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Titanium Tetrachloride-Mediated Enantioselective Synthesis of trans β-Lactones

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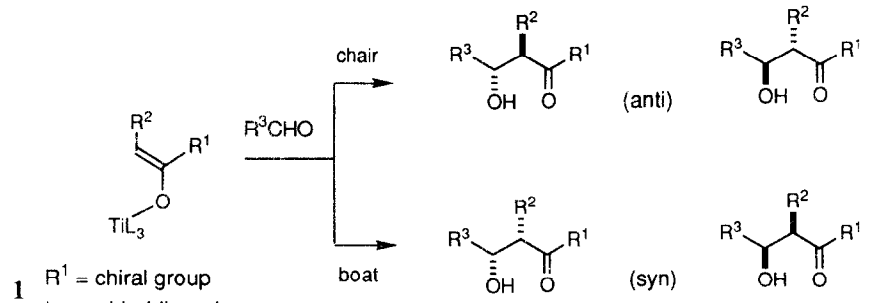
Abstract: *Pharmacologically interesting trans β-lactones* ***11*** *and* ***16*** *were synthesized using a titanium tetrachloride-mediated enantioselective aldol reaction as the key synthetic step (see* ***Scheme 2****).*

Titanium chemistry offers great advantages over group I-, II-A, and I-, II-, III-B metal chemistry due to the possibility of controlling the electronic property at titanium (e.g. Lewis acidity) and the steric environment around the metal simply by choosing the proper ligands.[1] In enolate chemistry, titanium has often successfully competed with the more popular lithium and boron. This includes asymmetric aldol reactions under either substrate control using chiral ketones and esters, as in **1**, or reagent control using chiral ligands attached to titanium, as in **2** (**Scheme 1**). A recent elegant example of this second type is the Ciba-Geigy chiral enolate based on a cyclopentadienyl titanium carbohydrate complex[2] (type **2** enolate). Type **1**, -O-TiX_3 enolate chemistry (X=Cl, OR), was developed by Thornton,[3] Heathcock,[4] Evans,[5] and is the descendant of more basic work done by Reetz,[6a,b] Nakamura and Kuwajima,[6c-e] and others.[6f-k]



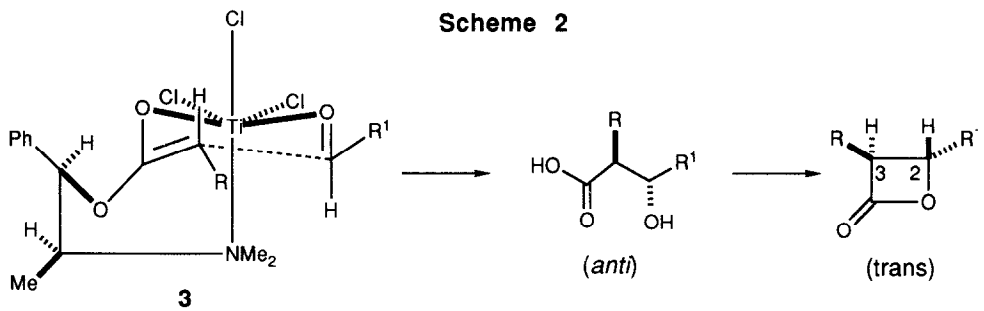
Scheme 1

The reaction of enolsilanes with aldehydes in the presence of $TiCl_4$ (the so called "Mukaiyama reaction")[7,8] is known *not* to involve trichlorotitanium enolates. These enolates have been synthesized from silyl enol ethers, characterized and shown to give a completely different stereochemical outcome to that of the $TiCl_4$-mediated reactions of silyl enol ethers.[6c-e] The major difference seems to be related to the timing of $TiCl_4$ addition: premixing of $TiCl_4$ with the enolsilane followed by addition of the aldehyde is most probably a trichlorotitanium enolate-mediated aldol reaction; premixing of $TiCl_4$ with the aldehyde followed by addition of the enolsilane promotes the $TiCl_4$-mediated "Mukaiyama reaction" of enolsilanes. The transition state structures for the titanium

