Synthesis of Optically Active 2-Furylmethanols as Useful Chiral Building Blocks and Its Application to the Synthesis of (5*R*,6*S*)-6-Acetoxyhexadecan-5-olide and (+)-Disparlure[1]

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Kinetic resolution of racemic secondary 2-furylmethanols using catalytic amounts of the titanium(IV)–tartrate complex was achieved successfully, providing optically active 2-furylmethanols (80–>98% ee) and corresponding pyranones. (*S*)-1-(2-Furyl)undecanol (**1f**) was utilised as a chiral building block in the synthesis of (5*R*,6*S*)-6-acetoxyhexadecan-5-olide and (+)-disparlure.

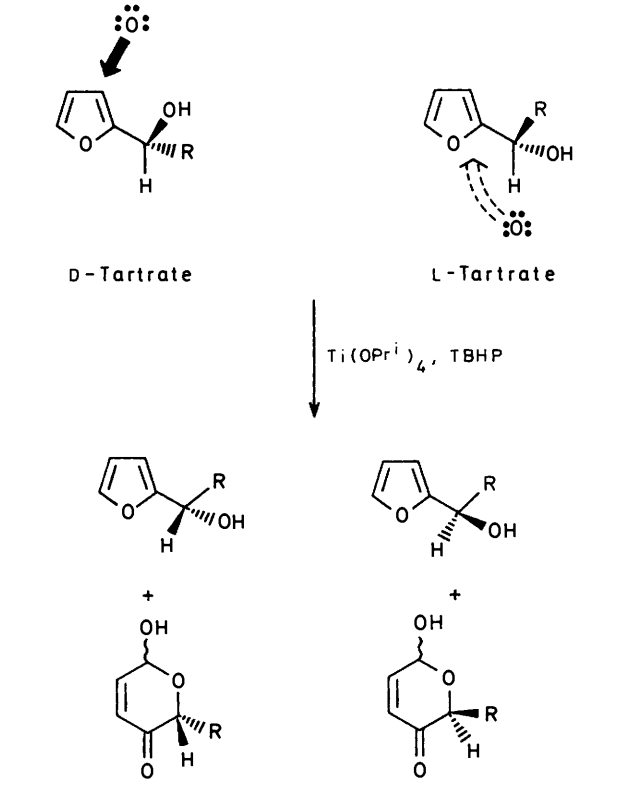
Development of synthesis from chiral building blocks has been one of the most attractive subjects in natural products chemistry, numerous efforts having been devoted to this field.[2] Chiral building blocks should have the advantage of the availability of both their enantiomers and should be versatile themselves. We chose furylmethanols as candidate chiral building blocks because utilisation of furylmethanols has already given results in natural products synthesis.[3] Although there have been many methods to prepare chiral furylmethanols, such as chemical transformation of sugars,[4] optical resolution of racemic furylmethanols,[5] chemoenzymatic techniques,[6] and asymmetric syntheses,[7] some of the methods suffer from limitation in the other possible function on the furylmethanol nucleus.

Here we report a general method for the synthesis of optically active furylmethanols, employing kinetic resolution of the racemates,‡ and its application to the synthesis of (5*R*,6*S*)-6-acetoxyhexadecan-5-olide and (+)-disparlure.

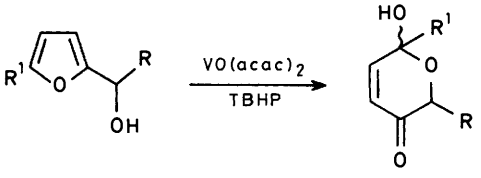
Results and Discussion

Our initial efforts were focused on the preparation of optically active 2-furylmethanols, and relied on kinetic resolution of racemic furylmethanols employing Sharpless' reagent[8] (Scheme 1). Previous studies on Sharpless oxidation of 2-furylmethanols [equation (1)][9] suggest that racemic secondary 2-furylmethanols could be good substrates for the kinetic resolution using the titanium–tartrate complex. In this reaction, the faster reacting isomer would be oxidised preferentially to afford the corresponding pyranone and the unchanged isomer would be recovered in optically active form. Therefore, either (*R*)- or (*S*)-2-furylmethanols could be obtained depending on the chirality of the tartrate used.

With this consideration in mind, we examined the kinetic resolution of 2-furylmethanols as follows. The reactions were performed with catalytic amounts of titanium tetraisopropoxide [$Ti(O^iPr)_4$], L-(+)-di-isopropyl tartrate (L-DIPT) and t-butyl hydroperoxide (TBHP) in the presence of molecular sieves 3 Å, except for entry 6. The results are summarised in Table 1. Reactions proceed smoothly affording, after work-up, the corresponding pyranones (**2a–f**) and the optically active furylmethanols (**1a–f**) with relatively high enantiomeric purity (80–>98% ee). (*R*)-2-Furylmethanols (**1a–e**) were obtained employing L-DIPT (entries 1–5), whereas the use of D-DIPT led to the formation of (*S*)-2-furylmethanol (**1f**) as expected (entry 6). Entry 4 shows an interesting feature of this reaction in that reaction of the furylmethanol (**1d**), having an allyl alcohol moiety, also afforded the corresponding pyranone (**2d**) and (*R*)-(**1d**), respectively.§ This result suggests that Sharpless oxidation of 2-furylmethanol is faster than that of allyl alcohol. The



Scheme 1. Kinetic resolution of 2-furylmethanols employing Sharpless' reagent.



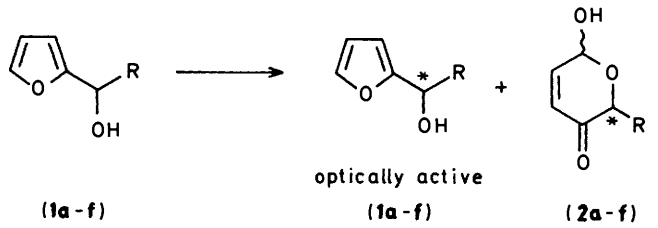
(1)

† Deceased October 11, 1988.

‡ During this research, similar work was published independently by Professor F. Sato.[7h]

§ Recently, we succeeded in the asymmetric synthesis of (+)- acetylphomalactone by employing (*S*)-(**2d**) prepared from the catalytic kinetic resolution of the racemate at <50% conversion: T. Kametani, Y. Tatsuzaki, M. Tsubuki, and T. Honda, *Heterocycles*, 1989, **29**, 1247.

