Pergamon

Tetrahedron, Vol. 53, No. 18, pp. 6281-6294, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00298-6

SYNTHESIS OF (4*S*)-HYDROXYMETHYL-(2*R*)-(2-PROPYL)-BUTYROLACTONE: A QUEST FOR A PRACTICAL ROUTE TO AN IMPORTANT HYDROXYETHYLENE ISOSTERE CHIRON.

Stephen Hanessian,* Teresa Abad-Grillo and Grant McNaughton-Smith.

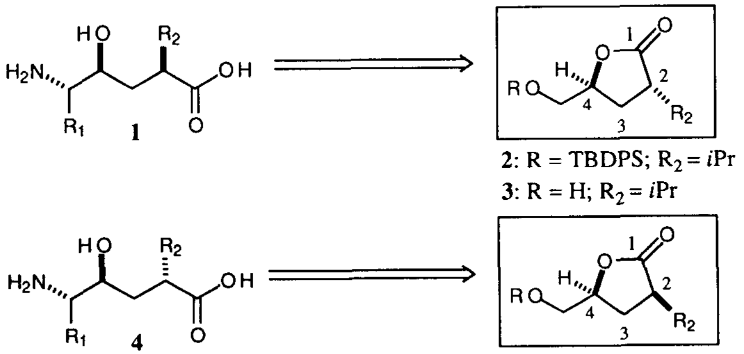
Department of Chemistry, Université de Montréal
P.O. Box 6128, Succ. Centre-ville, Montréal, P.Q., CANADA, *H3C 3J7*

Abstract: Several approaches for the stereocontrolled introduction of a 2-propyl group into (4*S*)-hydroxymethyl-1,4-butyrolactone *via* enolate chemistry were investigated. A practical synthesis of the (2*R*)- and (2*S*)-isomers was developed. © 1997 Elsevier Science Ltd.

The practical synthesis of small, versatile enantiopure molecules has become increasingly important in drug discovery.[1] An example of such a challenge can be found in the plethora of methods developed over the last decade for the synthesis of hydroxyethylene isosteres.[2] These molecules have been designed as mimics of the transition states in the cleavage of scissile peptide bonds by important enzymes such as HIV-protease[3] and renin.[4]

Enantiopure 4-hydroxymethyl butyrolactone and related derivatives have figured prominently in the synthesis of such motifs,[5] ultimately providing acyclic carboxylic acid derivatives harboring an amino alcohol functionality and an alkyl group (Figure 1). Although methylation and benzylation of the enolates generated from O-substituted 4-hydroxymethyl butyrolactones afford products with good *anti*-selectivity,[5] little is known concerning other more sterically demanding groups such as the 2-propyl group. Previous studies[6,7] suggested that the prospect of using a S_N2 type nucleophilic substitution between the lactone enolate and either 2-iodopropane or the triflate of 2-propanol was relatively unsuitable due to steric effects. In this paper, we report on four approaches to develop a practical route to 4(*S*)-hydroxymethyl-2(*R*)-(2-propyl)-butyrolactone **3**.

Figure 1

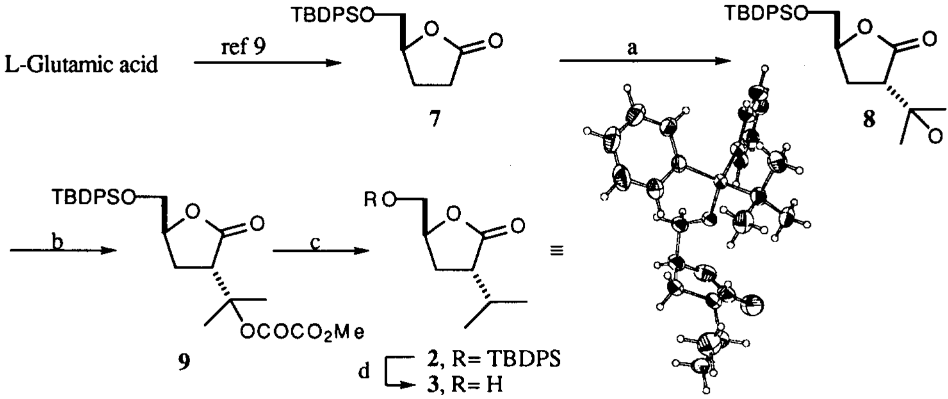


2: R = TBDPS; R_2 = *i*Pr
3: R = H; R_2 = *i*Pr

5: R = TBDPS; R_2 =*i*Pr
6: R = H; R_2 = iPr

Nishi and co-workers[8] described a mild and efficient method for the introduction of a 2-propyl group into a similar lactone utilizing a cross-aldol reaction with acetone followed by a radical-mediated deoxygenation. Following this precedent, the lithium enolate of the protected lactone **7**[9] was reacted with dry acetone to afford **8** as a 14:1 α:β mixture of diastereoisomers in near quantitative yield (Scheme 1). A single recrystallisation gave the diastereomerically pure **8** in 92% yield. The tertiary alcohol was efficiently transformed into the oxalyl derivative **9** which was deoxygenated using triphenyltin hydride in toluene to afford the desired product **2** in 89% yield as a white crystalline solid. In contrast to tributyltin hydride used by Nishi,[8] we found that triphenyltin hydride gave a cleaner reaction and significantly higher yields. Single crystal X-ray analysis of **2** confirmed the stereochemistry already attributed by n.O.e studies. The TBDPS group could be readily removed using TBAF to generate the free hydroxy compound **3**.

Scheme 1



Reagents. a) LiHMDS, THF, -78 °C, 1h then Me_2CO, 1h, 100% ; b) $ClCOCO_2Me$, Et_3N, DMAP, THF, RT, 1h, 99%; c) Ph_3SnH, AIBN (cat), Tol, reflux, 3h, 89%; d) TBAF, THF, 0 °C, 1h, 99%.

Although the procedure outlined in Scheme 1 provided the intended lactone **3** in 81% overall yield in only four steps from **7**, we wished to investigate other routes which would minimize the use of low temperatures and difficult to handle reagents, while reducing or eliminating chromatographic separations if possible.

