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Chiral γ and δ Hydroxysulfones via Lipase Catalyzed Resolutions - Synthesis of (*R*)(+)-4-Hexanolide and (2*R*,5*S*)-2-Methyl-5-Hexanolide Using Intramolecular Acylation†

Hollie K. Jacobs, Britta H. Mueller, and Aravamudan S. Gopalan*

Department of Chemistry
New Mexico State University
Las Cruces, NM 88003-0001

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Abstract:

Lipase PS-30 (Amano) was found to be an effective catalyst for enantioselective transesterification of a number of racemic γ and δ hydroxysulfones with isopropenyl acetate in ether. The intramolecular acylation of the ethyl carbonate derivatives obtained from the chiral hydroxysulfones **1d** and **1b** has been used for the preparation of *R*(+)-4-hexanolide, sex pheromone of the female dermestid beetle *Trogoderma glabrum* and (2*R*, 5*S*)-2-methyl-5-hexanolide, the sex pheromone of the carpenter bee.

The ease of acylation and alkylation of hydroxysulfones,[1] and the fact that subsequently the sulfonyl moiety can be removed either through a reductive or elimination procedure makes them valuable intermediates in asymmetric synthesis. Many chiral β-hydroxysulfones have been prepared by the bakers' yeast reduction of the corresponding β-ketosulfones.[2] The resultant products have been used for the synthesis of some chiral lactones, butenolides and 2,5 disubstituted tetrahydrofurans.[3] Mono or dianions of γ-alkoxy or γ-hydroxysulfones have also found a variety of synthetic applications.[4] Simple methods for the enantiospecific preparation of these intermediates need further development. Also, the intramolecular acylation of such sulfones has so far not received any attention.

Recently, we described the successful bakers' yeast reduction of some γ and δ ketosulfones to the corresponding (*S*)-hydroxysulfones[5] in high enantioselectivity and moderate yields. Intermediates from our study were used for the preparation of (*S*)(+)-parasorbic acid and (*S*)(+)-2-tridecanol acetate. Unfortunately, it was found that a number of ketosulfones are poor substrates for bakers' yeast. Also, for synthetic applications it is desirable to have a simple method for the preparation of both the (*R*) and (*S*)-hydroxysulfones in high enantioselectivity.

The use of lipases in organic solvents has recently been demonstrated to be a valuable tool for the resolution of a variety of alcohols, esters and carboxylic acids.[6] Recently, the resolution of some β, γ and δ-hydroxysulfones by porcine pancreatic lipase (PPL) using trichloroethyl butyrate in ether was reported.[7] PPL is not an efficient catalyst for this resolution reaction, as in many cases the reaction takes several days and provides products of only moderate optical purities. Attempts to accelerate this reaction using higher temperature results

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in lower enantioselectivity. It is interesting to note that the use of vinyl acetate, acetic anhydride, and O-acetylcyclohexanone oxime as acyl donors in this case failed, or afforded low yields. This prompts us to reveal the results of our own study on the resolution of racemic hydroxysulfones. Intermediates from our study have been subsequently utilized for the preparation of *R*-(+)-4-hexanolide and (2*R*, 5*S*)-2-methyl-5-hexanolide

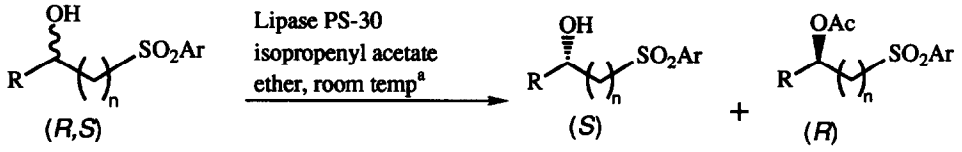
Of the various lipases that were studied for the resolution of hydroxysulfones, lipase PS-30 (Amano International Enzyme Co.) proved to be the most active and transesterification occurred when isopropenyl acetate was used as the acyl donor[8] at room temperature in ether. The results of our studies are given in Table 1. In all cases the (*R*) alcohol was preferentially esterified. The acylated product was readily separated from the unreacted alcohol by either column or preparative thin layer chromatography. The enantiomeric excess of the alcohols was determined by derivatization with (*S*)(+)-methoxytrifluoromethylphenylacetyl chloride followed by ^{1}H NMR analysis.[9] The corresponding acetates were analyzed in a similar manner after hydrolysis with potassium carbonate in methanol. The absolute configurations of the products were readily established by comparison with known values of their optical rotations.[5,7,10]