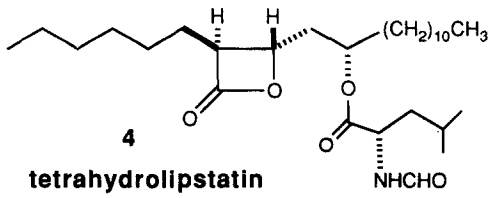
enolate-mediated aldol reactions are believed to be cyclic (six-membered); both chairs[3-6] and boats[2] have been proposed to account for the experimental results. The possibility of chelating another donating functional group, present in the aldehyde (e.g. α– or β-alkoxy aldehydes) or in the enolate (e.g. the oxazolidinone carbonyl) depends on the Lewis acidity of the metal and therefore on the ligands attached to the metal (Cl > OR > Cp).[1] For the "Mukaiyama reaction" of enolsilanes, acyclic transition structures have been proposed with no intimate involvement between the silyl enol ether and the Lewis acid,[8,9] and with the aldehyde carbonyl group activated for the nucleophilic addition by complexation with $TiCl_4$.[8] From the above discussion it is clear that there are no precise boundaries between the two reactions, and that small variations in the substrate structure or in the reaction procedure can have a strong influence on the reaction mechanism.

Chiral silyl ketene acetals have been developed by the groups of Helmchen,[10] Oppolzer,[11] and Gennari,[12] and their $TiCl_4$-mediated reactions with aldehydes studied in detail. The main success of these reagents is their ability to produce enantiomerically enriched (>90-95% e.e.) *anti* aldols, which are not easily synthesized using the other popular methods for enantioselective synthesis of aldol compounds.[13] The reagents developed at Milano are esters of N-methylephedrine and were conceived with the hope that they would be inclined to bind $TiCl_4$ through the NMe_2 group, with consequent dramatic conformational constraint. Based on mechanistic studies and the reasonable expectation that both the aldehyde carbonyl and the ephedrine NMe_2 group would bind to $TiCl_4$, which usually ligates two electron donating molecules to form cis-octahedral six-coordinate complexes, the transition structure model shown below (**3**, **Scheme 2**) was proposed for the asymmetric aldol reaction.[12] A trichlorotitanium enolate is postulated since the same stereoselectivity was observed by first adding $TiCl_4$ to the silyl ketene acetal, with evolution of Me_3SiCl, and then addition of the aldehyde, or by first adding $TiCl_4$ to the aldehyde, and then addition of the silyl ketene acetal.

Scheme 2



In this paper we describe a useful application of this methodology to the synthesis of β-lactones possessing interesting biological properties. Two main classes of β-lactones with important pharmacological activities are known: class A includes the inhibitors of HMG-CoA synthase and of cholesterol biosynthesis (Merck Sharp & Dohme's L-659,699; also known as ICI 1233A),[14] while class B includes the inhibitors of pancreatic lipase which are potential antiobesity agents (Esterastin, Ebelactone A and B, Valilactone, Hoffmann-La Roche's Lipstatin and Tetrahydrolipstatin **4**).[15] Using the chemistry outlined in **Scheme 2**, we have been synthesizing several compounds related to class B with the following basic characteristics: (a) a 2,3-trans-substituted oxetanone, with S absolute configuration at both stereogenic centres; (b) a six-carbon alkyl chain at C-3; (c) an alkyl or alkenyl chain at C-2 bearing various functional groups. Here we report two examples of these compounds, which have shown interesting inhibitory properties when subjected to *in vitro* assays (*vide infra*).