We next explored two other routes towards achieving these objectives. The literature records several examples,[10,11,12] where the presence of allylic or homoallylic hydroxyl groups have contributed to the stereocontrolled reduction of neighboring alkenes. We, therefore, considered the prospect of utilizing the free hydroxymethyl at C-4 to deliver hydrogen to the β-face of the α,β-unsaturated alkene in **10** (Scheme 2). Although the alkene was positioned one methylene group further away from the bis homoallylic hydroxyl group than in the known cases, it was hoped that the spacial disposition of the hydroxymethyl group would aid in hydrogen delivery. ^1H NMR studies of the trityl derivative corresponding to **7** by Koga[13] revealed that the hydroxymethyl appendage was located over the lactone ring rather than away from it. This unusual spacial ordering was also found in the X-ray structure of **2** (Scheme 1), which was considered to be due to a combination of the gauche effect and intramolecular orbital mixing.[13] From this information we postulated that the free hydroxymethyl group would also position itself across the lactone ring, and would hopefully facilitate the desired stereoselective reduction. Compound **10** was prepared expeditiously from **8** by dehydration ($POCl_3$, py, RT), followed by removal of the TBDPS group under standard conditions (Scheme 2). Initially we focused on the more

Scheme 2

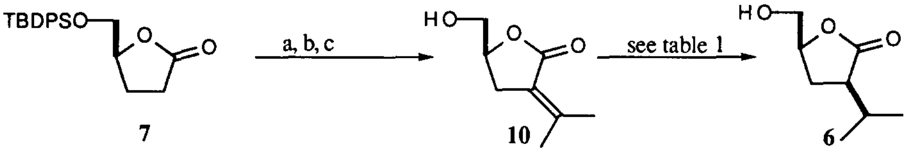


Table 1

Catalyst/Support	Time	Pressure	**6** : **3**	Yield
Ru/Carbon	72h	40psi	>30:1	87%
Rh/Carbon	48h	40psi	>30:1	99%
Pt/Carbon	72h	40psi	>30:1	98%
Pd/Carbon	10h	40psi	>30:1	99%
Rh^+[Diphos](NBD) BF_4^-	3h	40psi	-	-
Rh^+[Diphos](NBD) BF_4^-	8h	800psi	97:3	94%

Reagents. a) LiHMDS, THF, 0 °C, 10 min then Me_2CO, 15 min, 93% ; b)$POCl_3$, py, RT, 2h, 89%; c) TBAF, THF, 0 °C, 1h, 98%.

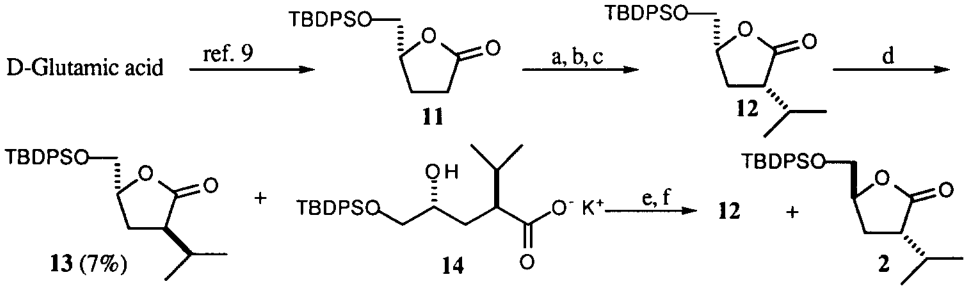
common catalysts used for hydrogenation (Pd, Pt, Ru and Rh), either on carbon or alumina supports. All of these heterogeneous catalysts resulted in the selective formation of the undesired *cis*-substituted lactone **6** (β:α >30:1) in good yield (87-99%). In an effort to generate more of the desired *trans*-substituted compound, we utilized the homogeneous catalyst Rh^+(4-Diphos)[NBD]BF_4^-[12] in dichloromethane at low dilution (0.0025 M). Although no reaction was observed at 30 psi, the reduction occurred smoothly at 800 psi. ^1H NMR analysis again confirmed that the overwhelming product was the *cis*-substituted lactone **6** (β:α >30:1, 94%). Evidently the anticipated effect of the proximal hydroxymethyl group was not operative and hydrogenation occurred without coordination to the catalyst.

Poss and Smyth[14] demonstrated in a similar compound that an endocyclic α,β-unsaturation favored hydroxyl-directed reduction. Several attempts to isomerize the alkene into the ring using conventional palladium and ruthenium catalysts or organic bases (DBU), gave only poor conversion ratios. Although this route did not furnish the desired *trans*-substituted compound **2**, it did provide easy access to the C-2 epimer **6**.

Reviewing the situation, it was clear that the preparation of the stereochemically pure *cis* diastereoisomers such as **5** and **6** could be achieved efficiently and under mild conditions, while the conditions used for the preparation of the *trans* diastereoisomer **2** generally gave a mixture of isomers.[15] Based on this knowledge, we embarked on another approach to generate the desired *trans* isomer **2** in predominance. We considered that if we started from D-glutamic acid as our chiral template and generated the readily accessible (*R*,*R*)-*cis*-substituted lactone **12**, we could then invert the stereochemistry at C-4 utilizing an intramolecular Mitsunobu ring closure[16] of the corresponding hydroxy acid (Scheme 3).

The *cis*-substituted lactone **12** (Scheme 3) was prepared from D-glutamic acid following the same mild procedure as outlined earlier for the L-series (Scheme 2). Saponification of the lactone with KOH in a THF/MeOH/H_2O solvent system at 0 °C yielded the desired hydroxy carboxylate **14** accompanied by a small amount of the C-2 lactone epimer **13**.[17] Extraction of the aqueous medium with ether afforded the undesired *trans*-lactone **18** in 7% yield. Mild acidification of the aqueous phase with pre-washed Amberlite IR-120 (H^+) resin gave the desired acid which was dried thoroughly over P_2O_5 under vacuum. Treatment of the acid under standard Mitsunobu reaction conditions (Ph_3P, DEAD, THF, 0 °C) resulted in a 5:1 mixture of the desired product **2** (64%) and starting material **12** (13%), which could be separated by column chromatography. Although the desired product **2** was prepared in good yield, and highlighted the usefulness of the intramolecular Mitsunobu reaction to invert the C-4 stereochemistry, the method was somewhat cumbersome.

Scheme 3

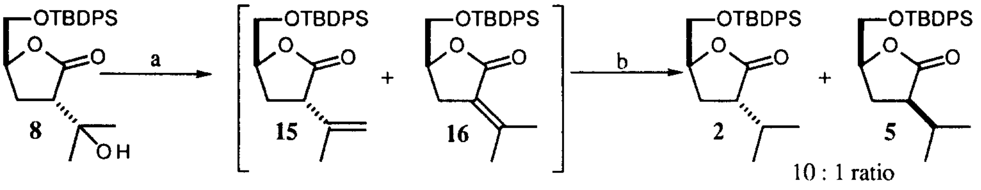


Reagents. a) LiHMDS, THF, -78 °C, 1h, Me_2CO, 1h, 97%; b) $POCl_3$, py, rt, 2h, 85%; c) Pt-black, H_2,(1 atm) EtOAc, 1h, 100%; d) KOH, THF/MeOH/H_2O (4:1:1), 0°C, **13** 7%; e) Amberlite IR 120 (H^+), pH 4; f) Ph_3P, DEAD, THF, **12**,13%; **2**, 64%.

From the above experiments it was evident that we would have to focus our attention on a stereoinduced, low temperature introduction of a 2-propyl precursor unit. It was obvious that if we could stereoselectively incorporate a 2-propenyl group at C-2 of the lactone, then we could simply reduce the alkene to reveal the desired 2-propyl group. Initial attempts to introduce the 2-propenyl unit *via* S_N2 type substitution of a β-triflate at C-2 with a di-(2-propenyl)-lithiocuprate were unsuccessful. The use of a nickel assisted insertion of 2-bromopropene into the lithium enolate of **7**, following a precedent by Rathke,[18] resulted in a complex mixture of products in addition to starting material being recovered.