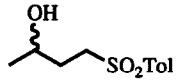
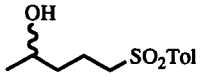
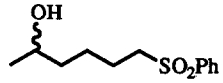
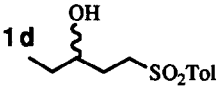
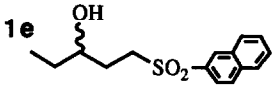
In general, in the examples that were studied, lipase PS-30 was found to exhibit good to moderate enantioselectivity and the reaction rates are faster in comparison to PPL. However, the extent of conversion is the crucial factor in obtaining the desired (*S*) or (*R*) alcohols of high optical purities. In all cases, the reactions were monitored by TLC or GC, and terminated after the appropriate extent of progress. This is particularly important, since the rates of these reactions showed some variability upon their scale up.

The preparation of the (*S*)-hydroxysulfones **1a** and **1b** in high optical purities could be accomplished when the extent of conversion was ~60% or more. However, it was disappointing to observe that the corresponding (*R*) alcohols were obtained only with moderate ee even under conditions of less than 50% conversion demonstrating that the enzyme transacylation was not highly stereoselective. In the case of 6-phenylsulfonyl-2-hexanol (**1c**) the enzyme selectivity was low and the extent of conversion had to be very high to obtain high optical purity of the residual alcohol. The preparation of the (*S*) alcohol **1c** was of particular interest to us, due to its use in the preparation of brefeldin A.[10] At ~25% conversion, *R*(-)-5-p-toluenesulfonyl-3-pentanol (**1d**) was obtained in high enantiomeric excess. The use of the corresponding naphthyl derivative **1e** did not improve the enantioselectivity of the reaction.

A new intramolecular acylation approach was used to convert the (*R*) enantiomer of the chiral hydroxysulfone **1d** obtained from our studies to *R*-(+)-4-hexanolide,[11] the sex pheromone of *Trogoderma glabrum* in 3 steps. Treatment of **1d** with ethyl chloroformate in pyridine gave the desired carbonate **2** in 98% yield. Deprotonation of the sulfone **2** with 2.2 eq. lithium hexamethyldisilylamide at -78°C in THF, leads to a clean intramolecular acylation[12] to yield the lactone **3** in 95% yield after chromatographic purification. The p-toluenesulfonyl moiety was then reductively removed using standard procedures to give *R*(+)-4-hexanolide (**4**).

Table 1. Resolution of Hydroxysulfones



	Substrate	time (h)	yield[b] (%)	S alcohol ee[c] (%)	S alcohol $[\alpha]_D$ (c,$CHCl_3$)	R acetate yield[b] (%)	R acetate $[\alpha]_D$ (c,$CHCl_3$)	R alcohol[d] ee (%)	R alcohol[d] $[\alpha]_D$ (c,$CHCl_3$)	E[e]
1a		16.5	40	>98	+20.8(0.8)	50	+5.2(1.7)	76	-16.8(1.1)	32
1b		48.0	42	>98	+9.0(1.2)	57	-5.1(1.3)	72	-6.9(1.3)	27
1c		7.0	47	71	+6.3(1.2)	51	+2.8(1.3)	57	-5.3(1.2)	7.5
1d		27.5	49	56	+12.6(1.2)	29	+9.6(2.0)	98	-23.6(1.2)	>50
1e		24.0	61	36	+5.9(1.1)	23	+9.7(0.9)	80	-14.8(1.0)	13

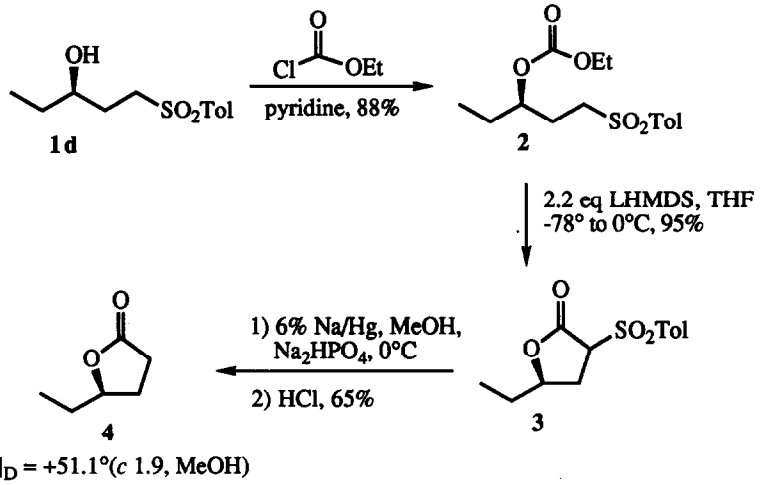
[a]A mixture of the hydroxysulfone in ether (1.0 M), isopropenyl acetate (5 eq) and lipase PS-30 from Amano (25,000 u/mmol of substrate) was stirred at room temperature, and worked up as described in the experimental.

