Enantioselective Syntheses of Substituted γ-Butyrolactones

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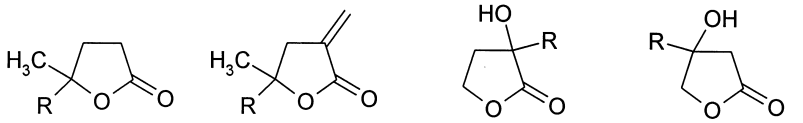
The previously described chiral 2-acyloxathianes **5** (Scheme I) are used in two different enantioselective syntheses of γ-butyrolactones. In one synthesis, Grignard addition, cleavage and reduction to carbinols RR'C(OH)CH_2OH is followed by tosylation, malonate homologation, lactonization, and removal of the carbomethoxy group to give optically active γ-lactones. A modification of this synthesis (Scheme I) leads to optically active α-methylene-γ-lactones.

In the second synthesis, reaction of a bromomagnesium enolate with ketones **5** leads to β-hydroxyesters, which, by appropriate sequences of reduction and cleavage (Scheme II) are converted to optically active α- or β-hydroxy-γ-lactones.

γ-Butyrolactones [(5H)-3,4-Dihydro-2-furanones] and 2-methylene-γ-butyrolactones, many of them optically active, are of wide occurrence in nature. They display a variety of interesting biological activities, such as antitumoral activity[1-6] (albeit often associated with cytotoxicity), allergenic effects,[7,8] inhibition of microbial growth,[9] inhibition of plant growth[10] and both convulsant and anti-convulsant activity.[11] As a result, these compounds have been extensively reviewed in the literature[12] and have been attractive synthetic targets.[12e] Here we report the syntheses of enantioenriched or enantiopure 5,5 disubstituted (5H)-3,4-dihydro-2-furanones **1a** and **1b** and their 3-methylene homologs **2a** and **2b**, and of 3- and 4-hydroxy-(3H)-4,5-dihydro-2-furanones **3a,c** and **4a,c** with additional phenyl or methyl substituents at positions 3 and 4, respectively. The preparations, shown in Schemes I and II, are based on our previously described13 synthesis using a 1,3-oxathiane derived chiral auxiliary.14 Compounds **1a**,[15] **1b**,[16] **2b**[17] and **4c**[18] have previously been synthesized in optically active form. Compounds **2a**,[19] **3a**[20] and **3c**[20a,c,21] have been described as racemates; we have found no previous reference to compound **4a**.

SYNTHESES

Ketones **5** (**a**, R = C_6H_5[13], **b**, R = Me_2CH[22], **c**, R = CH_3[23]) were obtained by addition of the lithium derivative of the parent oxathiane[14] (Ox-H, Scheme I) to RCHO followed by oxidation[13] or, in the case of **5a** and **5b**, by a recently developed[24] synthesis from Ox-Li and R-CN. Addition of methyl Grignard reagent to **5a** and **5b** proceeded in high yield; diastereomer excess (d.e.) of the product was 96% for **6a** and 80% for **6b** (determined by ^{1}H NMR), but **6b** could be purified up to 96% d.e. by chromatography.[22] Cleavage and reduction as previously described[13] yielded carbinols (*S*)-**7a** and (*S*)-**7b**[21] which were converted cleanly to the corresponding primary *p*-toluenesulfonates. Subsequent reaction with dimethyl sodiomalonate gave lactones (*R*)-**8a** and (*R*)-**8b**, presumably via an intermediate epoxide. Heating of **8** with aqueous dimethyl formamide[25] gave the target lactones (*R*)-**1a** and



1a R = C_6H_5 **1b** R = $(CH_3)_2CH$ **2a** R = C_6H_5 **2b** R = $(CH_3)_2CH$ **3a** R = C_6H_5 **3b** R = CH_3 **4a** R = C_6H_5 **4b** R = CH_3

Dedicated to the memory of the late Professor Ta-shue Chou (©P¤j ÓV)

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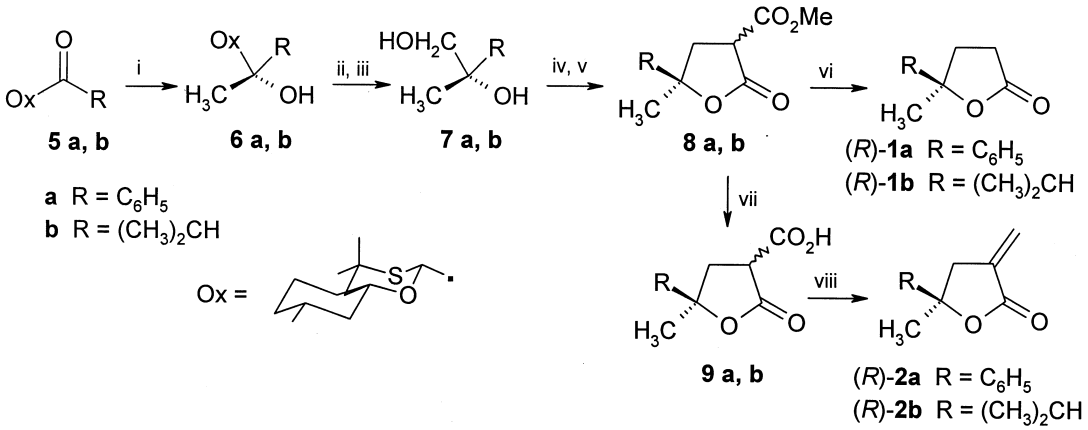
Scheme I



i, CH_3MgBr, THF, - 78° C; ii, NCS, $AgNO_3$, CH_3CN; iii, $NaBH_4$; iv, TsCl, C_5H_5N, 0° C; v, $NaCH(CO_2Me)_2$, MeOH/THF; vi, H_2O/DMF; vii, KOH, H_2O then HCl (aq); viii, CH_2O (aq), Et_2NH, heat

(*R*)-**1b** in one step (decarbalkoxylation). When the acids (*R*)-**9a** and (*R*)-**9b**, obtained by hydrolysis of **8,** were isolated and treated with formaldehyde and diethylamine, methylene lactones (*R*)-**2a** and (*R*)-**2b** were obtained.