Rehders and Hoppe[7] recently described the generation of an 2-propenyl group in a similar lactone environment by dehydrating a tertiary alcohol (PCl_5 in CH_2Cl_2, 0 °C) to afford a terminal alkene with a high degree of selectivity. Utilizing these conditions, **8** was expediently transformed into a 10:1 (^1H NMR) mixture of **15** and **16** in 92% (Scheme 4). The mixture of alkenes was hydrogenated (Pd/C, H_2, 1 atm) to afford a 10:1 mixture of **2** and **5** which could be separated at this stage by column chromatography to provide the desired core unit **2**. Removal of the TBDPS group using standard TBAF conditions, followed by chromatographic removal of the silanol by-product, gave the hydroxy lactone **3** in an overall yield of 72% from **7**. Although this procedure was highly efficient and short, its only flaw was the generation of the exocyclic alkene **16** as a by-product.

Scheme 4

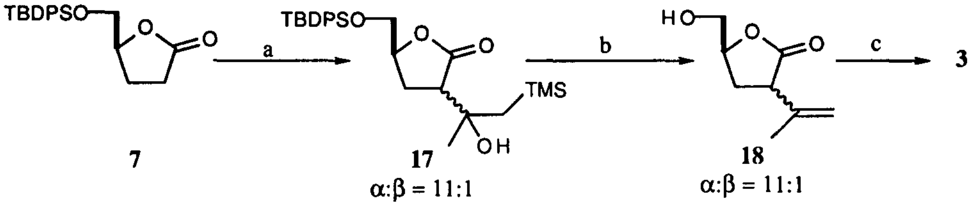


Reagents.a) PCl_5,CH_2Cl_2, 0 °C, 20 min, (**15**:**16**=10:1), 92%; b) Pd/C, EtOAc, H_2 1 atm, 2 h, 95%.

We therefore considered the possibility of generating the terminal alkene **15** *via* a more selective method. As the aldol reaction between the lithium enolate of the lactone and acetone had proved to be efficient and high yielding, we considered the possibility of positioning an trimethylsilyl group on the neighboring carbon to the newly formed tertiary alcohol.[19,20,21] A Peterson olefination reaction,[21] would then provide the terminal alkene selectively (Scheme 5).

Initially we used lactone **7** as our starting template since we could induce a concomitant formation of the alkene and a deprotection of the hydroxymethyl group with fluoride ion. The required 1-trimethylsilylpropan-2-one was easily prepared from acetic anhydride and trimethylsilylmethyl magnesium chloride at low temperature.[22,23] Unfortunately, the cross-aldol reaction, gave only a moderate yield (63%) of **17** which was obtained as an inseparable mixture of diastereoisomers (11:1 α:β).[24] Treatment of **17** with a buffered solution of TBAF in AcOH resulted in the deprotection of the hydroxymethyl group only, however, the use of an excess of HF-pyridine in THF at ambient temperature, furnished, after chromatographic removal of the silanol by-product, the desired hydroxyalkene **18** as a colorless solid in a rewarding 89% yield . ^1H NMR analysis of **18** revealed that no isomerization or epimerization had occurred during the elimination-deprotection sequence. Hydrogenation of the terminal alkene in **18** under standard conditions afforded the desired product **3** in a 54% yield from **7**.

Scheme 5

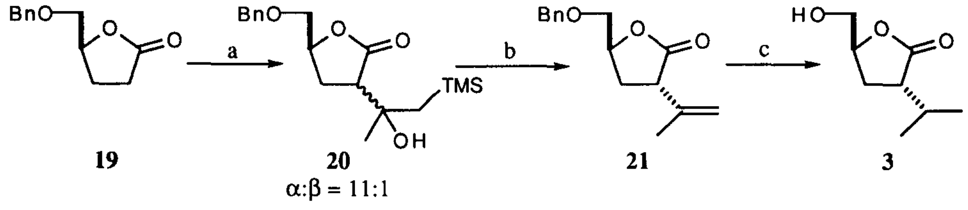


Reagents. a) LiHMDS, THF, -78 °C, 1 h, then 1-trimethylsilylpropan-2-one, 20 min, 63%; b) HF-py, THF, RT, 18 h, 81%; c) Pd/C, ethyl acetate, H_2, 1 atm, 1 h, 96%.

As the above reaction pathway (Scheme 5) successfully furnished **3** in high yield, we decided to exchange the silyl protecting group, for a benzyl group, which could be removed by hydrogenolysis at the same time as the reduction of the terminal alkene.

The now highly stereoselective cross-aldol type coupling with the 1-trimethylsilylpropan-2-one led to **20** as a colorless oil in an impressive 89% yield (Scheme 6). Although we knew that HF-pyridine would afford the desired terminal alkene **21**, we also investigated other commonly used reagents for the Peterson elimination reaction. The use of sodium or potassium hydride in THF at 0 °C resulted in the production of the starting mono-substituted lactone **19**, by a retro-aldol reaction. The use of acid ($HClO_4$) efficiently produced the olefin, but the product underwent substantial epimerization at C-2 (α:β=3:2). The use of boron trifluoride diethyl etherate complex at 0°C minimized this epimerization giving the alkene **21** in 94% yield (α:β = 9:1), while at lower temperatures the ratio was even better (α:β = 11:1). However, none of the reagents were found to be as efficient as HF-pyridine, which rapidly generated the alkene in near quantitative yield at RT. The two diastereoisomers could be separated at this stage by column chromatography. Removal of both the alkene and the benzyl group (Pd/C, MeOH, H_2, 40 psi) gave the target hydroxy lactone **3** in 72% yield from **19**. Although low temperatures were required in order to obtain a high level of stereochemical induction in the initial cross-aldol reaction, the mild and selective manner by which the terminal alkene was generated combined with the clean and high yielding reduction-deprotection step makes this route potentially suitable for the large scale preparation of the desired lactone **3**.

Scheme 6



Reagents. a) LiHMDS, THF, -78 °C, 1 h, then 1-trimethylsilylpropan-2-one, 20 min, 89%; b) HF-py, MeCN, RT, 30 min, 94%; c) Pd/C, MeOH, H_2 (40 psi), 4h, 86%.

To summarize, we have described several viable routes to the preparation of all four diastereomers of the 4-hydroxymethyl-2-(2-propyl)-butyrolactones. From a practical standpoint, the stereochemically pure *cis*-substituted butyrolactones were, as expected, readily prepared *via* a condensation-elimination-hydrogenation sequence, while the preparation of the corresponding *trans* compounds proved more challenging. Of the methods investigated to generate the *trans*-2,4-substituted butyrolactones, those methods shown in Schemes 4 and 6 were considered to be amenable to their large scale preparation. Although both routes required an initial low temperature reaction, they provided the desired 5-carbon chiron **3** in high yield in only four steps from commercially available (*R*) or (*S*)-4-hydroxymethylbutyrolactone, with only a minimal amount of chromatographic purification.