[b]Yields of the alcohol or acetate after purification, by chromatography.

[c]ee was determined by ^1H NMR analysis of the corresponding MTPA esters. Absolute configuration of the alcohols were assigned by comparisons with reported values[5,7] of their optical rotations.

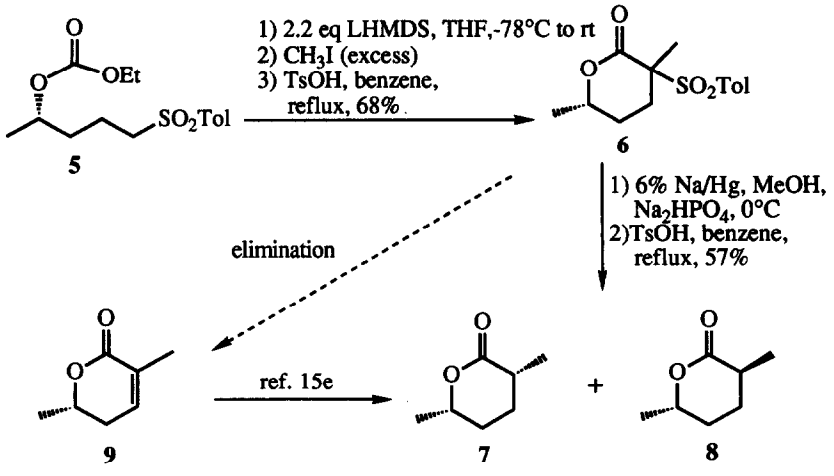
[d]Obtained by hydrolysis of the acetate with potassium carbonate in methanol; yields were usually in the range of 80-95%.

[e]Enantiomeric ratio (E) of the kinetic resolution calculated as described in Ref. 13.



$[\alpha]_D$ = +51.1°(*c* 1.9, MeOH)

In an analogous sequence of reactions, the mixed carbonate **5** was prepared from (*S*)-(-)-5-p-toluenesulfonylpentane-2-ol (**1b**).[14] Treatment of the carbonate **5** with lithium hexamethyldisilylamide (2.2 eq.) and trapping of the intermediate anion with methyl iodide gave the δ lactone **6** in 68% yield. Reductive removal of the sulfonyl moiety gave a 58:42 mixture of the diastereomeric *cis* and *trans* lactones **7** and **8**. The separation of these diastereomers to obtain pure *cis* (2*R*,5*S*)-2-methyl-5-hexanolide (sex pheromone of the carpenter bee) has already been achieved by several groups.[15] Preliminary studies to develop a more stereoselective synthesis of the *cis*-lactone **7**, via the conjugated lactone **9**, were unsuccessful. It is known that the catalytic hydrogenation of **9** gives a 96:4 ratio of the desired *cis* to *trans* lactone **7** and **8**.[15e] However, attempts to achieve the elimination of **6** with DBU in refluxing benzene or $tBuO^-K^+$ in refluxing tBuOH to give the conjugated lactone **9** were unsuccessful and led to isolation of unreacted starting material.



In conclusion, an improved method for the resolution of racemic hydroxysulfones using lipases has been developed.[16] The intramolecular acylation of the carbonates derived from these intermediates provides a new and simple route for the synthesis of chiral γ and δ lactones. The synthesis of *R*-(+)-4-hexanolide and (2*R*,5*S*)-2-methyl-5-hexanolide has been accomplished by this procedure.