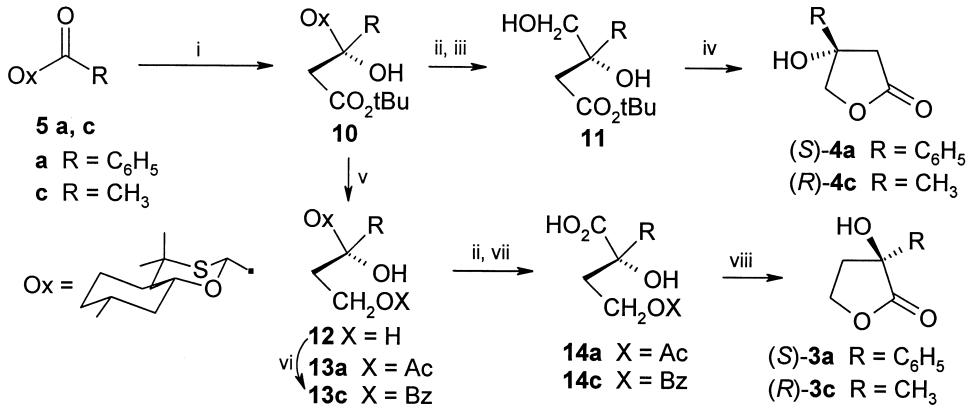
The enantiomer excess (e.e.) of (*R*)-**1a** and (*R*)-**2a** as measured by ^{1}H NMR in the presence of a chiral shift reagent was 96% and 93%, respectively, from oxathiane precursors **6a** and **6b** of 96% d.e., suggesting that there was little or no racemization in the elaboration of **6** to **1a** or **2a**. Accordingly, we assume that the e.e. of **1b** and **2b** was close to that of the starting material **6**, i.e. > 90%. In the case of (*R*)-**1a**[15a] and (*R*)-**1b**[16a] the above values agree reasonably closely with the optical purity determined by comparison of their specific rotations with those reported in the literature.

The second synthesis to be described involves addition of the magnesium enolate of *t*-butyl acetate (Reformatsky reaction of *t*-butyl bromoacetate) to **5** (R = C_6H_5 or Me) (Scheme II). Unfortunately, unlike the earlier studied Grignard additions, this reaction (and that of other enolates studied[27]) was found not to be highly stereoselective.

Perhaps internal chelation of the reagents interferes with chelate formation with the oxathianyl ketone **5** which seems to be essential for high stereoselectivity.[28] The highest diastereoselectivity was 78:22 for R= C_6H_5 (**10a**) and 88:12 for R = CH_3 (**10c**).

The elaboration of addition products **10a** and **10c** to the corresponding β-hydroxy-γ-lactones is summarized in the top row of Scheme II. Ester **10a** was purified to 99% d.e. by

Scheme II



i, $BrCH_2CO_2tBu$, Mg, THF; ii, NCS, $AgNO_3$, CH_3CN; iii, $NaBH_4$; iv, $NaHCO_3$, CH_3OH then HCl/H_2O; v, $LiAlH_4$, Et_2O; vi, Ac_2O, DMAP, CH_2Cl_2 (series **a**) or BzCl, DMAP, Et_3N, CH_2Cl_2 (series **c**); vii, $NaClO_2$, Me_2C=CHMe, KH_2PO_4; viii, NaOH (series **a**), then HCl or K_2CO_3/MeOH (series **c**).

HPLC. Cleavage and reduction (as described earlier[13a]) gave diol ester (*S*)-**11a**. Surprisingly the best method for cleaving this ester was by a suspension of sodium bicarbonate in methanol, which yielded essentially enantiomerically pure β-hydroxylactone (*S*)-**4a** in 78% yield from **11a**. Purification of **10c** by HPLC was less effective and the maximum d.e. achieved for this intermediate was 84%. Further elaboration shown in Scheme II yielded (*R*)-**4c** [via (*R*)-**11c**] of 90% e.e. It appears that some increase in enantiomeric purity occurred during the chromatography of (*R*)-**11a** and/or (*R*)-**4c.**[29]

The second row of Scheme II depicts the conversion of intermediates **10** to α-hydroxy-γ-lactones **3**. Crystalline diol **12a** was obtained by reduction either of diastereomerically pure **10a** (*vide supra*) or of the 78:22 diastereomer mixture followed by recrystallization. Direct cleavage and oxidation (aldehyde to acid) of this material gave lactone **3a** in only 33% yield. We therefore decided to protect the primary hydroxyl group by acetylation to **13a** (silyl protection with TBDMS proved insufficiently robust). Cleavage of **13a** in the usual way[13] followed by chlorite oxidation[30] gave acid (*S*)-**14a** which was converted , by base hydrolysis of the acetate function followed by acidification, to lactone (*S*)-**3a** whose e.e., determined by a chiral shift reagent, was over 98%. The α-methyl analog **3c** was synthesized similarly. In this case, crude **10c** (88:12 diastereomer ratio) was reduced to crystalline **12c** which was purified to 98% d.e. by recrystallization. Because of the low molecular weight and resulting solubility of the acetate intermediates, it proved more advantageous to benzoylate **13c** prior to cleavage and oxidation to (*R*)-**14c**. Hydrolysis of this ester was effected by a suspension of potassium carbonate in methanol; subsequent acidification yielded lactone (*R*)-**3c** with 96% e.e.

