 (2 H, m, CH_2 and CH) and 8.54 (1 H, br s, OH). The ^{1}H NMR spectrum was identical with that of the authentic sample **33**.[10]

To a solution of the mixture of acids **33** and **34** (38.7 mg, 136 μmol) in diethyl ether (1.0 cm^3) were added triethylamine (*d* 0.726; 20 mm^3, 143 μmol) and ethyl chloroformate (*d* 1.14; 20 mm^3, 210 μmol) at 0 °C and the mixture was stirred at this temperature for 30 min. To the mixture was added $Zn(BH_4)_2$[15] (145 mmol dm^{-3} in diethyl ether; 1.1 cm^3, 160 μmol) and the resulting mixture was stirred for 30 min before being quenched with saturated aqueous NH_4Cl. The mixture was extracted with diethyl ether and the extracts were washed with water, dried and evaporated. The residue was purified by PLC with hexane–ethyl acetate (2 : 1) as the developer to give a 8 : 1 mixture of malyngolide **36** and *epi*-malyngolide **35** (19.0 mg, 52%) as a colorless oil, δ_H(500 MHz) 0.88 (3 H, t, *J* 6.9, C_8H_{16}*Me*), 1.15–1.49 (17 H, m, CH_2 and Me), 1.53–1.84 (4 H, m, CH_2), 1.91–2.07 (2 H, m, CH_2), 2.37–2.55 (1 H, m, CH), 3.48 (8/9 H, d, *J* 12.0, CH_2OH),

3.60 (2/9 H, s, CH_2OH) and 3.65 (8/9 H, d, J 12.0, CH_2OH). The ^{1}H NMR spectrum was composed of the spectra of the authentic samples **35** and **36**.[8f]

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