Experimental

General Procedures. Infrared spectra were recorded on a Perkin Elmer 283B Spectrophotometer. ^1H NMR spectra were obtained on a Varian XL 200 MHz spectrometer and ^{13}C NMR spectra were obtained on a Varian Unity 400 MHZ Spectrometer with tetramethylsilane as an internal standard. Optical rotations were measured using a Perkin Elmer 241 polarimeter. Gas chromatographic analysis were carried out on an HP5880A gas chromatograph using a RSL500 column (25 m). Lipase PS-30 was obtained from Amano International Enzyme Co. Column chromatography was performed on silica gel 60 (70-230 mesh) using HPLC grade solvents obtained from Fisher Scientific. THF was freshly distilled from sodium/benzophenone. Analytical and preparative thin layer chromatography was done on silica 60/F254 plastic or glass backed plates obtained from E.M. Science. Racemic alcohols **1a-e** needed for comparison purposes were synthesized by BH_3 • THF reduction of the corresponding ketosulfones using standard procedures. The spectral data of all these compounds were in agreement with assigned structures. (*R*)-(+)-α-methoxy-α (trifluoromethyl)-phenylacetic acid was obtained from Aldrich.

Representative Procedure for Lipase Catalyzed Resolution-Preparation of (*S*)-1-(4-methylphenylsulfonyl)-3-pentanol (**1d**):. To a suspension of Lipase PS-30 (1.27 g, 43832u) in isopropenyl acetate (0.916 g, 9.1 mmol) was added a solution of the racemic hydroxysulfone **1d** (0.422g, 1.74 mmol) in ether (17 mL) and the suspension stirred at room temperature. Progress of the reaction was monitored by TLC and GC. After 27.5 h, the reaction mixture was extracted several times with ethyl acetate (5x25 mL), centrifuged, and the organic layer separated. The solvent was removed in vacuo and the crude product purified by silica gel chromatography (10%-50% ethyl acetate/hexane) to give the (*S*)-alcohol (0.209 g, 49%) {$[\alpha]_D$ +12.6° (*c* 1.2, $CHCl_3$)} and the (*R*)-acetate (0.154 g, 29%) {$[\alpha]_D$ +9.6° (*c* 2.0, $CHCl_3$)}. The optical purity of the (*S*)-alcohol was found to be 56% by analysis of its MTPA ester.

Representative hydrolysis procedure - Preparation of (*R*) **1d**. A solution of the acetate (0.154 g) in methanol (15 mL) and K_2CO_3 (0.20 g) was stirred at room temperature. After 16 h, ether was added until a precipitate formed and the suspension was then vacuum filtered through a short silica gel column in a sintered glass funnel. The solvent was removed in vacuo to give the pure (*R*)-alcohol **1d** (0.114 g, 93%). : $[\alpha]_D$ -23.6° (*c* 1.2, $CHCl_3$). The enantiomeric excess of this material was found to be 98% by analysis of its MTPA ester.

Preparation of mixed carbonate **2**. To a solution of the (*R*)-alcohol **1d** (0.62 g, 2.6 mmol, 98 %ee) in pyridine (6.2 mL, 77 mmol) at 0°C under N_2 was added dropwise ethyl chloroformate (1.2 mL, 13 mmol). The mixture was allowed to warm to room temperature and stirred for 16 h. The reaction was diluted with CH_2Cl_2 (100 mL) and washed with 2N HCl (2X100 mL), saturated $NaHCO_3$ (100 mL), and saturated NaCl (100 mL), dried ($MgSO_4$), filtered and the solvent removed in vacuo to give the crude carbonate (0.79 g). The crude

product was purified by silica gel chromatography (10% ethyl acetate/hexane) to give pure carbonate **2** (0.70 g, 88%).: $[\alpha]_D$ +17.3° (*c* 2.7, $CHCl_3$); IR (neat) 2973, 1742, 1597 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.79-7.31 (AB q, J=8.4 Hz, 4 H, arom), 4.76-4.63 (m, 1 H), 4.16 (q, J=7.3 Hz, 2 H), 3.21-3.11 (m, 2 H), 2.46 (s, 3 H), 2.16-1.94 (m, 2 H), 1.75-1.51 (m, 2 H), 1.29 (t, J=7.2 Hz, 3 H), 0.90 (t, J=7.3 Hz, 3 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 154.8, 144.8, 136.1, 130.0, 128.1, 77.4, 64.1, 52.6, 26.9, 26.7, 21.6, 14.2, 9.3; Analysis calc'd for $C_{15}H_{22}O_5S$: C, 57.30%; H, 7.05%; found: C, 57.44%; H, 7.07%.