EXPERIMENTAL

Nmr spectra were recorded in $CHCl_3$. The d.e. of **6a** and **6b** was calculated based on the integration of the ^{1}H nmr signals of the proton at C(2). The results of the nmr chiral shift experiments with **1a** and **2a** are based on the signals of the methyl groups in ^{1}H NMR. Melting points were observed on an electrothermal melting point apparatus and are uncorrected. The syntheses of **7a**[13a] and **7b**[22] have been reported elsewhere.

(*S*)-2-Phenyl-1-tosyloxy-2-propanol (Tosylate of 7a)

To 317 mg of (*S*)-**7a**[13a] in 2 mL dry pyridine under nitrogen at 0 °C, 530 mg (2.70 mmol) *p*-toluenesulfonyl chloride in 2 mL dry pyridine was added dropwise, stirred over 30 min at 0 °C, then the reaction flask was placed in a refrigerator (4 °C) overnight. After 20 mL Et_2O and 10 mL ice water were added with brief stirring, the organic layer was separated, washed 3 times with 2 N aqueous HCl (5 mL each) followed by saturated aqueous NaCl (5 mL), dried over Na_2SO_4, and concentrated to give 727 mg of tosylate as an oil.

^{1}H NMR: δ 1.54 (s, 3H), 1.92 (bs, 1H), 2.42 (s, 3H), 4.07 (s, 2H), 7.26-7.43 (m, 7H), 7.66-7.71 (m, 2H).

(*R*)-3-Carbomethoxy-5-methyl-5-phenyl-3,4-dihydro(5H)-furan-2-one [(*R*)-8a]

In a two-necked flask equipped with a reflux condenser, sodium metal (80 mg, 3.48 mmol) in one piece was added to 5 mL dry methanol under nitrogen. After all the metal was dissolved, 0.4 mL (3.48 mmol) dimethyl malonate was added dropwise from a separatory funnel. The solution was heated to boiling and 416 mg of the above tosylate in 2mL THF was added dropwise over 30 min. The reaction mixture became darker after the addition. Refluxing was continued for 4 h, then the solvents were removed under vacuum. The residue was treated with saturated aqueous NH_4Cl (10 mL), and the solution extracted 4 times with Et_2O (10 mL each). The combined organic solution was washed with 10 mL saturated aqueous NaCl, dried (Na_2SO_4), and concentrated to give 450 mg of crude liquid product. ^{1}H NMR (2.59-2.97, m, -CH_2-) indicated the presence of (*R*)-**8a**. The crude material was directly used in the following reactions.

(*R*)-3-Carboxy-5-methyl-5-phenyl-3,4-dihydro(5H)furan-2-one [(*R)*-9a]

A solution of 285 mg of (*R*)-**6a** and 0.27 g KOH in 2 mL water was boiled for 4 h. Concentrated hydrochloric acid (2mL) in water (3 mL) was then added, and the solution was extracted 4 times with CH_2Cl_2 (6 mL each). The combined extracts were washed with 6 mL of saturated aqueous NaCl, dried (Na_2SO_4) and concentrated to yield 131 mg of crude liquid product. The proton nmr spectrum showed the presence of two diastereomers of (*R*)-**9a** in a ratio of 65/35. This material was used directly for the next reaction.

^{1}H NMR: δ 1.71 (s, minor), 1.79 (s, major), 2.70-2.94 (m, major + minor), 3.44-3.94 (m, major + minor), 7.23-7.47 (m, major + minor).

(*R*)-3-Methylene-5-methyl-5-phenyl-4,5-dihydro(3H)furan-2-one [(*R)*-2a]

A mixture of 131 mg of crude (*R*)-**9a**, 0.36 mL formaldehyde (37% in water), and 0.7 mL diethylamine was refluxed for 0.5 h. Water (10 mL) was added, and the mixture was extracted 4 times with Et_2O (6 mL each). The combined organic layers were washed with 6 mL aqueous NaCl, dried (Na_2SO_4), and concentrated to yield 111 mg of crude products. Purifica-

tion by flash column chromatography on silica gel with EtAc/hexanes (15/85) gave 63 mg (44% from (*S*)-**7a**) of the pure liquid lactone (*R*)-**9a**. The proton NMR spectrum in the presence of the chiral shift reagent Eu(hfc)$_3$ (hfc = 3-heptaflourobutanoyl camphor) indicated 93 ± 2% e.e.

^{1}H NMR: δ 1.71 (s, 3H), 3.14 (t, J = 2.5 Hz, 2H), 5.62 (t, J = 2.5 Hz, 1H), 6.24 (t, J = 2.8 Hz, 1H), 7.23-7.39 (m, 5H). ^{13}C NMR: δ 30.0 (CH_3), 42.6 (CH_2), 83.9 (C), 122.5 (CH_2), 124.1 (CH), 127.6 (CH), 128.6 (CH), 135.0 (C), 144.5 (C), 169.6 (C). $[\alpha]_D^{20}$ -11.3, $[\alpha]_{578}^{20}$ -12.1, $[\alpha]_{546}^{20}$ -15.5 and $[\alpha]_{436}^{20}$ -44.3 (c = 1.2, $CHCl_3$).

[Lit.[19d] ^{1}H NMR ($CDCl_3$): δ 1.68 (s, 3H), 3.13 (dd, J = 1.0, 3.0 Hz, 2H), 5.69 (dd, J = 1.0, 3.0 Hz, 1H), 6.18 (dd, J = 1.0, 3.0 Hz, 1H), 7.20 (s, 5H). ^{13}C NMR[19a]: δ 30.16 (q), 42.69 (t), 83.98 (s), 122.66 (t), 124.18 (2d), 127.73 (d), 128.68 (2d), 135.09 (s), 144.61 (s), 176.17 (s) for the racemate].