We are currently investigating the use of 1-trimethylsilylpropan-2-one and related reagents for the introduction an 2-propyl functionality into other acyclic and cyclic carbonyl compounds.

General experimental.

^1H and ^{13}C NMR spectra were recorded on Bruker AMX-300 and ARX-400 spectrometers in $CDCl_3$ with tetramethylsilane as the internal standard. IR spectra were recorded on a Perkin-Elmer 781 spectrometer as solutions in $CHCl_3$. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter at ambient temperature. Low resolution EI mass spectra were recorded on a VG Micromass 1212 spectrometer and high resolution EI mass spectra were recorded on a AEI-MS 902 or Kratos MS-50 spectrometers. All solvents were dried by standard methods. Commercially obtained reagents were used without further purification. All reactions were monitored by tlc with Merck 60 F_{254} silica gel coated plates. Visualization of the reaction components was obtained by UV or by development using potassium permanganate or molybdenum ceric acid solutions. Flash column chromatography was carried out using 230-400 mesh silica (American Chemical Ltd), gel at increased pressure.

Experimental.

(2*S*)-(1-Hydroxy-1-methyl-ethyl)-(4*S*)-*tert*-butyldiphenylsilyloxymethyl-butyrolactone (8). A solution of LiHMDS in THF (1.42 ml, 1.0 M, 1.42 mmol) was added dropwise to a stirring solution of (4*S*)-*tert*-butyldiphenylsilyloxymethyl-butyrolactone **7** (460 mg, 1.30 mmol) in THF (3.25 ml) at -78 °C. After stirring for 1h dry acetone (0.114 ml, 1.42 mmol) was added. Stirring was continued for a further 1h after which a saturated aqueous solution of NH_4Cl (2 ml) and ether (10 ml) were added. Extraction of the aqueous phase with ether (3 x 10 ml) followed by drying ($MgSO_4$) the combined organic phases, solvent removal under reduced pressure and column chromatography (EtOAc:hexane, 3:7) gave the desired product **8** (540 mg, 100%) as a white solid, ($\alpha:\beta = 14:1$). Recrystallization (CH_2Cl_2-hexane) gave pure **8** (497 mg, 92%): mp 78° C; $[\alpha]^{25}_D$ +35.2° (c 0.965, $CHCl_3$); IR ($CHCl_3$) 3520, 1760 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.69-7.63 (m, 4H), 7.49-7.38 (m, 6H), 4.59-4.49 (m, 1H), 3.88 (dd, J = 11.4, 3.2 Hz, 1H), 3.58 (dd, J = 11.4, 2.8 Hz, 1H), 3.58 (br s, 1H), 3.01 (t, J = 10.2 Hz, 1H), 2.33 (ddd, J = 12.8, 10.0, 2.5 Hz, 3H), 2.15 (ddd, J =

13.0, 10.3, 9.1 Hz, 1H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 178.8, 135.6, 135.6, 132.8, 132.3, 130.0, 127.9, 127.8, 77.7, 71.1, 65.6, 50.0, 27.8, 27.1, 26.7, 25.3, 19.1; HRMS, calcd. for $C_{24}H_{33}O_4Si$, 413.2148 (M^++1); found, 413.2132.

(2*S*)-(1-Methyl-1-oxalic acid methyl ester-ethyl)-(4*S*)-*tert*-butyldiphenylsilyloxymethyl-butyrolactone (9).

Monomethyloxalyl chloride (0.140 ml, 1.47 mmol) was added dropwise to a stirring solution of **8** (351 mg, 1.34 mmol), triethylamine (0.205 ml, 1.47 mmol) and DMAP (8 mg, 0.07 mmol) in THF (5 ml) at 0 °C. Stirring was continued for 1h after which ether (20 ml) was added. The organic phase was washed with brine (2 x 10 ml), dried (Na_2SO_4) and concentrated under reduced pressure. Column chromatography (EtOAc:hexane, 3:7) gave the desired product **9** (664 mg, 99%) as a colorless oil; $[\alpha]^{25}_D$ +14.0° (c 1.00, $CHCl_3$); IR ($CHCl_3$) 1770 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68-7.63 (m, 4H), 7.47-7.37 (m, 6H), 4.63-4.57 (m, 1H), 3.89 (dd, J = 13.4, 3.0 Hz, 1H), 3.88 (s, 1H), 3.66 (dd, J = 13.4, 2.8 Hz, 1H), 3.58 (br s, 1H), 3.55 (t, J = 9.3 Hz, 1H), 2.46-2.29 (m, 2H), 1.81 (s, 3H), 1.66 (s, 3H), 1.08 (s, 9H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 178.8, 135.6, 135.6, 132.8, 132.3, 130.0, 127.9, 127.8, 77.7, 71.1, 65.6, 50.0, 27.8, 27.1, 26.7, 25.3, 19.1.

(4*S*)-*tert*-butyldiphenylsilyloxymethyl-(2*R*)-(2-propyl)-butyrolactone (2).

A solution of triphenyltin hydride (477 mg, 1.36 mmol) in dry toluene (5 ml) was added at RT to a mixture of **9** (340 mg, 0.68 mmol) and AIBN (25 mg, cat) in toluene (8.5 ml). After the addition was complete the reaction mixture was heated at reflux for 20 min (in the dark) followed by an additional 3h between 90-110° C. After cooling the solvent volume was reduced by half by evaporation under reduced pressure, and the remaining solution was chromatographed (hexane:ether, 4:1) to afford the product **2** (239 mg, 89%) as a colorless oil which crystallized on standing; mp 43-44° C; $[\alpha]^{25}_D$ +13.2° (c 1.00, $CHCl_3$); IR ($CHCl_3$) 1765 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68-7.64 (m, 4H), 7.48-7.37 (m, 6H), 4.54-4.49 (m, 1H), 3.85 (dd, J = 11.3, 3.4 Hz, 1H), 3.76 (dd, J = 11.3, 3.3 Hz, 1H), 2.76 (ddd, J = 9.8, 9.0, 5.0 Hz, 1H), 2.26-2.05 (m, 3H), 1.06 (s, 9H), 1.03 (d, J = 6.9 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 178.7, 135.5, 135.5, 132.9, 132.5, 129.8, 127.8, 77.8, 65.6, 45.5, 28.6, 26.7, 25.5, 20.4, 19.1, 18.1; HRMS, calcd. for $C_{24}H_{31}O_3Si$, 395.2042 (M^+-1); found, 395.2051.

(4*S*)-Hydroxymethyl-(2*R*)-(2-propyl)-butyrolactone (3).