Intramolecular acylation of **2**. To a solution of the sulfone **2** (0.33 g, 1.05 mmol) in freshly distilled THF (17 mL) at -78°C under N_2 was added dropwise a solution of lithium hexamethyldisilylamide in THF (1.0 M, 2.3 mL, 2.3 mmol). The solution was slowly allowed to warm to 0°C over a period of 1.5 h and stirred at 0°C for 15 min. The reaction was quenched in saturated NH_4Cl (40 mL) and extracted into ethyl acetate (2 X 30 mL). The organic layer was dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude lactone (0.29 g, 104%). The crude product was purified by silica gel chromatography (10%-20% ethyl acetate/hexane) to give the lactone **3** as a mixture of diastereomers (0.27 g, 95%).: IR (KBr) 2968, 2926, 2878, 1775, 1595, 1319 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.89-7.38 (m, 4 H, arom), 4.77-4.62 (m, 1 H), 4.46-4.20 (m, 1 H), 4.10-4.02 (dd, 1 H), 3.18-3.10 (m, 1 H), 2.84-2.20 (m, 1 H), 2.47 (s, 3 H), 1.70-1.60 (m, 2 H), 1.01 (t, 3 H); Analysis calc'd for $C_{13}H_{16}O_4S$: C, 58.19%; H, 6.01%; found: C, 58.32%; H, 5.92%.

(*R*)-(+)-4-hexanolide or (R)-(+)-γ-caprolactone (**4**). To a solution of the lactone **3** (0.26 g, 0.96 mmol) in methanol (43 mL) at 0°C was added Na_2HPO_4 (0.54 g, 3.8 mmol) and 6% sodium/mercury amalgam (4.4 g, 11.5 mmol) and the mixture stirred at 0°C for 3 h. The reaction mixture was filtered and rinsed with additional methanol (20 mL). The pH was adjusted to 1 with concentrated HCl and the solution stirred at room temperature for 16 h. The methanol was removed in vacuo and the residue was taken up in ether and dried ($MgSO_4$), filtered, and the solvent removed in vacuo to give the crude lactone (0.228 g). The crude product was filtered through a short silica gel column (50% ether/hexane) and the solvent removed. Kugelrohr distillation (45°C, 0.1 mm Hg) gave pure (*R*)-(+)-4-hexanolide (**4**) (0.071 g, 65%) as a colorless oil.: $[\alpha]_D$ +51.1° (*c* 1.9, MeOH) lit.[11] $[\alpha]_D$ +53.2° (*c* 1.0, MeOH). IR (neat) 2969, 2938, 2882, 1771 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.52-4.38 (m, 1 H), 2.59-2.50 (m, 2 H), 2.40-2.24 (m, 1 H), 1.96-1.52 (m, 3 H), 1.00 (t, 3 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 177.3, 82.2, 28.9, 28.5, 27.5, 9.4.

Preparation of mixed carbonate **5**. To a solution of the (*S*) alcohol **1b** (0.98 g, 4.1 mmol) in pyridine (9.8 mL, 122 mmol) at 0°C under N_2 was added dropwise ethyl chloroformate (1.9 mL, 20 mmol). The mixture was allowed to warm to room temperature and stirred for 16 h. The reaction was diluted with CH_2Cl_2 (80 mL) and washed with 2N HCl (60 mL), saturated $NaHCO_3$ (60 mL), and saturated NaCl (60 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude carbonate (1.3 g). The crude product was purified by silica gel chromatography (10% ethyl acetate/hexane) to give pure carbonate **5** (1.1 g, 90%).: $[\alpha]_D$ -0.83° (*c* 2.7, $CHCl_3$); IR (neat) 2981, 2931, 1738, 1598 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.79-7.31 (AB q, J=8.3 Hz, 4 H, arom), 4.77-4.63 (m, 1 H), 4.16 (q, J=7.3 Hz, 2 H), 3.09 (t, J=7.7 Hz, 2 H), 2.46 (s, 3 H), 1.90-1.57 (m, 2 H), 1.29 (t, J=7.2 Hz, 3 H), 1.25 (d, J=6.3 Hz, 3 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 154.7,

144.7, 136.1, 129.9, 128.1, 73.9, 63.8, 55.9, 34.3, 21.6, 19.8, 18.9, 14.2; Analysis calc'd for $C_{15}H_{22}O_5S$: C, 57.30%; H, 7.07%; found: C, 57.63%; H, 7.07%.