Table 1. Catalytic kinetic resolution of 2-furylmethanols.[a]



Entry	Racemic (1a–f) R	Temp. (°C)	Time (h)	Optically active (1a–f)[b] Yield (%)[c]	% ee[d]	$[\alpha]_D^{25}$ (c, $CHCl_3$)	Abs.	(2a–f) Yield (%)[c]
1	(1a) Me	−20	5	36	80	+17.4° (1.78)	R	38
2	(1b) Et	−20	3.5	32	95	+12.6° (2.09)	R	42
3	(1c) Bu	−35	6	43	94	+9.2° (1.07)	R	46
4	(1d) CH = CHMe	−30	7	32	82[e]	−40.4° (1.95)	R	52
5	(1e) cyclohexyl	−25	7	44	>98[f]	+20.0° (1.19)	R	52
6	(1f) $C_{10}H_{21}$	−25	4	44	>98	−9.6° (2.49)	S[g]	51

[a] All reactions were carried out with 10% $Ti(O^iPr)_4$, 15% L-(+)-DIPT, and 0.7 mol equiv. of TBHP–iso-octane in the presence of 3 Å molecular sieves, except as noted. [b] All isolated 2-furylmethanols had the depicted (*R*) stereochemistry, except (**1f**). [c] Isolated yields. [d] Determined by 400 MHz ^1H NMR analysis of the corresponding MTPA ester. [f] >98% ee indicates that the other enantiomer was not detectable by ^1H NMR spectroscopy. [e] Determined by 400 MHz ^1H NMR analysis of the MTPA ester of 2-furyl(propyl)methanol after hydrogenation of optically active (**1d**) because of the instability of the product on reaction with MTPA chloride. [g] D-(−)-DIPT was employed.

absolute configuration of the kinetically resolved furylmethanols (**1a–f**) was deduced from either comparison of their optical rotations with authentic specimens or their conversion into known compounds.

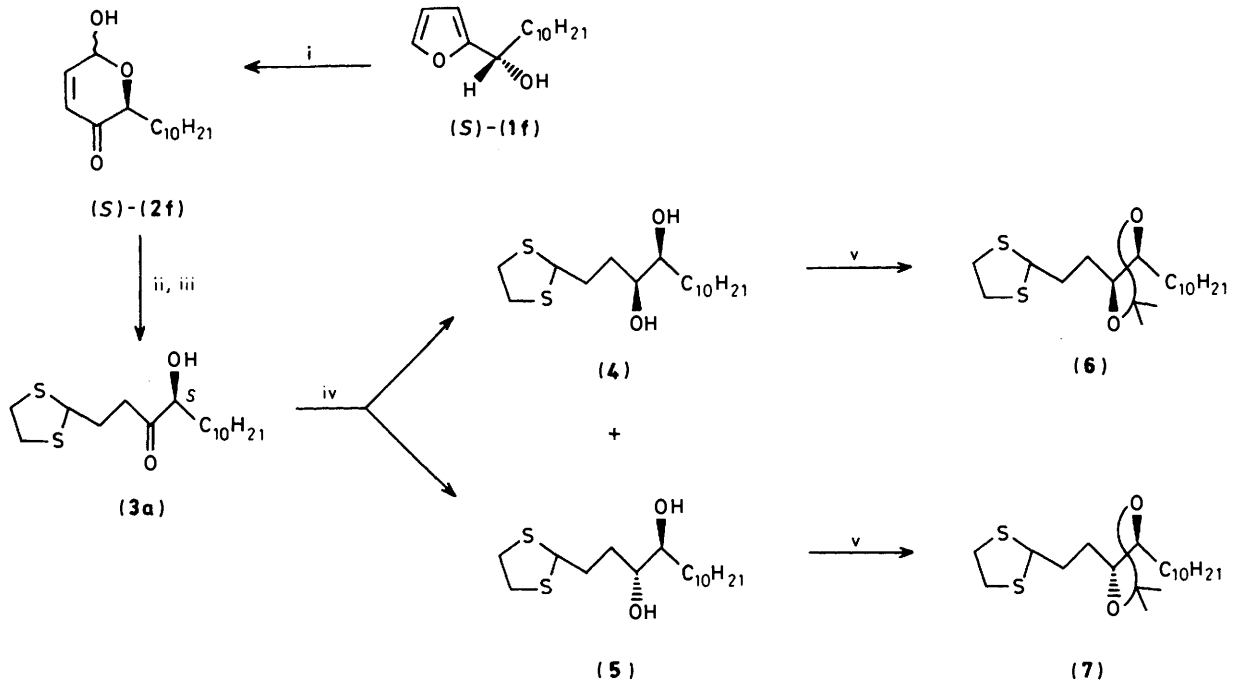
We then turned our attention to the utilisation of optically active furylmethanols in natural products synthesis.[10] Employing (*S*)-(**1f**) obtained above, we embarked on the synthesis of (5*R*,6*S*)-6-acetoxyhexadecan-5-olide (**11**),[11] an oviposition attractant pheromone of the mosquito *Celux pipens fatigans*, and (+)-disparlure (**15**),[12] a pheromone of the gypsy moth (*Porthetria dispar*). For their syntheses stereoselective construction of 1,2-*syn* and -*anti* diol functionalities could be a crucial step. Both the diols (**4**) and (**5**) were prepared as follows (Scheme 2). Treatment of (*S*)-(**1f**) with *N*-bromosuccinimide (NBS)[13] in aqueous tetrahydrofuran (THF) afforded quantitatively the corresponding pyranone (*S*)-(**2f**), whose catalytic hydrogenation (10% palladium on carbon) followed by acetalisation of the resulting lactol gave the thioacetal (**3a**) in 77% overall yield. Stereoselective reduction of the α-alkoxyketones (**3**) was investigated under various conditions[14] and the results are summarised in Table 2. Zinc borohydride reduction[14a,c] of acyloins (**3a**) and (**3c**) in ether proceeded with high diastereoselectivity, especially in entry 12, yielding the *anti* product. This *anti* selectivity can be rationalised by assuming the Cram's chelation model as a transition state. When the *t*-butyldiphenylsilyl ether (**3b**) was reduced with 'ate' complexes such as Red-Al[14a] and L-Selectride[14d] (entries 7–10), diverse selectivity occurred, preferentially affording the Cram product (**4**). It is of interest that sodium borohydride reduction of acyloin (**3a**) produced the *syn* diol (**4**) with moderate selectivity. Thus, either *syn* or *anti* diol was efficiently prepared by the combination of the proper reducing agents and alcohol protecting groups. Mixtures of *syn* and *anti* diols (**4**) and (**5**) were easily separated as the corresponding acetonides (**6**) and (**7**), which were next used for further reactions.