(*R*)-5-Methyl-5-phenyl-3,4-dihydro (5H) furan-2-one [(*R*)-1a]

A solution of 165 mg of (*R*)-**8a**, two droplets of water, and 3 mL DMF was refluxed for 12 h. The reaction mixture was diluted with 20 mL water, and extracted 3 times with Et_2O (6 mL each). The combined ether extracts were washed with 10 mL aqueous NaCl, dried (Na_2SO_4), and concentrated to give 62 mg of crude product which was purified by flash chromatography on silica gel with EtAc/hexanes (30/70) to yield 33 mg (43% from (*S*)-**7a**) of pure liquid (*R*)-**1a**. The proton nmr spectrum in the presence of the chiral shift reagent Eu(hfc)$_3$ showed 96 ± 2% e.e., which agrees with the value of $[\alpha]_D$ compared to that reported in reference 15a.

^{1}H NMR: δ 1.70 (s, 3H), 2.35-2.64 (m, 4H), 7.24-7.37 (m, 5H). ^{13}C NMR: δ 28.8 (CH_2), 29.3 (CH_3), 36.0 (CH_2), 86.8 (C), 124.0 (CH), 127.5 (CH), 128.5 (CH), 144.2 (C), 176.4 (C). $[\alpha]_D^{20}$ + 69.7, $[\alpha]_{578}^{20}$ + 72.7, $[\alpha]_{546}^{20}$ + 81.7 and $[\alpha]_{536}^{20}$ + 141.1 (c = 0.7, $CHCl_3$) [Lit[15a] $[\alpha]_D^{25}$ + 72.4 (c = 1.5, $CHCl_3$); lit.[15b] ^{1}H NMR: δ 1.72 (s, 3H), 2.39-2.71 (m, 4H) 7.27-7.40 (m, 5H). ^{13}C NMR: δ 28.9 (C-2), 29.3 (CH_3), 36.1 (C-3), 86.8 (C-4), 124.0, 127.6, 128.5, 144.2 (C-Ar), 176.3 (C-1)].

(*R*)-3-Carbomethoxy-5-methyl-5-(1′-methyl)ethyl-(3)H-4,5-dihydro-2-furanone [(*R*)-8b]

Crude liquid product (*R*)-**8b** (319 mg) was obtained from 220 mg of (*S*)-**7b**[21] by the procedure described for (*R*)-**8a**. The proton nmr spectrum indicated the presence of two diastereomers in a ratio of 38/62.

^{1}H NMR 0.83-1.09 (m, major + minor), 1.28 (s, major), 1.39 (s, minor), 1.63-2.58 (m, major + minor), and others.

(*R*)-3-Carboxy-5-methyl-5(1-methyl)ethyl-(3H)-4,5-dihydro -2-furanone [(*R*)-9b]

Liquid product (*R*)-**9b** (41 mg, 27% overall from (*S*)-**7b**) was obtained from 172 mg crude (*R*)-**8b** by the procedure described for (*R*)-**9a**. The proton nmr spectrum indicated two diastereomers in a ratio of 41/59.

^{1}H NMR: δ 0.91-1.01 (m, major + minor), 1.30 (s, major), 1.40 (s, minor), 1.78-2.03 (m, major + minor), 2.16-2.55 (m, major + minor), 3.70-3.84 (m, major + minor), 8.7 (bs). ^{13}C NMR: major: δ 16.7 (CH_3), 17.0 (CH_3), 21.2, (CH_3), 35.1 (CH_2), 37.3 (CH), 46.9 (CH), 89.3 (C), 171.3 (C), 172.2 (C); minor: 16.9 (CH_3), 17.2 (CH_3), 23.2 (CH_3), 34.2 (CH_2), 36.9 (CH), 47.6 (CH), 89.9 (C), 171.5 (C), 172.4 (C).

(*R*)-3-Methylene-5-methyl-5-(1′-methyl)ethyl-(5H)-3,4-dihydro-2-furanone [(*R*)-2b]

By the procedure described for (*R*)-**2a**, 30 mg (88%, 78% e.e.) of liquid product (*R*)-**2b** was obtained from 41 mg of (*R*)-**9b**[30]. A pure sample was obtained by chromatographic purification on silica gel with Et_2O/pentane. $[\alpha]_D^{20}$ -1.67 (c + 0.6, $CHCl_3$).

^{1}H NMR: δ 0.87 (d, J = 6.8 Hz, 33H), 0.93 (d, J = 6.8 Hz, 3H), 1.27 (s, 3H), 1.86 (septet, J = 6.8 Hz, 1H), 2.55 (A of ABXY, J = 17.1 Hz, J_{AX} = J_{BX} = 2.4 Hz, 1H), 2.79 (B of ABXY, J_{AB} = 17.1 Hz, J_{BX} = J_{BY} = 2.9 Hz, 1H), 5.56 (ABX, J_{XA} = J_{XB} = 2.5 Hz, 1H), 6.16 (ABY, J_{YB} = J_{YA} = 2.8 Hz, 1H) [lit.[30] ^{1}H NMR: δ 0.97 (d, J = 6.75 Hz, 3H), 1.02 (d, 6.75, 3H), 1.37 (s, 3H), 1.50-2.25 (m, 1H), 2.68-2.88 (m, 2H), 5.71 (t, J = 3.0 Hz, 1H), 6.22 (t, J = 3.0 Hz, 1H) for the racemate]. ^{13}C NMR: δ 16.9 (CH_3), 23.2 (CH_3), 37.1 (CH), 37.5 (CH_2), 86.4 (C), 121.8 (CH_2), 136.5 (C).