A solution of TBAF (0.288 ml, 0.288 mmol) in THF was added dropwise to a solution of **2** (93 mg, 0.24 mmol) in THF (1 ml) at 0 °C (ice bath). After 5 min at 0 °C the ice-bath was removed and stirring was continued for 1h. EtOAc (10 ml) was added and the organic phase was washed with brine (2 x 5 ml) and dried ($NaSO_4$). Removal of the solvent followed by column chromatography (CH_2Cl_2:EtOAc, 4:1) gave the desired product **3** (36 mg, 99%) as a colorless oil: $[\alpha]^{25}_D$ +16.8° (c 1.125, $CHCl_3$); IR ($CHCl_3$) 3620, 3440, 1770 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.57-4.52 (m, 1H), 3.85 (ddd, J = 13.4, 6.4, 3.0 Hz, 1H), 3.62 (ddd, J

= 12.3, 6.1, 4.7 Hz, 1H), 2.68 (ddd, J = 9.9, 8.0, 5.1 Hz, 1H), 2.64 (t, J = 6.4 Hz, 1H), 2.19-2.06 (m, 3H), 1.01 (d, J = 6.9 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 179.2, 77.8, 64.6, 45.6, 28.9, 25.3, 20.3, 20.3, 18.2; HRMS, calcd. for $C_8H_{15}O_3$, 159.1021 (M^++1); found, 159.1030.

(4*S*)-*tert*-butyldiphenylsilyloxymethyl-2-(2-propylidene)-butyrolactone (16).

Method A:

Freshly distilled $POCl_3$ (195 mg, 1.77 mmol) was added dropwise to a stirring solution of **8** (350 mg, 0.848 mmol) in pyridine (4.24 ml) at 0 °C. The reaction was maintained between 0-10 °C for a further 2h. Ether (30 ml) was added and the reaction mixture was repeatedly washed with a 10% aq. $CuSO_4$ solution. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. Column chromatography (hexane-ether, 4:1) gave the desired compound **16** (297 mg, 89%) as a white solid. Recrystallization (hexane:ether, 4:1) gave the product (273 mg, 82%) as colorless needles: $[\alpha]^{25}_D$ +33.2° (c 1.03, $CHCl_3$); mp 87° C; IR ($CHCl_3$) 1745, 1675 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67-7.61 (m, 4H), 7.47-7.36 (m, 6H), 4.56-4.49 (m, 1H), 3.84 (dd, J = 11.1, 3.6 Hz, 1H), 3.68 (dd, J = 11.1, 3.4 Hz, 1H), 2.94-2.77 (m, 2H), 2.26 (t, J = 2.1 Hz, 3H), 1.87 (t, J = 1.4 Hz, 3H), 1.02 (s, 9H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 170.1, 149.0, 135.7, 135.6, 135.6, 135.5, 133.2, 132.8, 129.8, 129.8, 127.8, 119.6, 75.3, 65.7, 30.9, 29.9, 26.6, 24.4, 19.7, 19.2; HRMS, calcd. for $C_{24}H_{31}O_3Si$, 395.2042 (M^++1); found, 395.2031.

Method B:

Methanesulfonyl chloride (0.690 ml, 8.92 mmol) was added dropwise to a stirring solution of **8** (920 mg, 2.23 mmol), triethylamine (1.24 ml, 8.92 mmol) and DMAP (1.09 g, 8.92 mmol) in CH_2Cl_2 (20 ml) at RT. The resulting orange solution was stirred for 4h before being quenched with a saturated solution of NH_4Cl (10 ml). The organics were extracted with CH_2Cl_2 (20 ml), washed with brine and dried (Na_2SO_4). Removal of the solvent followed by column chromatography (hexane:ether, 4:1) gave the desired compound **16** (761 mg, 87%) as a white solid. Physical and spectral data were identical to those reported above.

(4*S*)-Hydroxymethyl-2-(2-propylidene)-butyrolactone (10).

A solution of TBAF in THF (0.19 ml, 1.0 M, 0.19 mmol) was added smoothly to a solution of **16** (50 mg, 0.127 mmol) in THF (0.5 ml) at RT. Stirring was continued for 2h whereupon ether (20 ml) and a saturated aqueous solution of NH_4Cl were added respectively. The organic phase was separated, washed with brine (2 x 10 ml) and dried (Na_2SO_4). Solvent removal under reduced pressure, followed by column chromatography (CH_2Cl_2:EtOAc, 4:1) gave the desired product **10** (19.3 mg, 98%) as a waxy solid: mp 56-57° C; $[\alpha]^{25}_D$ +73.4° (c 0.965, $CHCl_3$); IR ($CHCl_3$) 3620, 3450, 1750, 1670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.59-4.51 (m, 1H), 3.83 (dd, J = 12.3, 3.2 Hz, 1H), 3.62 (dd, J = 12.3, 5.2 Hz, 1H), 2.94-2.83 (m, 1H), 2.75-2.65 (m, 1H), 2.50 (br s, 1H), 2.24 (t, J = 2.2 Hz, 3H), 1.87 (t, J = 1.6 Hz, 3H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 170.0, 150.8, 118.8, 75.8, 64.5, 29.0, 24.4, 19.7; HRMS, calcd. for $C_8H_{13}O_3$, 157.0865 (M^++1); found, 157.0874.

(4*S*)-Hydroxymethyl-(2*S*)-(2-propyl)-butyrolactone (6).

A mixture of hydrogenation catalyst and **10** in dry CH_2Cl_2 (0.0025 M) were vigorously stirred under hydrogen (see Table 1) until tlc analysis indicated the absence of starting material. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. ^1H NMR of the product indicated that the *cis* isomer **6** was the major or sole product; $[\alpha]^{25}_D$ +71.0° (c 1.33, $CHCl_3$); IR ($CHCl_3$) 3620, 3450, 1770 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.49-4.45 (m, 1H), 3.92 (dd, J = 12.6, 2.8 Hz, 1H), 3.64 (dd, J = 12.6, 5.0 Hz, 1H), 2.64 (ddd, J = 14.2, 9.1, 5.1 Hz, 1H), 2.29-2.11 (m, 2H), 2.00-1.83 (m, 3H), 1.05 (d, J = 6.9 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 177.7, 78.2, 63.8, 46.6, 27.6, 24.9, 20.5, 18.1; HRMS, calcd. for $C_8H_{15}O_3$, 159.1021 (M^++1); found, 159.1030.

(4*R*)-*tert*-Butyldiphenylsilyloxymethyl-(2*R*)-(2-propyl)-butyrolactone (12).