Synthesis of (5*R*,6*S*)-6-acetoxyhexadecan-5-olide was accomplished as outlined in Scheme 3. Hydrolysis[15] of the thioacetal (**7**) with red mercury(II) oxide and boron trifluoride–diethyl ether gave the aldehyde (**8**), which was treated with 2-lithio-2-trimethylsilyl-1,3-dithiane to afford the ketene thioacetal (**9**). Treatment of compound (**9**) with mercury(II) chloride[16] in aqueous methanol gave a mixture of the resulting dihydroxy carboxylic acid and the hydroxy lactone (**10**), which without separation was subjected to lactonisation to furnish (5*R*,6*S*)-(**10**) in 50% overall yield. The optical rotation of compound (**10**), $[\alpha]_D^{22}$ −12.5° ($CHCl_3$), is in agreement with literature values (−12.37°[11f], −12.5°[11b,d]), thus confirming the absolute configuration of the kinetically resolved alcohol (**1f**) to be *S*. Acetylation of the alcohol (**10**) has already been accomplished by several groups,[11b,d–g,i,j] and this constitutes a synthesis of (5*R*,6*S*)-6-acetoxyhexadecan-5-olide (**11**).

Compound (**6**) was next converted into the hydroxy lactone (**14**), the intermediate for synthesis of (+)-disparlure, as follows (Scheme 4). Hydrolysis of the thioacetal (**6**) followed by oxidation[17] of the aldehyde (**12**) with sodium chlorite gave the carboxylic acid (**13**) in 86% yield from (**6**). Finally, deprotection of the acetonide (**13**) in aqueous acetic acid and subsequent lactonisation afforded the hydroxy lactone (**14**), whose optical rotation, $[\alpha]_D^{25}$ +25.76° ($CHCl_3$), agreed reasonably with the literature value {$[\alpha]_D$ +29.2°}.[12a]* The *anti* acetonide (**8**) was also converted in the same sequence, *via* the carboxylic acid (**16**), into the lactone (**17**), $[\alpha]_D^{23}$ −13.72° ($CHCl_3$){lit.,[12a] its enantiomer: $[\alpha]_D$ +14.8°},* in 78% overall yield. The enantiomeric excesses of both lactones (**14**) and (**17**) were determined on the basis of 270 MHz ^1H NMR analysis for the corresponding MTPA† esters, which indicated the optical purities of lactones (**14**) and (**17**) to be >98%. Since compound (**14**) was converted into (+)-disparlure (**15**),[12a] this constitutes a synthesis of (+)-disparlure.

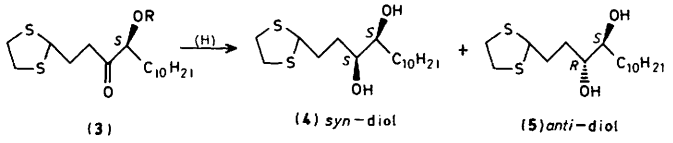
In summary, we have developed a new method for the preparation of optically active 2-furylmethanols employing catalytic amounts of the titanium–tartrate complex. The absolute configuration of the kinetically resolved 2-furylmethanols could be predicted by the chirality of the tartrate used. Utilisation of (*S*)-(**1f**) was accomplished in the synthesis of (5*R*,6*S*)-5-acetoxyhexadecan-5-olide and (+)-disparlure. Further exploration of the synthetic utility of optically active 2-furylmethanols is currently in progress.

* S. Marumo and co-workers reported that the lactones obtained from (*S*)-glutamic acid were contaminated with 5.8% of their enantiomers.[12a]
† α-Methoxy-α-trifluoromethylphenylacetate.



Scheme 2. *Reagents and conditions*: i, NBS, aq. THF; ii, H_2, 10% Pd–C, AcOEt; iii, $HSCH_2CH_2SH$, $BF_3{\cdot}OEt_2$, CH_2Cl_2; iv, H, see Table 2; v, 2,2-dimethoxypropane, acetone, PTSA.

Table 2. Stereoselective reduction of α-alkoxyketones (**3**).



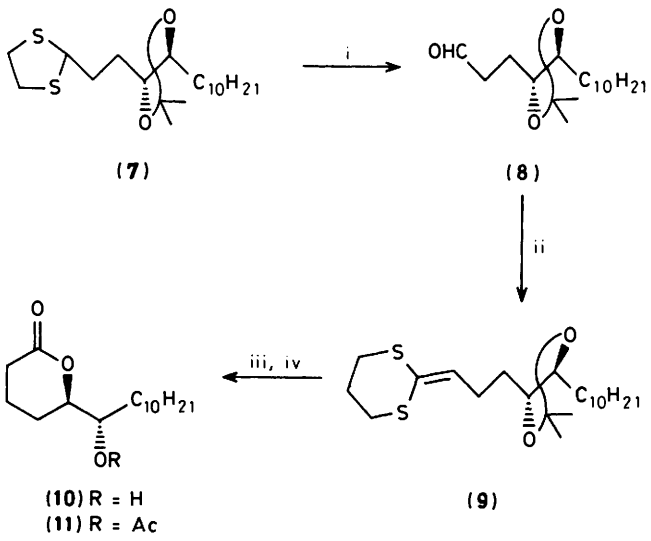
Entry	(3a–c)	Reaction conditions [H]	Solvent	Temp. (°C)	*syn*/*anti* (Ratio)[a]	Yield[b] (%)
1	(3a) R = H	$NaBH_4$	MeOH	0	75/25	86
2				−30	84/16	82
3			MeOH–CH_2Cl_2	−78	77/23	99
4		$Zn(BH_4)_2$	Et_2O	0	19/81	92
5				−30	18/82	87
6		$LiAlH_4$	Et_2O	−30	26/74	83
7	(3b) R = $SiPh_2Bu^t$	$LiAlH_4$	THF	−35	87/13	60
8		Red-Al	Toluene	−78	88/12	75
9		Bu^i_3Al	Pentane	18	42/58	36
10		L-Selectride	THF	−78	93/7	42
11	(3c) R = CH_2OCH_2Ph	$LiAlH_4$	Et_2O	−10	41/59[c]	99
12		$Zn(BH_4)_2$	Et_2O	−30	<2/>98[c]	99

[a] Based on 270 MHz ^1H NMR analysis of the corresponding acetonides unless otherwise mentioned. [b] Isolated yields as the acetonides, except entries 11 and 12. [c] Determined by 270 MHz ^1H NMR analysis of the crude products.