(*R*)-5-Methyl-5-(1′-methyl)ethyl-(3H)-4,5-dihydro-2-furanone [(*R*)-1b]

According to the procedure described for (*R*)-**1a**, the crude liquid product (*R*)-**9b** (147 mg) yielded 53 mg of crude product which was purified to give 25 mg [17.5% overall from (*S*)-**7b** (90% d.e.] of (*R*)-**1b**.[16]

^{1}H NMR: δ 0.89 (d, J = 6.9 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H), 1.27 (s, 3H), 1.76-2.15 (m, 3H), 2.31-2.72 (m, 2H). [lit.[16a] ^{1}H NMR: δ 0.92 (d, J = 7 Hz, 3H), 0.97 (d, J = 7 Hz, 3H), 1.28 (s, 3H), 1.6-2.7 (m, 5H)]. ^{13}C NMR: δ 17.0 (CH_3), 17.1 (CH_3), 21.6 (CH_3), 29.2 (CH_2), 37.1 (CH), 89.6 (C), 173.3 (C). $[\alpha]_D^{20}$ - 8.5 (c = 0.75, $CHCl_3$) [lit.[16a] $[\alpha]_D^{21}$ - 10.2 (c = 1.07, $CHCl_3$); lit[16b] $[\alpha]_D^{20}$ 10° (c = 0.64, $CHCl_3$)] 92.4% e.e. by nmr determination using Eu(hfc)$_3$; 83% on the basis of $[\alpha]_D$.

β-Hydroxy Ester 10a

A mixture of 880 mg (32.9 mmol) of magnesium turnings, 4.00 g (13.2 mmol) of 2-benzoyl-1,3-oxathiane **5a**[14] and 1.50 g (15.8 mmol) of anhydrous $MgCl_2$ in ca. 200 mL dry THF was refluxed under dry nitrogen for 30 min. The mixture

was allowed to cool to ambient temperature and then a small iodine crystal was added to activate the magnesium surface. To the resulting yellowish solution was added 2.13 mL (13.8 mmol) of *t*-butyl bromoacetate in ca. 30 mL of THF over 10 min at 32 °C. After being stirred for 4 h, the reaction mixture was poured into 50 mL of cold saturated aqueous NH_4Cl. The aqueous layer was extracted with 3 × 100mL of ether and the combined organic layer was washed with 30 mL of saturated aqueous NaCl and dried ($MgSO_4$). Concentration of the solvent gave 5.64 g of crude products as a yellow oil. The diastereomer ratio of **10a** was determined by ^{1}H NMR to be 78:22. This material was purified by flash chromatograph (5:95 EtOAc/petroleum ether) on silica gel to give 3.63 g (8.63 mmol, 63%) of **10a** as a mixture of two diastereomers. Further purification by HPLC (6:94 EtOAc/petroleum ether) gave 2.21 g (5.26 mmol, 40%) of diastereomerically pure β-hydroxy ester (*S*)-**10a** (99.4:0.6 by ^{1}H NMR):

^{1}H NMR: δ 0.91 (d, *J* = 5.0 Hz, 3H), 1.17 (s, 3H), 1.28 (s, 9H), 1.34 (s, 3H), 2.96 and 3.08 (AB, *J* = 17.5 Hz, 2H), 3.37 (dt, *J* = 5.0, 12.5 Hz, 1H), 4.59 (s, 1H), 5.09 (s, 1H), 7.24-7.36 (m, 3H), 7.52 (d, *J* = 10 Hz, 2H) and others. ^{13}C NMR: δ 22.1, 22.7, 24.4, 27.9, 29.7, 31.5, 34.8, 41.8, 42.4, 43.1, 50.7, 76.7, 77.8, 81.5, 85.7, 126.5, 127.4, 142.2, 171.9. Anal. calcd. for $C_{24}H_{36}SO_4$: C, 68.53; H, 8.63; S, 7.62. Found: C, 68.46; H, 8.74; S,7.40.

(3*S*)-*t*-Butyl 3,4-Dihydroxy-3-phenylbutanoate (11a)

To a solution of 765 mg (5.61 mmol) of NCS in ca. 100 mL of 80% aqueous acetonitrile solution was added, sequentially, 988 mg (5.81 mmol) of $AgNO_3$ and 1.112 g (2.65 mmol) of oxathiane **10a** in 10 mL of CH_3CN at -5 °C. After stirring for 10 min, the resulting white precipitate was filtered off. The filtrate was stirred for 20 min and treated, successively, at 1 min intervals, with saturated aqueous Na_2SO_3, saturated aqueous Na_2CO_3, and saturated aqueous NaCl (2 mL of each). The mixture was filtered and the filter cake was washed with Et_2O-hexanes (1:1). To the filtrate was added 1.40 g of $NaBH_4$ and the resulting solution was stirred for 1 h at ambient temperature and then quenched with acetone. The reaction mixture was filtered, concentrated, extracted, with 3 x 50 mL ether, dried ($MgSO_4$) and concentrated to yield 850 mg of crude products as a yellow oil. Purification by flash chromatography (20:80 ethyl acetate/chloroform) on silica gel gave 362 mg (54%) of diol (*S*)-**11a** and 410 mg (77%) of sultines (cf. ref 13). A small sample was further purified by recrystallization from EtOAc-pentane (9:1) $[\alpha]_D^{20}$ +15.0 (c = 4.2, EtOH), mp 84-85 °C.

Anal. calcd. for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.74; H, 7.85. ^{1}H NMR: δ 1.26 (s, 9H), 2.24 (dd, *J* = 4.8, 8.8 Hz, 1H), 2.86 and 3.01 (AB, *J* = 15.6 Hz, 2H), 3.53 and 3.63 (A'B', *J* = 1.5, 4.6, 11.6 Hz, 2H), 2.77 (d, *J* = 1.4 Hz, 1H), 7.23-7.47 (m, 5H) and others. ^{13}C NMR: δ 27.7, 42.2, 70.4, 75.9, 81.9, 125.3, 127.3, 128.2, 142.8, 172.6.