A mixture of platinum-on-alumina (100 mg) and (4*R*)-*tert*-butyldiphenylsilyloxymethyl-2-(2-propylidene)-butyrolactone (prepare as **16**) (1.048g, 2.66 mmol) in EtOAc (10 ml) was stirred under a 1 atmosphere pressure of hydrogen for 2h. Filtration of the mixture through a pad of Celite followed by concentration gave the desired product **17** (1.05g, 100%) as a white solid: mp 57-58° C; $[\alpha]^{25}_D$ -30.4° (c 1.00, $CHCl_3$); IR ($CHCl_3$) 1767 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76-7.66 (m, 4H), 7.49-7.36 (m, 6H), 4.48-4.40 (m, 1H), 3.90 (dd, J = 11.5, 3.6 Hz, 1H), 3.76 (dd, J = 11.5, 4.2 Hz, 1H), 2.63 (ddd, J = 14.0, 9.1, 4.9 Hz, 1H), 2.29-2.19 (m, 1H), 2.17-1.98 (m, 2H), 1.08 (s, 9H), 1.05 (d, J = 6.9 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 177.8, 135.6, 135.5, 133.0, 129.8, 127.7, 77.9, 64.4, 46.6, 27.5, 26.7, 25.2, 20.6, 19.2, 18.1; HRMS, calcd. for $C_{24}H_{31}O_3Si$, 395.2051 (M^++1); found, 395.2055.

Preparation of (2) by Mitsunobu inversion:

An aqueous solution of potassium hydroxide (0.270 ml, 1.0 M, 2.70 mmol) was added slowly to a stirring solution of **17** (107 mg, 2.70 mmol) in THF-H_2O-MeOH (4:1:1, 3 ml) at 0 °C. Stirring was continued at 0 °C (5-8h) until tlc analysis indicated the absence of starting material. The resulting solution was then extracted with ether (3 x 5 ml) to remove the C-2 epimer **13** (7.3 mg, 7%). Pre-washed Amberlite IR-120 resin (H^+) and CH_2Cl_2 (20 ml) were added to the aqueous phase until pH~4 was attained. The mixture was vigorously stirred for 30 min after which the mixture was filtered and the aqueous phase was repeatedly extracted with CH_2Cl_2 (5 x 10 ml). The combined organic phases were dried (Na_2SO_4) and solvent was removed under reduced pressure. The residue was further dried over P_2O_5, under reduced pressure, for 1h. to afford the crude ω-hydroxy acid intermediate (104 mg, 0.252 mmol) as a viscous oil. The residue was dissolved in THF (3 ml), the solution was cooled to 0 °C, and triphenylphosphine (66 mg, 0.252 mmol) was added followed after ~2-3 min by the dropwise addition of DEAD (0.039 ml, 0.252 mmol). The faint yellow solution was stirred for a further 30 min. Evaporation of the solvent followed by column chromatography (hexane:ether, 8:1) gave **2** (69 mg, 64%); $[\alpha]^{25}_D$ +13.2° (c 1.00, $CHCl_3$) and **12** (13.5 mg, 13%); $[\alpha]^{25}_D$ -30.4° (c 1.03, $CHCl_3$).

(4*S*)-*tert*-Butyldiphenylsilyloxymethyl-(2*S*)-(2-propenyl)-butyrolactone (15)

PCl$_5$ (29 mg, 0.139 mmol) was added dropwise to a solution of **8** (52 mg, 0.126 mmol) in CH$_2$Cl$_2$ (2 ml) at 0° C. After 10 min a saturated aqueous solution of NaHCO$_3$ (10 ml) was added and the organics were extracted with CH$_2$Cl$_2$ (4 x 10 ml), dried and removed of solvent. Elution of the crude product through a short silica plug (hexane:ether, 4:1) followed by solvent removal gave a 10:1 inseparable mixture of **15** and **16** (45.8 mg, 92%); For the major product **2** (*trans* 2-propenyl): IR (CHCl$_3$) 1765 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.70-7.66 (m, 4H), 7.47-7.39 (m, 6H), 5.01 (p, J = 1.4 Hz, 1H), 4.95 (d, J = 0.9 Hz, 1H), 4.63-4.57 (m, 1H), 3.91 (dd J = 3.2, 11.4 Hz, 1H), 3.71 (dd, J = 3.1, 11.4 Hz, 1H), 3.57 (gt, J = 0.6, 9.5 Hz, 1H), 2.47-2.26 (m, 2H), 1.83 (dd, J = 0.8, 1.3 Hz, 3H), 1.68 (s, 9H); ^{13}C NMR (75 MHz, CHCl$_3$) δ 177.0, 140.3, 135.6, 135.5, 132.8, 132.3, 129.9, 127.8, 114.7, 77.9, 65.4, 47.6, 29.4, 26.7, 26.0, 19.1.

(4*S*)-*tert*-Butyldiphenylsilyloxymethyl-(2*R*)-(2-propyl)-butyrolactone (2).

Pd-C (40 mg) was added to a solution of **15** and **16** (46.0 mg, 0.116 mmol) in CH$_2$Cl$_2$ (2 ml) and a 1 atmosphere pressure of hydrogen was applied for 1h. Filtration of the mixture through Celite followed by solvent removal and column chromatography (hexane:ether, 4:1) gave the desired product **2** (40.0 mg, 86%) and the *cis* isomer **5** (3.6 mg, 6%) as colorless oils. Physical and spectral data were identical to those reported above.

(4*S*)-*tert*-Butyldiphenylsilyloxymethyl-(2S)-(1-hydroxy-1-methyl-2-trimethylsilyl-ethyl)-butyrolactone (17).

LiHMDS (0.31 ml, 0.31 mmol) was added to a solution of **7** (100 mg, 0.28 mmol) in THF (5 ml) at -78° C. After 1 h 1-(trimethylsilyl)-propan-2-one (0.062 ml, 0.396 mmol) was added rapidly followed after 20 min by a saturated aqueous solution of NH$_4$Cl (1 ml). The organics were extracted with ether (2 x 10 ml) and dried (Na$_2$SO$_4$). Removal of the solvent followed by column chromatography (hexane:ether, 1:1) gave the desired product **17** (89 mg, 63%) as a colorless oil (α:β = 11:1).

Major product (*trans* isomers):IR (CHCl$_3$) 1765 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.68-7.64 (m, 4H), 7.47-7.33 (m, 6H), 4.59-4.51 (m, 1H), 3.90-3.84 (m, 1H), 3.66 (dd, J = 11.4, 3.0, 1H), 3.00 (ddd appears as dt, J = 10.1, 5.7, 1H), 2.40-2.04 (m, 3H), 1.30-1.28 (m, 3H), 1.08 (s, 9H), 0.98-0.82 (m, 2H), 0.10 (s, 9H); ^{13}C NMR (75 MHz, CHCl$_3$) δ 179.5, 179.1, 135.6, 135.6, 132.7, 132.7, 132.4, 132.3, 130.0, 127.8, 77.8, 77.6, 73.8, 73.8, 65.6, 52.7, 51.9, 30.4, 28.3, 27.3, 26.8, 26.1, 19.1, 0.6, 0.4; HRMS, calcd. for C$_{27}$H$_{40}$O$_4$Si$_2$, 485.2543 (M$^+$+1); found, 485.2508.