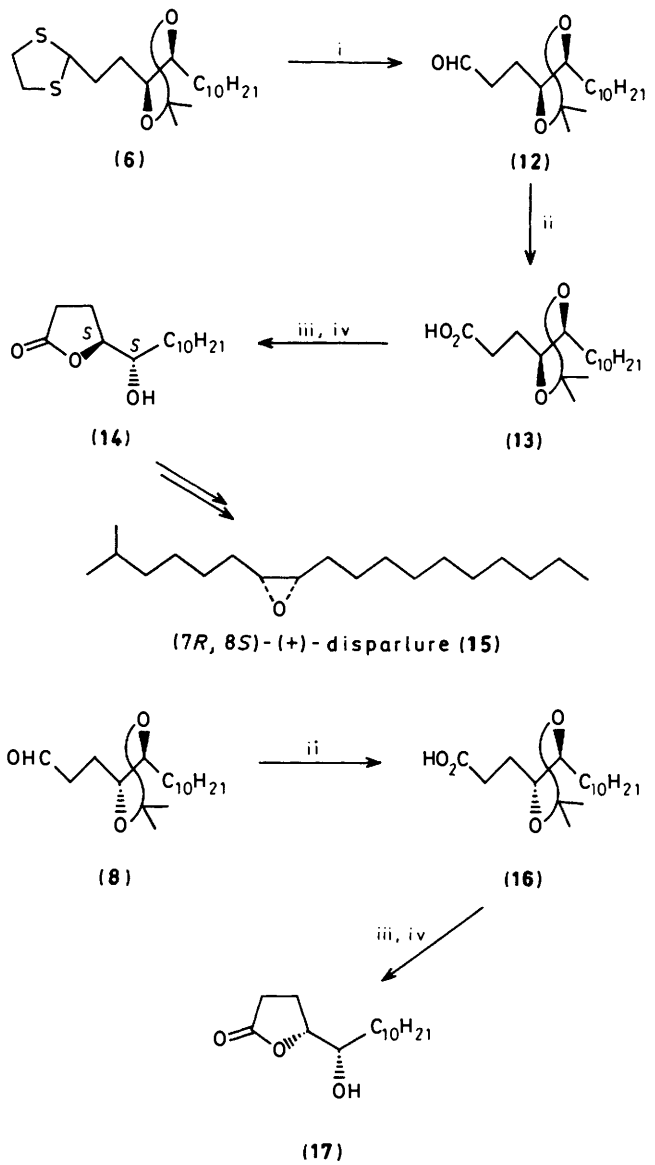
Experimental

M.p.s were measured with a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded on a Hitachi 260-10 spectrophotometer. ^1H NMR spectra were obtained for solutions in $CDCl_3$ on a JEOL PMX-60, GSX-270, or GX-400 instrument, and chemical shifts are reported in ppm on the δ scale from internal Me_4Si. Mass spectra were measured with a JEOL HMS D-300 spectrometer. Column chromatography was carried out on Wakogel C-200 (silica gel). The racemic secondary 2-furylmethanols used in this experimental were prepared by either reaction of the appropriate Grignard reagents to 2-furaldehyde or treatment of 2-lithiofuran to the aldehydes according to conventional methods.[18] L- or D-DIPT, $Ti(O^iPr)_4$, and 3M-TBHP in 2,2,4-trimethylpentane were used as received from Aldrich Chemical Co. Dichloromethane (CH_2Cl_2) was distilled over P_2O_5 and stored over activated molecular sieves 3 Å. All new compounds described in the Experimental section were homogeneous on TLC.

General Procedure for Mosher Ester Analyses.[19]—A solution



Scheme 3. *Reagents and conditions:* i, HgO, BF_3·OEt_2, aq. THF; ii, 2-lithio-2-trimethylsilyl-1,3-dithiane, THF; iii, $HgCl_2$, aq. MeOH, 100 °C; iv, benzene, PTSA, 80 °C.



Scheme 4. *Reagents and conditions:* i, HgO, BF_3·OEt_2, aq. THF; ii, $NaClO_2$, KH_2PO_4, 2-methylbut-2-ene, aq. Bu^{t}OH; iii, aq. AcOH, 100 °C; iv, benzene, PTSA, 100 °C.

of the alcohol (10–20 mg) in pyridine (1 ml) was treated with (−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride [(−)-MTPA-Cl] (1.2 mol equiv.). After 12 h at room temperature the reaction was quenched with water and the mixture extracted with ether. The organic layer was washed successively with saturated aqueous potassium hydrogen sulphate, saturated aqueous sodium hydrogen carbonate, and brine, and dried over Na_2SO_4. Evaporation of the solvent gave the crude esters. 270 MHz ^{1}H NMR analysis focused on the benzylic methine proton. The enantiomeric excess was calculated from integration of the signals.

General Notes for Work-up Procedures.—The procedures are described for reactions employing substrate (10 mmol), $Ti(O^iPr)_4$ (1 mmol), L-DIPT (1.5 mmol), and TBHP (7 mmol).

Work-up A. A freshly prepared solution of iron(II) sulphate heptahydrate (0.55 g, 2 mmol) and tartaric acid (1.8 g, 12 mmol) in deionised water (18 ml) was added to the reaction mixture at −20 to −30 °C and the resulting mixture was stirred vigorously without cooling for 30 min until two clear phases appeared. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave the crude product, which was purified by column chromatography on silica gel.

Work-up B. The reaction mixture was poured into a precooled (−20 °C) mixture of acetone (100 ml) and water (2 ml) and stirred vigorously for 10 min. The resulting precipitate was removed by filtration through a pad of Celite, and the filtrate was removed under reduced pressure to give the crude product, which was purified as described above.

General Procedure for the Catalytic Kinetic Resolution of Racemic Secondary 2-Furylmethanols.—To a room temperature solution of the racemic 2-furylmethanol (1 mol equiv.) and L-DIPT (0.15 mol equiv.) in CH_2Cl_2 (0.2M in substrate) were added activated molecular sieves 3 Å (30 wt% based on the 2-furylmethanol), except as noted in Table 1. The stirred mixture was cooled, treated with $Ti(OPr^i)_4$ (0.1 mol equiv.), and stirred for 30 min at the same temperature. The reaction mixture was treated with a solution of TBHP in 2,2,4-trimethylpentane (3.0 M; 0.7 mol equiv.) and was stirred under the conditions shown in Table 1. After more than 50% conversion (monitored by ^{1}H NMR analysis), the reaction was quenched as described above.

Catalytic Kinetic Resolution of 1-(2-*Furyl*)*ethanol* (**1a**).—The reaction was performed on an 18 mmol scale (2.0 g). After 5 h, work-up A as described above provided compound (*R*)-(**1a**) (0.728 g, 36.4%); $[\alpha]_D^{25}$ +17.4° (*c* 1.78 in $CHCl_3$){lit.,[7h] $[\alpha]_D^{25}$ + 20.8° ($CHCl_3$)}, 80% ee by Mosher ester analysis, and the corresponding (*S*)-pyranone (**2a**) (0.869 g, 38.0%). Spectral data of kinetically resolved (**1a**) and (**2a**) were identical with those reported for the racemates.[7g,18b]

Catalytic Kinetic Resolution of 1-(2-*Furyl*)*propan*-1-*ol* (**1b**).—The reaction was performed on a 16 mmol scale (2.0 g). After 3.5 h, work-up A provided compound (*R*)-(**1b**) (0.64 g, 32.0%); $[\alpha]]_D^{25}$ +12.6° (*c* 2.09 in $CHCl_3$), 95% ee by Mosher ester analysis, and (*S*)-pyranone (**2b**) (0.94 g, 41.9%). Spectroscopic

data of kinetically resolved (**1b**) and (**2b**) were identical with those of the racemates.[20]