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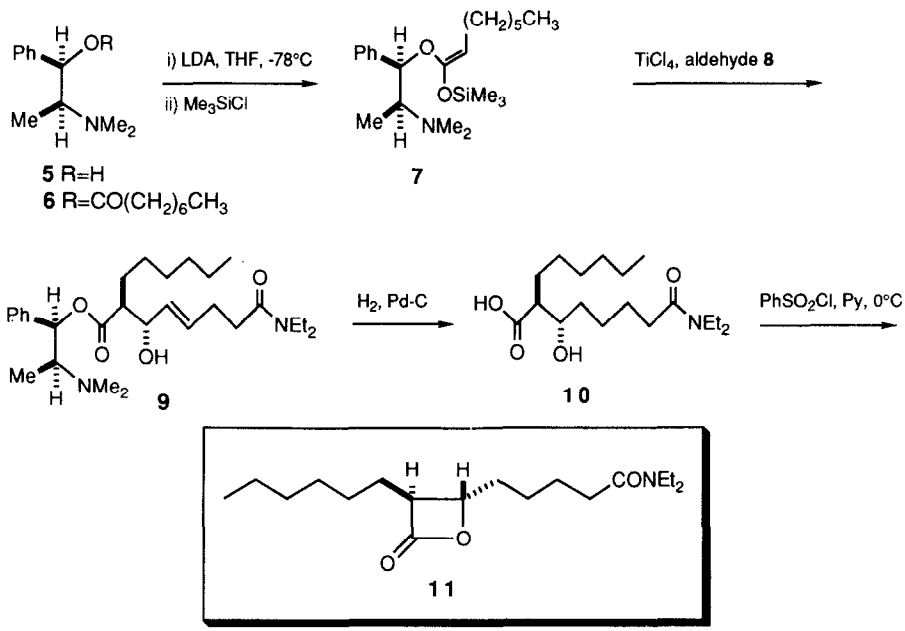
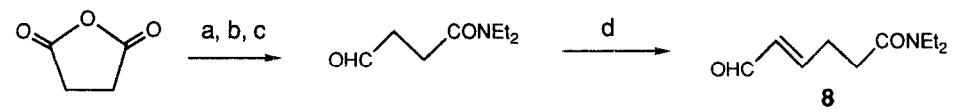
tetrahydrolipstatin

Caprylic acid was transformed into the chloride ($SOCl_2$), and then treated with commercially available 1R,2S N-methylephedrine (**5**) (**Scheme 3**). The resulting ester (**6**) was treated with LDA in THF at -78°C and then with Me_3SiCl to give exclusively-E silyl ketene acetal (**7**) in quantitative yield.[12] By slow addition of 3 equivalents of $TiCl_4$ (typically 30 min for 1 mmol of $TiCl_4$) to a 2:1 mixture of silyl ketene acetal (**7**) and aldehyde (**8**) [for preparation of aldehyde (**8**) see **Scheme 4**] in dichloromethane at -78°C, the *anti* α-alkyl-β-hydroxyester (**9**) was obtained in 50% isolated yield.

Scheme 3



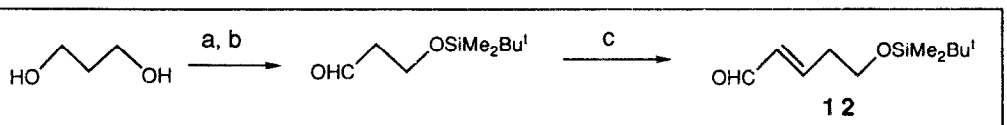
It should be noted here that although the addition yield is not excellent, the stereoselectivity of the process is very good. The small amount of *syn* aldol (≤5%) was easily separated by flash chromatography, and unreacted aldehyde (**8**) and ester (**6**) could be recovered through chromatography and recycled. The usual reaction protocol, i.e. precomplexation of the aldehyde with $TiCl_4$ and subsequent addition of the silyl ketene acetal,[12] could not be followed in this case because of the formation of a thick $TiCl_4$-aldehyde precipitate caused by the presence of the strongly basic $CONEt_2$ group of the aldehyde. This is also the reason why a threefold excess of $TiCl_4$ was needed. α,β-Unsaturated aldehydes were chosen as substrates since they result in higher yields and better stereoselectivities compared to saturated aldehydes.[12a]