Minor product (*cis* isomers):^{1}H NMR (400 MHz, CDCl$_3$) 7.68-7.64 (m, 4H), 7.47-7.33 (m, 6H), 4.47-4.40 (m, 1H), 3.90-3.84 (m, 1H), 3.74 (dd, J = 11.6, 3.9, 1H), 2.86 (ddd appears as dt, J = 12.6, 9.2, 1H), 2.40-2.04 (m, 3H), 1.30-1.28 (m, 3H), 1.08 (s, 9H), 0.98-0.82 (m, 2H), 0.10 (s, 9H).

(4*S*)-(Hydroxymethyl)-(2*R*)-(2-propenyl)-butyrolactone (18).

HF-pyridine (1 ml) was added to a stirring solution of **17** (80 mg, 0.165 mmol) in THF (2 ml) at 0° C. After 40 min the reaction was allowed to warm to RT and stirring was continued for a further 10 h. The reaction was quenched by pouring it into a 1:1 mixture of EtOAc and a saturated aqueous solution of $NaHCO_3$ (30 ml) followed by vigorous stirring for 20 min. The organic phase was separated, dried (Na_2SO_4) and concentrated under reduced pressure. Elution of the crude product through a short silica plug (hexane:EtoAc, 7:3) followed by solvent removal gave a mixture of the desired product **18** and its C-2 epimer (α:β = 11:1) (21 mg, 81%) as a colorless solid; Major product (*trans* isomers):IR ($CHCl_3$) 1765 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 5.00 (m, 1H), 4.94 (m, 1H), 4.65-4.62 (m, 1H), 3.92 (dd, J = 12.5, 2.9 Hz, 1H), 3.67 (dd, J = 12.5, 3.7 Hz, 1H), 3.44 (ddd, J = 9.6, 7.2, 0.7 Hz, 1H), 2.41-2.22 (m, 3H), 1.82 (dd, J = 1.3, 0.9 Hz, 3H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 177.1, 140.1, 114.3, 78.8, 64.2, 47.6, 30.0, 20.3; HRMS, calcd. for $C_8H_{12}O_3$, 155.0706 (M^+-1); found, 155.0911.

(4*S*)-Hydroxymethyl-(2*R*)-(2-propyl)-butyrolactone (3).

Hydrogen (1 atm) was applied to a mixture of 10% Pd-C (20 mg) and **18** (100 mg, 0.64 mmol) in ethyl acetate (1 ml) for 1 h, after which the mixture was filtered through Celite. Solvent removal gave **3** (96 mg, 95%) as a colorless oil. Physical and spectral data were identical to that reported above.

(4*S*)-(Benzyloxy-methyl)-(2*S*)-(1-hydroxy-1-methyl-2-trimethylsilyl-ethyl)-butyrolactone (20).

LiHMDS (0.625 ml, 0.625 mmol) was added to a solution of **19** (100 mg, 0.521 mmol) in THF (5 ml) at -78° C. After 1 h 1-(trimethylsilyl)-propan-2-one (0.114 ml, 0.73 mmol) was added rapidly followed after 20 min by a saturated aqueous solution of NH_4Cl (1 ml). The organics were extracted with ether (2 x 10 ml) and dried (Na_2SO_4). Removal of the solvent followed by column chromatography (hexane:EtOAc, 7:3) gave the desired product **20** (142 mg, 89%) as a colorless oil (α:β = 11:1).

Major product (*trans* isomers):IR ($CHCl_3$) 1765 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.28 (m, 5H), 4.65-4.51 (m, 3H), 3.75-3.45 (m, 3H), 2.99 (t, J = 10.0 Hz, 0.5H), 2.93 (t, J = 10.0 Hz, 0.5H), 2.34-2.12 (m, 2H), 1.29 (s, 1.5H), 1.26 (s, 1.5H), 1.04-0.85 (m, 2H), 0.1 (s, 4.5H), 0.08 (s, 4.5H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 179.3, 179.0, 137.5, 137.4, 128.5, 128.4, 127.9, 127.8, 127.7, 127.6, 76.7, 76.5, 73.8, 73.6, 71.6, 71.5, 52.2, 51.1, 30.5, 28.2, 27.8, 27.5, 26.9, 26.3, 0.4, 0.4; HRMS, calcd. for $C_{18}H_{27}O_4Si$, 335.1678 (M^+-1); found, 335.1710.

Minor product (*cis* isomers):^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.28 (m, 5H), 4.65-4.51 (m, 3H), 3.75-3.45 (m, 3H), 2.84 (dd, J = 9.3, 12.2 Hz, 1H), 2.34-2.12 (m, 2H), 1.29 (s, 1.5H), 1.26 (s, 1.5H), 1.98-1.65 (m, 2H), 0.1 (s, 4.5H), 0.08 (s, 4.5H).

(4*S*)-(Benzyloxy-methyl)-(2*R*)-(2-propenyl)-butyrolactone (21).

HF-pyridine (200 μl) was added dropwise to a stirring solution of **20** (200 mg, 0.60 mmol) in acetonitrile (10 ml) at 0° C. After 10 min the reaction was allowed to warm to RT and stirring was continued for a further 30 min. The reaction was quenched by pouring it into a 1:1 mixture of EtOAc and a saturated aqueous solution of $NaHCO_3$ (30 ml) followed by vigorous stirring for 20 min. The organic phase was separated, dried (Na_2SO_4)

and concentrated under reduced pressure. Elution of the crude product through a short silica plug (hexane:ether, 1:1) followed by solvent removal gave the desired product **21** (138 mg, 94%) as a colorless oil, (α:β = 11:1).

Major product (*trans* isomers):IR ($CHCl_3$) 1760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.31 (m, 5H), 4.99 (p, J = 1.3 Hz, 1H), 4.95-4.93 (m, 1H), 4.68-4.64 (m, 1H), 4.61 (d, J = 12.0 Hz, 1H), 4.55 (d, J = 12.0 Hz, 1H), 3.769 (dd, J = 10.7, 3.4 Hz, 1H), 3.60 (dd, J = 10.7, 3.9 Hz, 1H), 3.46 (t, J = 9.2 Hz, 1H), 2.37-2.29 (m, 2H), 1.82 (dd, J = 1.12, 0.8 Hz, 3H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 176.9, 140.45, 128.5, 127.8, 127.6, 114.5, 73.6, 71.5, 47.3, 29.8, 20.2; HRMS, calcd. for $C_{15}H_{19}O_3$, 247,1334 (M^{+}+1); found, 247,1343.

(4*S*)-Hydroxymethyl-(2*R*)-(2-propyl)-butyrolactone (3).

Hydrogen (50 psi) was applied to a mixture of 10% Pd-C (10 mg) and **21** (100 mg, 0.04 mmol) in methanol (1 ml) for 4 h, after which the mixture was filtered through celite. Solvent removal gave **3** (56 mg, 94%) as a colorless oil. Physical and spectral data were identical to that reported above.

Acknowledgments. We thank NSERCC for generous financial assistance through the Medicinal Chemistry Chair program. We thank Dr. M. Simard for the X-ray crystallographic analysis. We also thank Drs. Jürgen Maibaum and Walter Schilling (Ciba-Geigy) for helpful discussions.