Catalytic Kinetic Resolution of 1-(2-*Furyl*)*pentan*-1-*ol* (**1c**).—The reaction was performed on a 14 mmol scale (2.0 g). After 7 h, work-up A provided compound (*R*)-(**1c**) (0.86 g, 43.2%); $[\alpha]_D^{25}$ +9.2° (*c* 1.07 in $CHCl_3$), 94% ee by Mosher ester analysis, and (*S*)-pyranone (**2c**) (1.17 g, 52.3%). Spectroscopic data of (*R*)-(**1c**) were identical with those of the racemate.[18c]

Catalytic Kinetic Resolution of (E)-1-(2-*Furyl*)*but*-2-*en*-1-*ol* (**1d**).—The reaction was performed on an 11 mmol scale (1.5 g). After 7 h, work-up B as described above provided compound (*R*)-(**1d**) (0.49 g, 32.4%); $[\alpha]_D^{25}$ −40.4° (*c* 1.95 in $CHCl_3$); δ ($CDCl_3$) 1.76 (3 H, d, *J* 4.9 Hz, Me), 2.11 (1 H, d, *J* 4.3 Hz, OH), 5.15 (1 H, t, *J* 4.9 Hz, C*H*OH), 5.7–5.9 (2 H, m, olefinic H), 6.22 (1 H, d, *J* 3.7 Hz, 3-H), 6.32 (1 H, dd, *J* 1.8 and 3.7 Hz, 4-H), and 7.38 (1 H, d, *J* 1.8 Hz, 5-H); *m/z* 138 (M^+, 138.0679. $C_8H_{10}O_2$ requires *M*, 138.0679), and (2S)-6-*hydroxy*-2-[(E)-*prop*-1-*enyl*]-6H-*pyran*-3(2H)-*one* (**1d**) (0.87 g, 52.0%) as an oil; ν_{max}($CHCl_3$) 3 280 and 1 690 cm^{-1}; δ($CDCl_3$) 1.77 (3 H, br d, *J* 4.5 Hz, Me), 4.53 and 4.93 (1 H, each br d, *J* 6.0 Hz, 2-H), 5.5–5.9 (3 H, m, 6-H and C*H*=C*H*Me), 6.05 (1 H, br d, *J* 10.0 Hz, 4-H), and 6.87 (1 H, dd, *J* 10.0 and 3.0 Hz, 5-H); *m/z* 154 (M^+) (Found: M^+, 154.0632. $C_8H_{10}O_3$ requires *M*, 154.0630). Owing to its instability, the enantiomeric excess of (*R*)-(**1d**) was determined to be 82% ee from ^1H NMR analysis of the Mosher ester of (*R*)-1-(2-furyl)butan-1-ol obtained by hydrogenation.

Catalytic Kinetic Resolution of Cyclohexyl-2-*furylmethanol* (**1e**).—The reaction was performed on an 11 mmol scale (2.0 g). After 7 h, work-up A provided compound (*R*)-(**1e**) (0.89 g, 44.3%); $[\alpha]_D^{25}$ +20.0° (*c* 1.19 in $CHCl_3$), >98% ee by Mosher ester analysis; δ($CDCl_3$) 0.93–2.03 (12 H, m, C_6H_{11} and OH), 4.1–4.5 (1 H, m, C*H*OH), 6.07–6.37 (2 H, m, 3- and 4-H), 7.30 (1 H, d, *J* 1.0 Hz, 5-H), and (2*S*)-2-cyclohexyl-6-hydroxy-6*H*-pyran-3(2*H*)-one (**2e**) (1.13 g, 52.1%) as an oil; δ($CDCl_3$) 1.0–2.5 (11 H, m, C_6H_{11}), 2.87 (1 H, d, *J* 5.0 Hz, OH), 4.30 (1 H, d, *J* 3.0 Hz, 2-H), 5.5–5.7 (1 H, m, 6-H), 6.00 (1 H, d, *J* 10.5 Hz, 4-H), and 6.80 (1 H, dd, *J* 10.5 and 3.0 Hz, 5-H).

Catalytic Kinetic Resolution of 1-(2-*Furyl*)*undecan*-1-*ol* (**1f**) *with* D-*DIPT*.—The reaction was performed with D-DIPT on a 20 mmol scale (4.76 g). After 4 h, work-up A provided compound (*S*)-(**1f**) (2.08 g, 43.7%); $[\alpha]_D^{25}$ −9.6° (*c* 2.49 in $CHCl_3$), >98.5% ee by Mosher ester analysis, and (2*R*)-2-decyl-6-hydroxy-6*H*-pyran-3(2*H*)-one (**2f**) (2.57 g, 50.5%) as an amorphous solid, m.p. 66–67 °C (from hexane–ethyl acetate); ν_{max}($CHCl_3$) 3 300 and 1 680 cm^{-1}; δ($CDCl_3$) 0.90 (3 H, t, *J* 7.1 Hz, Me), 1.30 (16 H, br s, 8 × CH_2), 3.95–4.75 (2 H, m, 2-H and OH), 5.7–5.8 (1 H, m, 6-H), 6.12 (1 H, distorted d, *J* 10.0 Hz, 4-H), 6.98 (1 H, dd, *J* 10.0 and 4.0 Hz, 5-H). Spectroscopic data of (*S*)-(**1f**) were identical with those of the racemate.[18d]

(2S)-2-*Decyl*-6-*hydroxy*-6H-*pyran*-3(2H)-*one* (**2f**).—To a solution of the kinetically resolved alcohol (*S*)-(**1f**) (395 mg, 1.66 mmol) in 80% aqueous THF (7 ml) at 0 °C was added portionwise NBS (295 mg, 1.66 mmol) and the reaction mixture was stirred for 1 h at the same temperature, then was washed successively with 10% aqueous potassium iodide (1 ml), saturated aqueous sodium thiosulphate (1 ml), and saturated aqueous sodium hydrogen carbonate (1 ml), and the product was extracted with CH_2Cl_2. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure, yielding the crude product. Purification of the crude product by column chromatography on silica gel (15 g) with hexane–ethyl acetate (85:15) as eluant gave the pyranone (**2f**) (393 mg, 93.2%) as an amorphous solid, m.p. 65–66.5 °C (from hexane–ethyl acetate). Spectroscopic data of (2*S*)-(**2f**) were identical with those of its enantiomer (2*R*)-(**2f**).

(5S)-1,1-(*Ethylenedithio*)-5-*hydroxypentadecan*-4-*one* (**3a**).—A suspension of (2*S*)-(**2f**) (290 mg, 1.14 mmol) and 10% palladium on carbon (40 mg) in ethyl acetate (10 ml) was shaken in a hydrogen atmosphere for 1 h. After removal of the catalyst, the solvent was evaporated off to give the ketone. The crude product was used for the next reaction without further purification because of its instability.