Scheme 4. Reagents and yields: **a)** excess Et_2NH, benzene, 40°C, 3h; 98% **b)** BH_3-Me_2S, THF-CH_2Cl_2, 25°C, 3h; 86% **c)** ClCO-COCl, DMSO, CH_2Cl_2, -70°C; Et_3N, -30°C/0°C; 90% **d)** Ph_3P=CHCHO, benzene, reflux, 8h; 82%.

Anti α-alkyl-β-hydroxyester (**9**) was then treated with H_2 in the presence of Pd-C to give acid (**10**) in quantitative yield. Finally, treatment with $PhSO_2Cl$ (2 equiv.)[16] in pyridine at 0°C gave trans β-lactone (**11**) in 75-80% yield ($J_{H2\text{-}H3}$ = 3.9 Hz, $\nu_{max.}$ = 1815 cm^{-1}).[17] Ester (**9**) was also transformed (KOH, MeOH, RT) into the corresponding α,β-unsaturated acid, but all attempts to cyclize this material under the above mentioned conditions failed due to accompanying decarboxylation and diene formation.[15],[18]

The same reaction sequence described in Scheme 3 was repeated using aldehyde (**12**), which contains an alcohol protected as the t-butyldimethylsilyl ether. This protecting group is known by ^1H- and ^{13}C-NMR studies to shield the alcohol from chelation with $TiCl_4$.[19] Aldehyde (**12**) was synthesized according to **Scheme 5**.



Scheme 5. Reagents and yields: **a)** NaH, THF, Me_2Bu^tSiCl; 83% **b)** ClCO-COCl, DMSO, CH_2Cl_2, -70°C; Et_3N, -30°C/0°C; 85% **c)** Ph_3P=CHCHO, benzene, reflux, 5h; 80%.

The aldol condensation of silyl ketene acetal (**7**) with aldehyde (**12**) was run either by slow addition of $TiCl_4$ (3 eq.) (typically 40 min for 1 mmol of $TiCl_4$) to a 2:1 mixture of (**7**) and (**12**), or by precomplexation of the aldehyde (**12**) (1 eq.) with $TiCl_4$ (1.5 eq) and then addition of the ketene acetal (**7**) (1.5 eq.) (**Scheme 6**). Both procedures resulted in a 50% isolated yield of *anti* adduct (**13**). The small amount of *syn* aldol (≤5%) was easily separated by flash chromatography, and unreacted aldehyde (**12**) and ester (**6**) could be recovered through chromatography and recycled. *Anti* α-alkyl-β-hydroxyester (**13**) was then treated with H_2 in the presence of Pd-C to give acid (**14**) in quantitative yield. Treatment with $PhSO_2Cl$ (2 equiv.)[16] in pyridine at 0°C gave trans β-lactone (**15**) in 70% yield. Removal of the silyl protecting group (HF, CH_3CN, 0°C; 95%) and acylation with N-formyl-L-leucine (DCC, 4-PP, CH_2Cl_2; 88%) gave the desired β-lactone (**16**).

β-Lactones (**11**) and (**16**) were found to be good inhibitors of pancreatic lipase activity.[20] 67-71% inhibition was observed at 1 μM concentration (10^{-6} M) for both compounds. 96-97% inhibition was reached at 1mM concentration (10^{-3} M). Further pharmacological studies are at present being carried out.