References and notes.

1) For recent pertinent reports, see a) Ager, D.J.; East, M.B. "*Asymmetric Synthetic Methodology*", CRC Boca Raton, 1996. b) Seyden-Penne, J. "*Chiral Auxiliaries and Ligands in Asymmetric Synthesis*", J. Wiley & Sons, Inc. New York, N.Y., 1995. c) Sheldon, R.A. Chirotechnology: "*Industrial synthesis of Optically Active Compounds*", M. Dekker Inc., New York, N.Y., 1993. d) Blaser, H.U. *Chem. Rev.* **1992**, *92*, 935. e) Terashima, S. *Synlett.* **1992**, 691.

2) For selected examples, see a) Chakraborty, T.K.; Hussain, K.A.; Thippeswamy, D. *Tetrahedron* **1995**, *51*, 3873. b) Boyd, S.A.; Mantei, R.A.; Hsiao, C.; Baker, W.R. *J. Org. Chem.* **1991**, *56*, 438. c) Bühlmayer, P.; Caselli, A.; Fuhrer, W.; Göschke, R.; Rasetti, V.; Rüeger, H.; Stanton, J.L.; Criscione, L.; Wood, J.M. *J. Med. Chem.* **1988**, *31*, 1839. d) Kemp, D.J. *J. Org. Chem.* **1986**, *51*, 3921. e) Rich, D.H. *J. Med. Chem.* **1985**, *28*, 264.

3) For a review, see a) Huff, J. R. *J. Med. Chem.* **1991**, *34*, 2305. b) Thaisrivongs, S. *Annu. Rep. Med. Chem.* **1994**, *29*, 133.

4) a) Greenlee, W.J *J. Med. Res. Rev.* **1990**, 173. b) Boger, J. *Trends Pharm. Sci.* **1987**, 370. c) Ocain, D.; Abou-Gharbia, M. *Drugs of the Future* **1991**, *16*, 37.

5) For selected examples, see a) Peyrat, J.-F.; Chaboche, C.; Figadère, B.; Cavé, A. *Tetrahedron Lett.* **1995**, *36*, 2757. b) Dorsey, B.D.; Levin, R.B.; McDaniel, S.L.; Vacca, J.P; Guare, J.P.; Darke, P.L.; Zugay, J.A.; Emmi, E.A.; Schleif, W.A.; Quintero, J.C.; Lin, J.H.; Chen, I.-W.; Holloway, H.K.; Fitzgerald, P.M.D.; Axel, M.G.; Ostovic, D.; Anderson, P.S.; Huff, J.R. *J. Med. Chem.* **1994**, *37*, 3445. c) Baker, W.; Pratt, J.K. *Tetrahedron* **1993**, *49*, 8739. d) Poss, M.A.; Reid, J.A.; *Tetrahedron Lett.* **1992**, *33*, 1411. e) Chakravarty, P.K.; de Laszlo, S.E.; Sarnella, C.S.; Springer, J.P.; Schuda, P.F. *Tetrahedron Lett.* **1989**, *30*, 415.

6) a) Wolf, J.P.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 3164. b) Beard, C.D.; Baum, K.; Grakausas, V. *J. Org. Chem.* **1973**, *38*, 3673.
7) Rehders, F.; Hoppe, D. *Synthesis* **1992**, 859.
8) Nishi, T.; Kataoka, M.; Morisawa, Y. *Chemistry Lett.* **1989**, 1993.
9) Rouessac, F.P.; Gringore, O.H. *Org. Syn.* **1984**, *63*, 121.
10) a) Evans, D.A.; Morrissey, M.M.; Dow, R.L. *Tetrahedron Lett.* **1985**, *26*, 6005. b) Evans, D.A.; Morrissey, M.M. *J. Am. Chem. Soc.* **1984**, *106*, 3866;
11) Stork, G.; Kahne, D.E. *J. Am. Chem. Soc.* **1983**, *105*, 1072.
12) Hanessian, S; Pougny, J.-R; Bossenkool, I.K. *Tetrahedron* **1984**, *40*, 1289.
13) Tomioka, K.; Cho, Y.-S.; Sato, F.; Koga, K. *J. Org. Chem.* **1988**, *53*, 4094.
14) Poss, A.J. and Smyth, M.S. *Tetrahedron Lett.* **1989**, *30*, 5201.
15) Studies to try and epimerize the C-2 centre in compound **5** using a variety of bases proved challenging. Only *tert*-butoxide/THF gave a reasonable ratio (**2**:**5** = 1:1), while other bases including DBU, failed to generate any of the desired isomer. Formation of the lithium enolate (dianion) of **6** followed by protonation with a variety of compounds bearing acidic protons on either oxygen or carbon were unrewarding.
16) See for example a) Hanessian, S.; Faucher, A.-M. *J. Org. Chem.* **1991**, *56*, 2947. b) Melillo, D.G.; Liu, T.; Ryan, K.; Stetzinger, M.; Shinkai, I. *Tetrahedron Lett.* **1981**, *22*, 913. c) Hughes, D.L. *Org. React.* **1992**, *42*, 335. d) Mitsunobu, O. *Synthesis* **1981**, 1.
17) Encouragingly, the amount of C-2 epimer **13** was found to increase when LiOH was employed as the hydroxide source, however, further epimerization experiments using LiOH proved capricious.
18) Millard, A.A.; Rathke, M.W. *J. Am. Chem. Soc.* **1977**, *99*, 4833.
19) For the use of α-trimethlysilylketones and aldehydes as alkene precursors, see a) Hudrlik, P.F.; Kulkarni, A.K. *J. Am. Chem. Soc.* **1981**, *103*, 6251 and references therein. b) Hudrlik, P.F; Peterson, D. *Tetrahedron Lett.* **1972**, 1785. c) Hudrlik, P.F; Peterson, D. *J. Am. Chem. Soc.* **1975**, *97*, 1464. d) Ruden, R.A.; Gaffney, B.L. *Synth. Commum.* **1975**, *5*, 15.
20) α-Phenylselenoketones and aldehydes have also been used as similar alkene precursors, see a) Clive, D.L. J.; Russell, C.G. *J. Chem. Soc., Chem Commun.* **1981**, 434. b) Ryu, I.; Murai, S.; Niwa, I.; Sonada, N. *Synthesis* **1977**, 874.
21) For a review see, Ager, D.R. *Synthesis* **1984**, 384.
22) Hauser, C.R.; Hance, C.R. *J. Am. Chem. Soc.* **1952**, *74*, 5091.
23) In order to obtain consistently high yields for the cross-aldol step with 1-trimethylsilylpropan-2-one, it must be stored at 0 °C and re-distilled prior to use.
24) The use of diethyl ether as the solvent resulted in a 3:1 α:β ratio.

(*Received in USA* 23 *December* 1996; *revised* 13 *March* 1997; *accepted* 14 *March* 1997)