To a solution of the crude product in dry CH_2Cl_2 (5 ml) at 0 °C was added ethanedithiol (160 mg, 1.7 mmol) containing a catalytic amount of boron trifluoride–diethyl ether. The mixture was stirred for 2 h at the same temperature. After being quenched with water (1 ml), the resulting mixture was extracted with ethyl acetate. The organic layer was washed successively with 0.5M-sodium hydroxide and saturated aqueous ammonium chloride and dried (Na_2SO_4). Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel (15 g) with hexane and ethyl acetate (94:6) as eluant to afford the dithioacetal (**3a**) (310 mg, 81.8%) as an oil; $[\alpha]_D^{25}$ +32.33° (*c* 1.6 in $CHCl_3$); ν_{max}($CHCl_3$) 3 470, 2 850, and 1 750 cm^{-1}; δ($CDCl_3$) 0.85 (3 H, t, *J* 6.8 Hz, Me), 1.28 (16 H, br s, 8 × CH_2), 2.0–2.4 (2 H, m, 2-H), 2.47–2.88 (2 H, m, 3-H), 3.22 (4 H, s, SCH_2CH_2S), 3.25–3.47 (1 H, m, OH), 3.95–4.28 (1 H, m, 5-H), and 4.50 (1 H, t, *J* 6 Hz 1-H); *m/z* 332 (M^+) (Found: M^+, 332.1844. $C_{17}H_{32}O_2S_2$ requires *M*, 332.1844).

Reduction of Compound (**3a**).—*With sodium borohydride* (*entry* 1). To a stirred solution of compound (**3a**) (27 mg, 0.081 mmol) in methanol (1 ml) at 0 °C was added sodium borohydride (3.1 mg, 0.081 mmol) and the reaction mixture was stirred for 1 h. After quenching with water, the product was isolated by extraction (ethyl acetate). The extract was dried over Na_2SO_4, and the solvent was evaporated off to give the crude product. A solution of the product in acetone (2 ml) and 2,2-dimethoxypropane (0.5 ml) containing a catalytic amount of toluene-*p*-sulphonic acid (PTSA) was stirred for 1 h at room temperature. The reaction mixture was diluted with ethyl acetate, and the organic layer was washed with brine and dried (Na_2SO_4). Evaporation of the solvent gave a crude oil, which was purified by column chromatography on silica gel (10 g) with hexane–ethyl acetate (96:4) as eluant to give the acetonides (**6**) and (**7**) (26 mg, 86%) as a mixture. The ratio of the acetonides was determined from ^1H NMR analysis to be 75:25, respectively.

With sodium borohydride (*entry* 2). The reaction was performed on the same scale as described in entry 1 at −30 °C. Acetonisation of the crude product afforded a mixture of acetonides (**6**) and (**7**) in the ratio 84:16 in 82% yield.

With sodium borohydride (*entry* 3). To a solution of compound (**3a**) (18.9 mg, 0.057 mmol) in methanol (1 ml) and CH_2Cl_2 (1 ml) at −78 °C was added sodium borohydride (8 mg, 0.21 mmol) and the reaction mixture was stirred for 2.5 h at the same temperature. Work-up as described in entry 1 gave acetonides (**6**) and (**7**) (21.1 mg, 99%) in the ratio 77:23.

With zinc borohydride (*entry* 4). To a stirred solution of compound (**3a**) (88 mg, 0.265 mmol) in anhydrous ether (2 ml) at 0 °C was added 0.12M-zinc borohydride in ether (1.1 ml, 0.132 mmol) and the reaction mixture was stirred for 1 h at the same temperature. Work-up as described in entry 5 provided a mixture of the acetonides (**6**) and (**7**) in the ratio 19:81 in 92% yield.

With zinc borohydride (*entry* 5). To a solution of compound (**3a**) (273 mg, 0.83 mmol) in anhydrous ether (8 ml) at −30 °C was added 0.12M-zinc borohydride in ether (4 ml, 0.48 mmol). The mixture was stirred for 8 h at room temperature. After quenching with water (2 ml) and 25% aqueous acetic acid (3 ml), the resulting mixture was extracted with ethyl acetate.

The extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent gave the diol. A solution of the crude product and PTSA (100 mg, 0.53 mmol) in acetone (10 ml) was stirred for 2.5 h at room temperature. After addition of saturated aqueous sodium hydrogen carbonate (1 ml), removal of the solvent gave a yellowish oil. The product was extracted with ethyl acetate. The extract was washed with saturated aqueous ammonium chloride and dried (Na_2SO_4). Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel (25 g) with hexane–ethyl acetate (98:2) as eluant to afford (4S,5S)-1,1-(*ethylenedithio*)-4,5-O-*isopropylidenedioxypentadecane* (**6**) (less polar; 47.7 mg, 15.5%) as an oil; $[\alpha]_D^{25}$ −22.4° (*c* 0.64 in $CHCl_3$); δ($CDCl_3$) 0.81 (3 H, t, *J* 6.7 Hz, Me), 1.20 (14 H, br s, 7 × CH_2), 1.30 (6 H, s, CMe_2), 1.35–2.1 (8 H, m, 4 × CH_2), 3.11–3.21 (4 H, m, SCH_2CH_2S), 3.51–3.54 (2 H, m, 4- and 5-H), and 4.45 (3 H, t, *J* 7.3 Hz, 1-H); *m/z* 374 (M^+) (Found: M^+, 374.2314. $C_{20}H_{38}O_2S_2$ requires *M*, 374.2313), and (4R,5S)-1,1-(*ethylenedioxy*)-4,5-O-*isopropylidenedioxypentadecane* (**7**) (more polar; 219.8 mg, 71.5%) as an oil; $[\alpha]_D^{22}$ +11.11° (*c* 1.31 in $CHCl_3$); δ($CDCl_3$) 0.81 (3 H, t, *J* 6.7 Hz, Me), 1.20 (14 H, br s, 7 × CH_2), 1.25 and 1.36 (3 H × 2, each s, CMe_2), 1.60–2.10 (2 H, m, 3-H_2), 3.10–3.20 (4 H, m, SCH_2CH_2S), 3.90–4.00 (2 H, m, 4- and 5-H), and 4.46 (1 H, t, *J* 7.3 Hz, 1-H); *m/z* 374 (M^+) (Found: M^+, 374.2313).

With lithium aluminium hydride (*entry* 6). To a suspension of lithium aluminium hydride (3 mg, 0.079 mmol) in anhydrous ether (1.5 ml) at −30 °C was added a solution of compound (**3a**) (26 mg, 0.078 mmol) in anhydrous ether (1.0 ml) and the reaction mixture was stirred for 1 h at the same temperature, then quenched with 0.25M-sodium hydroxide (1 ml). The precipitate was filtered through a pad of Celite and the filtrate was extracted with ethyl acetate. The extract was washed with brine and dried over Na_2SO_4. Acetonisation and purification as described in entry 1 afforded acetonides (**6**) and (**7**) (24.4 mg, 83%) in the ratio 26:74.