(*S*)-4-Hydroxy-4-phenyl-3,4-dihydro(5H)-furan-2-one [(*S*)-4a]

A mixture of 140 mg (0.555 mmol) of diol (*S*)-**11a** and 790 mg of $NaHCO_3$ in 25 mL of MeOH was stirred. The progress of the hydrolysis was followed by TLC. After 3 h, 6 mL of saturated aqueous NH_4Cl was added and the MeOH was evaporated. The aqueous layer was extracted with 3 × 15 mL of Et_2O and the combined organic layer was dried ($MgSO_4$) and concentrated to leave 105 mg of crude products. Purification by flash chromatography on silica gel (30:70, ethyl acetate/hexanes) gave 77 mg (0.432 mmol, 78%) of crystalline lactone (*S*)-**4a**. Its enantiomeric purity was determined by means of a chiral shift experiment [**4a**/Eu(hfc)$_3$ = 0.2) to be ~100% e.e; mp 77-78 °C, $[\alpha]_D^{20}$ -30.7 (c = 3.92, EtOH).

^{1}H NMR: δ 2.81 (ABX, J_{AX} = 1.1, J_{AB} = 17.3 Hz, 1H), 3.02 (AB, J_{AB} = 17.3 Hz, 1H), 4.40 (XY, J_{XY} = 9.9 Hz, 1H), 4.46 (AXY, J_{AX} = 1.1, J_{XY} = 9.9 Hz, 1H), 7.30-7.39 (m, 5H). ^{13}C NMR: δ 43.5, 78.2, 79.85, 125.0, 128.5, 128.9, 140.2, 175.9.

(*S*)-Diol 12a

To a suspension of 271 mg (7.14 mmol) of $LiAlH_4$ in 20 mL of dry ether was added dropwise 1.10 g (2.62 mmol, 99% d.e) of β-hydroxy ester **10a** in 10mL of dry ether. After refluxing for 2h, the reaction mixture was quenched with a minimum amount of water. The resulting white precipitate was filtered and the cake was washed with Et_2O. The filtrate was dried ($MgSO_4$) and concentrated to give 851 mg (93% yield) of crude crystalline **13a**. Recrystallization from $CHCl_3$-pentane (3:7) gave 794 mg (87% yield) of diastereomerically pure diol **12a**: mp 143-144 °C. Anal. calc'd for $C_{20}H_{30}SO_3$: C, 68.53; H, 8.63. Found C, 68.72; H, 8.63.

^{1}H NMR: δ 0.88 (d, *J* = 7.5 Hz, 3H), 1.07 (q, *J* = 12.5 Hz, 1H), 1.23 (s, 3H), 1.35 (s, 3H), 1.60-1.72 (br m, 1H), 1.72-1.90 (br m, 2H), 2.18 (dt, *J* = 5.0, 15.0 Hz, 1H), 2.25-2.38 (m, 1H), 2.83 (bs, 1H), 3.37 (dt, *J* = 5.0, 10 Hz, 1H), 3.45-3.66 (br m, 2H), 3.86 (s, 1H), 5.04 (s, 1H), 7.20-7.38 (m, 3H), 7.44-7.54 (m, 2H) and others. ^{13}C NMR: δ 22.0, 22.7, 24.4, 29.7, 31.4, 34.7, 38.9, 41.6, 43.2, 50.9, 59.4, 77.8, 78.9, 86.4, 126.3, 127.1, 127.8, 142.45.

Monoacetate (*S*)-13a (X = CH_3CO)

To a solution of 406 mg (1.16 mmol, 98% d.e.) of diol **12a** and a catalytic amount of 4-dimethylaminopyridine in 3 mL of CH_2Cl_2 was added 5 mL of acetic anhydride at 0 °C. After stirring for 1 h, the above reaction mixture was poured into

20 mL of ice water, the aqueous layer was extracted with 4 × 10 mL of CH_2Cl_2, and the combined organic layer was washed with 15 mL of saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and concentrated to leave 464 mg of monoacetate **13a** whose diastereomeric purity was determined by 1H NMR to be 98% d.e.

^{1}H NMR: δ 0.89 (d, J = 6.4 Hz, 3H), 1.24 (s, 3H), 1.32 (s, 3H), 1.90 (s, 3H), 2.32 and 2.42 (ABXY, J_{AB} = 14.1, J_{AX} = 6.4, J_{BX} = 5.7, J_{AY} = J_{BY} = 8.6 Hz, 2H), 3.38 (dt, J = 4.3, 10.5 Hz, 1H), 3.99 and 4.12 (ABXY, J_{XY} = 11.0 Hz, 2H), 4.98 (s, 1H), 7.22-7.38 (m, 3H), 7.46-7.53 (m, 2H) and others. ^{13}C NMR: δ 20.5, 21.8, 22.3, 24.0, 29.3, 31.0, 34.3, 35.1, 41.2, 42.9, 50.4, 60.7, 76.4, 77.3, 85.9, 125.9, 126.7, 127.5, 141.4, 170.5.