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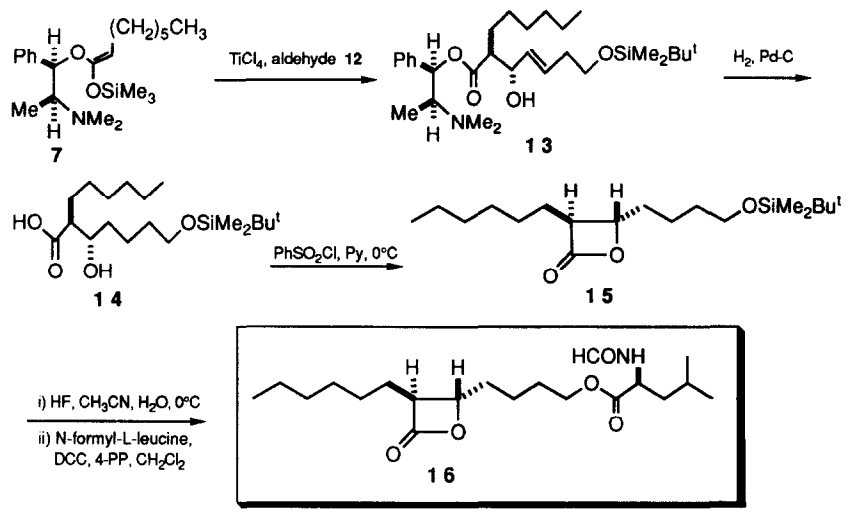
Scheme 6



Experimental Section

Ester (6). A solution of (1R,2S)-N-methyl ephedrine (**5**) (9.34 g, 52.1 mmol) in dichloromethane (104 ml) was treated with octanoyl chloride (b.p. 85°C/16 mmHg) (10.61 g, 62.5 mmol). After stirring for 8 h at room temperature, the mixture was treated with 1N NaOH (130 mmol) and stirred for further 8 h. The organic phase was separated, washed with water, dried (Na_2SO_4) and evaporated. The crude product was purified by flash chromatography (CH_2Cl_2-MeOH 95:5) to give ester (**6**) in 95% yield. IR (film) 1740, 1160 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.9 (t, 3H, J=6.0 Hz, CH_3CH_2), 1.1 (d, 3H, J=7.0 Hz, CH_3CHN), 1.2-1.4 (m, 8H, CH_2), 1.6-1.7 (m, 2H, CH_2), 2.3 (s, 6H, Me_2N), 2.4 (t, 2H, J=7.0 Hz, CH_2CO), 2.9 (m, 1H, $CHNMe_2$), 6.0 (d, 1H, J=4.0 Hz, CHPh), 7.3 (m, 5H, ArH).

Silyl ketene acetal (7). A solution of diisopropylamine (0.76 ml, 5.4 mmol) in THF (11.0 ml) was treated with n-BuLi (1.6 M solution in n-hexane; 3.23 ml, 5.17 mmol) at 0°C under nitrogen, with stirring. The mixture was stirred at 0°C for 20 min, then cooled to -78°C. A solution of ester (**6**) (1.375 g, 4.5 mmol) in THF (9.0 ml) was slowly added and the resulting mixture was stirred at this temperature for 1 h. Me_3SiCl (0.683 ml, 5.4 mmol) was added dropwise, stirring continued for 30 min and then the mixture was slowly warmed to room temperature over 1 h. The solvent was removed under vacuum, and the resulting oil was pumped at 0.1 mmHg for several hours. The crude compound (*free from THF !*) was then taken up in dichloromethane (5.4 ml), and the solution thus obtained (0.8 M of **7** in CH_2Cl_2) was kept as a stock solution at -20°C (in the freezer) without appreciable decomposition for several weeks. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.0 (s, 9H, $SiMe_3$), 0.9 (t, 3H, J=6.0 Hz, CH_3CH_2), 1.1 (d, 3H, J=7.0 Hz, CH_3CHN), 1.2-1.4 (m, 8H, CH_2), 2.0-2.1 (m, 2H, $CHCH_2CH_2$), 2.3 (s, 6H, Me_2N), 2.7-2.8 (m, 1H, $CHNMe_2$), 3.5 (t, 1H, J=6.8 Hz, $CHCH_2$), 5.3 (d, 1H, J=4.0 Hz, CHPh), 7.3 (m, 5H, ArH).