Reduction of Compound (**3b**).—*With lithium aluminium hydride* (*entry* 7). Reduction of compound (**3b**) (63.3 mg, 0.12 mmol), prepared from (**3a**) with t-butyldiphenylsilyl chloride,[21] was performed with lithium aluminium hydride as described in entry 6, except in this case the reaction was carried out in anhydrous THF at −35 °C. Quenching as described in entry 6 afforded the silyl ether, which was treated with 1M-tetrabutylammonium fluoride in THF (0.12 ml, 0.12 mmol) to give the crude diol. Acetonisation and purification as described in entry 1 furnished acetonides (**6**) and (**7**) (26.7 mg, 60%) in the ratio 87:13.

With Red-Al (*entry* 8). To a stirred solution of compound (**3b**) (29.5 mg, 0.056 mmol) in dry toluene (1 ml) at −78 °C was added 3.4M-Red-Al in toluene (0.0165 ml, 0.056 mmol) and the reaction mixture was stirred for 1 h at the same temperature. After quenching with water, the reaction mixture was diluted with ethyl acetate and the precipitate was filtered through a pad of Celite. The organic layer was washed with brine and dried (Na_2SO_4). Evaporation of the solvent gave the silyl ether, whose desilylation, acetonisation, and purification as described in entry 7 afforded acetonides (**6**) and (**7**) (15.7 mg, 75%) in the ratio 88:12.

With tri-isobutylaluminium (*entry* 9). To a stirred solution of compound (**3b**) (39 mg, 0.0735 mmol) in dry pentane (1 ml) was added 0.756M-tri-isobutylaluminium in hexane (0.4 ml, 0.3 mmol) at room temperature and the reaction mixture was stirred for 8 h. Quenching, desilylation, acetonisation, and purification as described in entry 8 afforded acetonides (**6**) and (**7**) (102 mg, 36%) in the ratio 42:58.

With L-*Selectride* (*entry* 10). To a stirred solution of compound (**3b**) (39 mg, 0.0735 mmol) in anhydrous THF (1 ml) at −78 °C was added 1M-L-Selectride in THF (0.11 ml, 0.11 mmol). After being stirred for 1.5 h at −78 °C, the reaction mixture was treated with 0.5M-sodium hydroxide (1.5 ml) and 30% H_2O_2 (0.25 ml) and stirred for 1 h at room temperature. The precipitate was filtered through a pad of Celite and the filtrate was extracted with ethyl acetate. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave the crude product, whose desilylation, acetonisation, and purification as described in entry 7 afforded acetonides (**6**) and (**7**) (11.5 mg, 42%) in the ratio 93:7.

Reduction of Compound (**3c**).—*With lithium aluminium hydride* (*entry* 11). Reduction of the benzyloxymethyl ether (**3c**) (9.9 mg, 0.022 mmol), prepared from compound (**3a**),[22] was performed as described in entry 6, except in this case the reaction mixture was maintained at −10 °C. Quenching as described in entry 6 gave (4S,5S)-1,1-(ethylenedithio)-5-benzyloxymethylpentadecan-4-ol (9.9 mg, 99%) and its (4R,5S)-epimer in the ratio 41:59. The ratio was determined by ^1H NMR analysis of the mixture.

With zinc borohydride (*entry* 12). The reaction was performed on an 11.3 mg (0.025 mmol) scale as described in entry 5 to afford the *anti*-alcohol (11.3 mg, 99%). ^1H NMR analysis of the product showed that none of the *syn*-epimer was detectable.

(4R,5S)-4,5-O-*Isopropylidenedioxypentadecanal* (**8**).—To a suspension of red mercury(II) oxide (191 mg, 0.88 mmol) and boron trifluoride–diethyl ether (0.108 ml, 0.88 mmol) in 15% aqueous THF (2.5 ml) was added a solution of the thioacetal (**7**) (165 mg, 0.44 mmol) in THF (2 ml) in the course of 5 min at room temperature. After being stirred for 1.5 h, the mixture was treated with ether and the precipitated salts were filtered off. The filtrate was washed successively with saturated aqueous sodium carbonate and brine. After drying over Na_2SO_4, the solvent was evaporated off to give a residue, which was purified by column chromatography on silica gel (10 g) with hexane–ethyl acetate (97:3) as eluant to afford the *aldehyde* (**8**) (96.5 mg, 86%) as an oil; $[\alpha]_D^{23}$ +22.69° (*c* 0.61 in $CHCl_3$); ν_{max}($CHCl_3$) 1 730 cm^{-1}; δ($CDCl_3$) 0.88 (3 H, t, *J* 6.1 Hz, Me), 1.29 (14 H, br s, 7 × CH_2), 1.32 and 1.42 (3 H × 2, each s, CMe_2), 1.68–1.77 (2 H, m, 3-H_2), 2.50–2.70 (2 H, m, 2-H_2), 3.98–4.11 (2 H, m, 4- and 5-H), and 9.82 (1 H, s, CHO); *m/z* 298 (M^+) (Found: M^+, 298.2511. $C_{18}H_{34}O_3$ requires *M*, 298.2508).

(4R,5S)-1-[2-(1,3-*Dithianylidene*)]-4,5-O-*isopropylidenedioxypentadecane* (**9**).—To a solution of 2-trimethylsilyl-1,3-dithiane (25 mg, 0.13 mmol) in dry THF (1 ml) was added 1.6M-butyl-lithium (0.065 ml, 0.104 mmol) at 0 °C. After the mixture had been stirred for 15 min at 0 °C, a solution of the aldehyde (**8**) (30 mg, 0.1 mmol) in dry THF (1 ml) was added and the reaction mixture was maintained at −30 °C for 1 h, then for 10 min at 0 °C. Saturated aqueous ammonium chloride was added, the product was extracted with ethyl acetate, and the extract was dried (Na_2SO_4). Evaporation of the solvent gave a residue, whose purifcation by column chromatography on silica gel (10 g) with hexane–ethyl acetate (98.5:1.5) as eluant afforded the ketene thioacetal (**9**) (28.7 mg, 71.3%) as an oil; $[\alpha]_D^{24}$ +7.08° (*c* 0.51 in $CHCl_3$); ν_{max}($CHCl_3$) 2 850 cm^{-1}; δ($CDCl_3$) 0.88 (3 H, t, *J* 6.7 Hz, Me), 1.30 (14 H, br s, 7 × CH_2), 1.33 and 1.43 (3 H × 2, each s, CMe_2), 2.1–2.5 (4 H, m, 2- and 3-H_2), 2.84–2.88 (4 H, t, *J* 6.6 Hz, 2 × SCH_2), 3.95–4.1 (2 H, m, 4- and 5-H), and 5.97 (1 H, t, *J* 7.6 Hz, olefinic H).