Intramolecular acylation of **5**. To a solution of the sulfone (0.40 g,1.3 mmol) in freshly distilled THF (30 mL) at -78°C under N_2 was added a solution of lithium hexamethyldisilylamide in THF (1.0 M, 2.8 mL, 2.8 mmol). The solution was slowly allowed to warm to room temperature over a period of 1 h. After stirring for 2 h, TLC showed no more starting material. Methyl iodide (1.12 mL, 18 mmol) was added and the mixture stirred for 20 h. TLC showed residual nonmethylated starting material so methyl iodide (0.80 mL, 13 mmol) was again added and the mixture stirred for another 2 h. The reaction was then poured into 2N HCl (40 mL) and extracted into ethyl acetate(2x50 mL). The organic layer was then washed with 10% $Na_2S_2O_3$ (20 mL) and saturated NaCl (30 mL), dried ($MgSO_4$), filtered and the solvent removed in vacuo to give the crude methylated lactone containing some of the corresponding hydroxyacid (0.39 g). The crude product was completely converted to the lactone by dissolving in benzene (3 mL) and adding a catalytic amount of p-toluenesulfonic acid. The mixture was refluxed for 1.5 h, cooled and diluted with ethyl acetate (30 mL). The organic layer was washed with saturated $NaHCO_3$ (20 mL) and saturated NaCl(20 mL), dried ($MgSO_4$), filtered and the solvent removed in vacuo to give the crude lactone (0.30 g). The crude lactone was purified by silica gel chromatography (10% ethyl acetate/hexane) to give the pure methylated lactone **6** as an inseparable mixture of diastereomers (0.24 g, 68%).: IR (KBr) 2979, 2936, 1722, 1596 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.81-7.33 (m, 4 H,arom), 4.78-4.50 (m, 1 H), 3.07-2.76 (m, 1 H), 2.45 (s, 3 H), 2.43-1.82 (m, 3 H), 1.55 (s, 3 H), 1.46 (d, J=6.3 Hz, 3 H), 1.43 (s, 3 H,), 1.38 (d, J=6.4 Hz, 3 H); MS (m/z) 282 (M^+), 283 (M^+ +1), 284 (M^+ +2), 267 (M^+ -15); Analysis calc'd for $C_{14}H_{18}O_4S$: C, 59.55%; H, 6.43%; found: C, 59.77%; H, 6.63%.

(*2R,5S*)-2-methyl-5-hexanolide (**7**) and (*2S, 5S*)-2-methyl-5-hexanolide (**8**). To a solution of the lactone **6** (0.16 g, 0.57 mmol) in methanol (25 mL) under N_2 at 0°C was added Na_2HPO_4(0.32g, 2.3 mmol) and 6% sodium/mercury amalgam(2.6 g, 6.8 mmol) and the mixture stirred at 0°C for 3 h. The mixture was then vacuum filtered through a short silica gel column with ethyl acetate (100 mL) as eluant. The solvent was removed in vacuo. The remaining residue was taken up in ethyl acetate and refiltered though a short silica gel column. The remaining residue was then dissolved in benzene (4 mL) and a catalytic amount of p-toluenesulfonic acid added and the mixture then heated at reflux for 2 h. The mixture was cooled and diluted with ethyl acetate (20 mL) and then washed with saturated $NaHCO_3$ (10 mL) and saturated NaCl (10 mL), dried ($MgSO_4$), filtered, and the solvent removed in vacuo to give crude lactone (0.076 g). The crude lactone was purified by preparative thin layer chromatography (50% ethyl acetate/hexane) to give **7** and **8** (0.042 g, 57%) as a mixture of *cis* and *trans* isomers: IR (neat) 2926, 2861, 1732 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.57-4.40 (m, 1 H), 2.70-2.17 (m, 1 H), 2.22-1.84 (m, 2 H), 1.73-1.48 (m, 2 H), 1.37 (d, J=6.3 Hz, 3 H, *trans*), 1.36 (d, J=6.2 Hz, 3 H, *cis*), 1.31 (d, J=7 Hz, 3 H, *trans*), 1.23 (d, J=6.7 Hz, 3 H, *cis*); ^{13}C NMR (400 MHz, $CDCl_3$) δ 176.3 (c), 174.4 (t), 78.2 (t), 74.4 (c), 35.8 (t), 33.0 (c), 31.0 (t), 28.6, 28.4, 25.6 (c), 22.2 (c), 21.1 (c), 17.4 (t), 16.2 (c); GC analysis on RSL 500 showed two peaks corresponding to the *cis* isomer, (58.2%, 9.34 min retention time) and *trans* isomer (41.8%, 8.72 min retention time).

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