(2*S*)-4-Acetoxy-2-hydroxy-2-phenylbutanoic acid 14a (X = CH_3CO) and Lactone (*S*)-3a

To a solution 506 mg (3.79 mmol) of NCS, 649 mg (3.82 mmol) of $AgNO_3$ and 318 mg (3.79 mmol) of $NaHCO_3$ in 40 mL of 80% aqueous acetonitrile solution was added 425 mg (108.mmol, 98% d.e) of the monoacetate of **13a** in 15 mL of acetonitrile. After stirring for 10 min, the white precipitate formed was filtered and the filtrate was stirred for an additional 15 min. Saturated aqueous Na_2SO_3 and saturated aqueous NaCl (2 mL of each) were succesively added to the above solution, and the precipitate formed was removed by filtration. To the filtrate was added 4.0 mL of 3-methyl-2-butene and a solution of 980 mg (8.67 mmol, 80% purity) of $NaClO_2$ and 1.18 g (8.67 mmol) of KH_2PO_4 in 20 mL of water at ambient temperature. After vigorous stirring for 40 min, the solvent was concentrated to leave a mixture of crude products and water. This material was first extracted with 3 x 20 mL hexanes and then 3 x 20 mL of CH_2Cl_2 and the remaining aqueous layer was continuously extracted with 300 mL $CHCl_3$ for one day. The combined CH_2Cl_2 and $CHCl_3$ extracts were concentrated to leave 674 mg of crude acid **14a** as a mixture of oil and crystals (succinimide). This material was dissolved in 5 mL of 1 N NaOH solution and the resulting mixture was stirred for 1 h, acidified with 2 N aqueous HCl and extracted with 3 x 30 mL of ether. The combined organic layer was dried ($MgSO_4$) and concentrated to leave 179 mg of crude lactone **3a**. Purification by flash chromatography on silica gel (30:70 EtOAc/hexanes) gave 117 mg (61%) **3a**. Its enantiomeric purity was determined by means of a chiral shift [Eu(hfc)$_3$] experiment to be >98% e.e.

Acid 14a (succinimide signals deducted)

^{1}H NMR: δ 1.87 (s, 3H), 2.28 (ABX, J = 4.5, 11.4 Hz, 1H) and 2.60 (J = 5.9, 11.4 Hz, 1H), 4.16 (d, J = 4.9 Hz, 1H), 4.19 (dd, J = 2.1, 5.6 Hz, 1H), 7.18-7.33 (m, 3H), 7.52-7.59 (m, 2H), 9.18 (bs, 2H).

(S)-3-Hydroxy-3-phenyl-(5H)3,4-dihydro-furan-2-one (S-3a)

$[\alpha]_D^{23}$-56.6 (C 4.4, EtOH) ^{1}H NMR: δ 2.53 and 2.68 (ABXY, J_{AB} = 13.1 Hz, 2H), 4.15 and 4.41 (ABXY, J_{XY} = 9.0, J_{AX} = 7.0, J_{BX} = 7.0 Hz, J_{AY} = 5.0, J_{BY} = 8.0 Hz), 7.27-7.41 (m, 5H). ^{13}C NMR: δ 38.5, 65.1, 77.0, 125.2, 128.6, 128.7, 139.6, 178.0. [Lit.[20d] δ 2.35 (m,1H), 2.90 (m, 3H), 7.0-8.0 (m, 5H). Lit.[20c] reports J_{gem} 13.4 Hz and 9.1 Hz for H(3) and H(4), respectively.]

Ester 10c

This compound was obtained similarly as **10a** from **5c**[23] in 89% yield and 76% d.e. The diastereomer excess was enriched to 84% by HPLC (6:94, EtOAc/hexanes) purification.

^{1}H NMR ($CDCl_3$): δ 0.92 (d, J = 6.48 Hz, 3H), 1.27 (s, 3H), 1.31 (s, 3H), 1.41 (s, 3H), 1.43 (s, 9H), 2.45, 2.68 (AB, J = 15.5 Hz, 2H), 3.38 (dt, J = 4.3, 10.5 Hz, 1H), 4.9 (s, 1H) and others. ^{13}C NMR ($CDCl_3$): δ 22.0, 22.7, 23.5, 24.3, 28.1, 29.7, 31.3, 34.6, 41.6, 42.6, 42.9, 50.7, 73.0, 77.6, 81.1, 85.2, 171.8.

(2*R*)-*t*-Butyl 3,4-Dihydroxy-3-methylbutanoate [(*R*)-11c]

This compound was similarly prepared from **10c** as **11a** from **10a** (*vide supra*). The resulting oil-water mixture was first extracted with 2 x 25 mL of hexanes and then 3 x 25 mL of CH_2Cl_2 and the remaining aqueous layer was continuously extracted with 300 mL of chloroform for one day. The combined CH_2Cl_2 and $CHCl_3$ extracts were concentrated to leave 1.70 g of crude products as a mixture of oil and crystals (succinimide). Most of the succinimide was crystallized out by dissolving in ether-hexanes (1:1) and filtering. Concentration of the filtrate gave 892 mg of crude **11c** as an oil. This material was further purified by flash chromatography on silica gel (50:50, EtOAc/hexanes) to give 644 mg (3.49 mmol, 65%) of pure diol **11b**.

^{1}H NMR: δ 1.18 (s, 3H), 1.44 (s, 9H), 2.29 (AB, J = 15.5 Hz, 1H) and 2.57 (ABX, J = 1.23, 15.5 Hz, 1H), 3.38 and 3.43 (A'B', J = 11.2 Hz, 2H). ^{13}C NMR: δ 23.7, 27.9, 42.8, 69.3, 71.6, 81.5, 172.3.

(*R*)-4-Hydroxy-4-methyl-(3H)-4,5-dihydro-2-furanone [(*R*)-4c]

Compound (*R*)-**11c** (288 mg) was lactonized by the procedure described above for **11a** to give 144 mg (*R*)-**4c** after purification by flash chromatography. Its enantiomeric purity was determined by means of a chiral shift experiment [**4c**/Eu(hfc)$_3$ = 0.22] to be 90% e.e.