(5R,6S)-6-*Hydroxyhexadecan*-5-*olide* (**10**).—A mixture of compound (**9**) (36 mg, 0.09 mmol) and mercury(II) chloride (73 mg, 0.27 mmol) in 8% aqueous methanol (4 ml) was refluxed for 3 h. After removal of the solvent, the residue was diluted with ethyl acetate, precipitated salts were filtered off, and the

filtrate was dried (Na_2SO_4). Evaporation of the solvent gave a crude product, which was used for the next reaction without purification.

A solution of the crude product in benzene (3 ml) containing a catalytic amount of PTSA was refluxed for 1 h. After dilution with ethyl acetate, the organic layer was washed successively with saturated aqueous sodium hydrogen carbonate and brine, and then dried (Na_2SO_4). Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel (15 g) with hexane–ethyl acetate (7:3) as eluant to afford the lactone (**10**) (12.2 mg, 50.1%) as prisms, m.p. 68–69 °C (hexane) (lit.,[11b] 67–68 °C; lit.,[11f] 67–69 °C); $[\alpha]_D^{22}$ −12.49° (*c* 0.208 in $CHCl_3$){lit.,[11b] $[\alpha]_D^{19}$ −12.37° (*c* 1.25 in $CHCl_3$); lit.,[11b,d] $[\alpha]_D$ −12.5° ($CHCl_3$)}. Its spectroscopic data were identical with those reported.[11b,d]

(4S,5S)-4,5-O-*Isopropylidenedioxypentadecanal* (**12**).—The same procedure as for compound (**7**) was applied to the thioacetal (**6**) (43 mg, 0.115 mmol) to afford the *aldehyde* (**12**) (29.8 mg, 87%) as an oil; $[\alpha]_D^{23}$ −25.51° (*c* 0.29 in $CHCl_3$); ν_{max}($CHCl_3$) 1 710 cm^{-1}; δ($CDCl_3$) 0.88 (3 H, t, *J* 6.1 Hz, Me), 1.26 (14 H, br s, 7 × CH_2), 1.36 (6 H, s, CMe_2), 1.60–2.00 (2 H, m, 3-H_2), 2.60–2.70 (2 H, m, 2-H_2), 3.50–3.65 (2 H, m, 4- and 5-H), and 9.81 (1 H, s, CHO); *m/z* 298 (M^+, 298.2504. $C_{18}H_{34}O_3$ requires *M*, 298.2508).

(4S,5S)-4,5-O-*Isopropylidenedioxypentadecanoic Acid* (**13**).—To a stirred solution of the aldehyde (**12**) (12.5 mg, 0.042 mmol) in Bu^tOH (1.5 ml) containing 2-methylbut-2-ene (0.06 ml, 0.57 mmol) was added dropwise a solution of sodium chlorite (28.4 mg, 0.31 mmol) and potassium dihydrogen phosphate (37.6 mg, 0.27 mmol) in water (0.9 ml) during 10 min at room temperature. After being stirred for 30 min, the reaction mixture was evaporated to give a residue. The crude product was extracted with CH_2Cl_2 and the extract was dried over Na_2SO_4. Evaporation of the solvent gave an oil, which was purified by column chromatography on silica gel (10 g) with hexane–ethyl acetate (8:2) as eluant to afford the carboxylic acid (**13**) (13 mg, 99%) as an oil; $[\alpha]_D^{26}$ −25.90° (*c* 1.79 in $CHCl_3$); ν_{max}($CHCl_3$) 3 150 and 1 700 cm^{-1}; δ($CDCl_3$) 0.88 (3 H, t, *J* 6.7 Hz, Me), 1.26 (14 H, br s, 7 × CH_2), 1.37 (6 H, s, CMe_2), 1.70–2.00 (2 H, m, 3-H_2), 2.40–2.70 (2 H, m, 2-H_2), and 3.55–3.70 (2 H, m, 4- and 5-H); *m/z* 298 (M^+ − 15).

(4S,5S)-5-*Hydroxypentadecan*-4-*olide* (**14**).—A solution of the acetonide (**13**) (179.5 mg, 0.57 mmol) in acetic acid (2.25 ml) and water (0.75 ml) was heated at 100 °C for 1 h. Evaporation of the solvent gave the crude product, which was used for the next reaction without further purification.

A solution of the above compound in benzene (5 ml) containing a catalytic amount of PTSA was refluxed for 1 h. After cooling, the reaction mixture was diluted with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel (25 g) with hexane–ethyl acetate (8:2) as eluant to afford the lactone (**14**) (133.4 mg, 91%) as an amorphous solid, m.p. 66–67 °C (from hexane) (lit.,[12a] 66 °C); $[\alpha]_D^{25}$ +25.76° (*c* 1.31 in $CHCl_3$){lit.,[12a] $[\alpha]_D^{20}$ +29.2° (*c* 1.2 in $CHCl_3$)}. Its spectroscopic data were identical with those reported.[12a] The enantiomeric excess of compound (**14**) obtained above was determined to be >98% by Mosher ester analysis.

(4R,5S)-4,5-O-*Isopropylidenedioxypentadecanoic Acid* (**16**).—The same procedure as for compound (**13**) was applied to the aldehyde (**8**) (91.2 mg, 0.306 mmol) to afford the carboxylic acid (**16**) (92 mg, 96%) as an oil; $[\alpha]_D^{27}$ +18.3° (*c* 1.486 in $CHCl_3$); ν_{max}($CHCl_3$) 3 150 and 1 700 cm^{-1}; δ($CDCl_3$) 0.88 (3 H, t, *J* 6.7 Hz, Me), 1.26 (14 H, br s, 7 × CH_2), 1.33 and 1.43 (3 H × 2, each s, CMe_2), 1.60–1.80 (2 H, m, 3-H_2), 2.30–2.70 (2 H, m, 2-H_2), and 4.00–4.20 (2 H, m, 4- and 5-H); *m/z* 298 (M^+ − 15).

(4R,5S)-5-*Hydroxypentadecan*-4-*olide* (**17**).—The same procedure as for the compound (**14**) was applied to the carboxylic acid (**16**) (148.6 mg, 0.47 mmol) to afford the lactone (**17**) (97.6 mg, 81%) as needles, m.p. 63–64 °C (from hexane) (lit.,[12a] its enantiomer: 63.5 °C); $[\alpha]_D^{23}$ −13.72° (*c* 0.976 in $CHCl_3$){lit.,[12a] its enantiomer: $[\alpha]_D^{20}$ +14.8° (*c* 1.2 in $CHCl_3$)}. Its spectroscopic data were identical with those reported.[12a] The enantiomeric excess of compound (**17**) obtained above was determined to be >98% by Mosher ester analysis.

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