^{1}H NMR: δ 1.51 (d, J = 1.2 Hz, 3H), 2.58 (ABXY, J_{AX} = J_{AY} = 1.4, J_{AB} = 17.5 Hz, 1H), 2.64 (AB, J_{AB} = 17.5 Hz, 1H),

4.14 (XY, J_{AX} = 1.2, J_{XY} = 9.6 Hz, 1H), 4.26 (XY, J_{AY} = 1.4, J_{XY} = 9.6 Hz, 1H). ^{13}C NMR: δ 24.4, 43.2, 74.3, 79.6, 176.8. [Lit.[18] ^{1}H NMR: δ 1.51 (s, 3H), 2.54-2.68 (AB, 2H), 2.54-2.68 (AB, 2H), 2.76 (s, 1H), 4.13-4.29 (AB, 2H). ^{13}C NMR: δ 25.2, 43.8, 74.9, 80.0, 176.6.]

Diol (*R*)-12c

Compound **10c** (2.03 g, 5.66 mmol) was reduced with 0.66 g $LiAlH_4$ by the procedure for **12a** above to give 1.56 g (93%) of crude (*R*)-**12c**. This material was recrystallized from hexanes-$CHCl_3$ (10 mL/0.5 mL) to give 1.15 g (69%) of pure diol (*R*)-**12c** as white crystals. The purity of this diol was determined by ^{1}H NMR to be 98% d.e, mp 103-10 °C.

^{1}H NMR: δ 0.93 (d, *J* = 6.5 Hz, 3H), 1.29 (s, 6H), 1.42 (s, 3H), 2.56 (bs, 2H), 3.44 (dt, *J* = 4.3, 10.5 Hz, 1H), 3.74 (ABXY, *J* = 4.7, 5.7, 11.8 Hz, 1H), 3.83 (ABXY, *J* = 4.2, 8.1, 11.8 Hz, 1H), 4.86 (s, 1H) and others. ^{13}C NMR: δ 22.0, 22.6, 23.7, 24.2, 29.6, 31.3, 34.5, 38.7, 41.5, 43.1, 50.8, 59.2, 74.8, 77.6, 85.9.

Benzoate (R)-13c (R = C_6H_5CO)

To a solution 951 mg (3.30 mmol) of diol (*R*)-**12c** and a catalytic amount of 4-dimethylaminopyridine in 10 mL of CH_2Cl_2 was successively added 2 mL of triethylamine and 0.58 mL (5.00 mmol) of benzoyl chloride. After stirring for 30 min, the reaction mixture was poured into 20 mL of ice water, the aqueous layer was extracted with 3 x 20 mL of CH_2Cl_2 and the combined organic layer was washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and concentrated to leave 1.63 g of crude products as an oil. This material was further purified by flash chromatography on silica gel (30:70), EtOAc/hexanes) to give 1.29 g (99%) of the pure benzoate **13c**.

^{1}H NMR: δ 0.91 (d, *J* = 6.4 Hz, 3H), 1.28 (s, 3H), 1.31 (s, 3H), 1.41 (s, 3H), 3.39 (dt, *J* = 4.3, 10.5 Hz, 1H), 4.54 (t, *J* = 7.1 Hz, 2H), 4.84 (s, 1H), 7.38-7.59 (m, 3H), 8.01-8.07 (m, 2H) and others. ^{13}C NMR: δ 22.0, 22.6, 23.7, 24.2, 29.6, 31.3, 34.5, 36.1, 41.5, 43.1, 50.7, 61.5, 73.2, 77.5, 85.9, 128.2, 129.4, 130.4, 132.7, 166.4.

(1*R*)-2-Hydroxy-2-methyl-4-benzoyloxybutanoic acid [(*R*)-14c]

The procedure was similar to that described for **14a** above to produce 927 mg of the crude acid **14c** as the major product. This material was used without further purification.

^{1}H NMR: δ 1.52 (s, 3H), 2.09 (ABX, *J* = 5.0, 14.0 Hz, 1H), 2.44 (ABX, *J* = 6.9, 14.0 Hz, 1H), 4.47 (d, *J* = 5.0 Hz, 1H), 4.50 (d, *J* = 1.5, 5.0 Hz, 1H), 5.57 (bs, 2H), 7.36-7.60 (m, 3H), 7.96-8.03 (m, 2H).

(*R*)-3-Hydroxy-3-methyl-(3H) 4,5-dihydro-2-furanone [(*R*)-3b]

A mixture of 927 mg of acid (*R*)-**14c** and 850 mg of K_2CO_3 in 15 mL of dry methanol was stirred at ambient temperature. The progress of the hydrolysis was followed by TLC. After stirring for 5.5 h and filtration to remove K_2CO_3, 2 mL of 2 N aqueous HCl was added and the methanol was distilled at reduced pressure to leave an aqueous layer. It was extracted with 6 x 20 mL of CH_2Cl_2 and the combined extracts were dried ($MgSO_4$). Concentration of the solvent afforded 178 mg of crude products. Purification by flash chromatography on silica gel (5:95 EtOH/CH_2Cl_2) gave 151 mg (1.51 mmol, 50% in three steps from benzoate **13c**) of pure lactone (*R*)-**3c**. Its optical purity was determined by a chiral shift experiment [**3c**/Eu(hfc)$_3$ = 0.71] to be 96% e.e..

^{1}H NMR: δ 1.48 (s, 3H), 2.23 (ABXY, *J* = 4.5, J_{AX} = 7.0, J_{AB} =13.0 Hz, 1H), 2.41 (ABXY, J_{BX} = J_{BY} = 7.7, J_{AB} = 13.0 Hz, 1H), 4.2 (ABXY, J_{AX} = 7.1, J_{BX} = 7.8, J_{XY} = 9.2 Hz, 1H), 4.39 (ABXY, J_{AY} = 4.2, J_{BY} = 8.2, J_{XY} =9.2 Hz, 1H) [lit.[21a] ^{1}H NMR: δ 1.47 (s, 3H), 1.98-2.70 (m, 2H), 4.21 (s, 1H), 4.02-4.63 (m, 2H) for the racemate]. ^{13}C NMR: δ 23.5, 36.6, 72.1, 85.2, 179.6.

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