General procedure for the $TiCl_4$-mediated aldol addition. A 0.8 M solution of silyl ketene acetal (**7**) in CH_2Cl_2 (0.83 ml, 0.66 mmol) was added to a stirred solution of aldehyde (**8** or **12**) (0.33 mmol) in dichloromethane (0.66 ml) at -78°C under nitrogen. The mixture was then treated with a 1 M solution of $TiCl_4$ in CH_2Cl_2 (1.0 ml, 1.0 mmol) over 30-40 min, and stirred at -78°C for an additional 90 min before being quenched with 1 N NaOH and 5% $NaHCO_3$ aqueous solution. The resulting mixture was filtered through celite, the organic phase washed with water, dried (Na_2SO_4) and evaporated. The crude product was purified by flash chromatography to give *anti* α-alkyl-β-hydroxyester (**9** or **13**).

***Anti* α-alkyl-β-hydroxy ester (9).** Flash chromatography: EtOAc: n-hexane: MeOH 74:16:10. Yield: 50%. ^{1}H-NMR ($CDCl_3$ + D_2O, 200 MHz): δ 0.86 (t, 3H, J=6.5 Hz, CH_3-CH_2), 1.10 (d, 3H, J=6.5 Hz, CH_3CH), 1.12 (t, 3H, J=7.0 Hz, CH_3CH_2N), 1.17 (t, 3H, J=7.0 Hz, CH_3CH_2N), 1.2-1.8 (m, 10H), 2.3-2.6

(m, 6H, CH_2CH_2CON, $CHNMe_2$, OCOC*H*), 2.40 (s, 6H, Me_2N), 3.31 (q, 2H, J=7.0 Hz, $MeCH_2N$), 3.39 (q, 2H, J=7.0 Hz, $MeCH_2N$), 4.22 (dd, 1H, $J_1=J_2=8.0$ Hz, C*H*OH), 5.50 (dd, 1H, $J_1=15.5$, $J_2=8.0$ Hz, HOCH-C*H*=C), 5.75-5.92 (m, 1H, C=C*H*-CH_2), 6.40 (d, 1H, J=2.9 Hz, C*H*Ph), 7.15-7.45 (m, 5H, Ar*H*).

***Anti* α-alkyl-β-hydroxy acid (10).** A solution of *anti* α-alkyl-β-hydroxy ester (**9**) (200 mg, 0.41 mmol) in MeOH (4.1 ml) was treated with 10% Pd/C (87 mg) under hydrogen (1 atm). After stirring for 3 h at room temperature, the mixture was filtered and the solvent evaporated. The crude product was dissolved in EtOAc, and the organic phase was washed twice with 5% aqueous HCl and once with water. The organic phase was then dried (Na_2SO_4) and evaporated. The crude compound was purified by flash chromatography (EtOAc-MeOH 92:8) to give *anti* α-alkyl-β-hydroxy acid (**10**) in >95% yield. ^{1}H-NMR ($CDCl_3$ + D_2O, 200 MHz): δ 0.86 (t, 3H, J=5.6 Hz, CH_3CH_2C), 1.11 (t, 3H, J=6.9 Hz, CH_3CH_2N), 1.18 (t, 3H, J=6.9 Hz, CH_3CH_2N), 1.2-1.8 (m, 16H), 2.31 (t, 2H, J=6.8 Hz, CH_2CO), 2.3-2.5 (m, 1H, OCOC*H*), 3.28 (q, 2H, J=6.9 Hz, CH_2N), 3.36 (q, 2H, J=6.9 Hz, CH_2N), 3.66-3.80 (m, 1H, C*H*OH).

β-Lactone (11). A solution of *anti* α-alkyl-β-hydroxy acid (**10**) (180 mg, 0.546 mmol) in pyridine (5.5 ml) was treated at 0°C with $PhSO_2Cl$ (0.14 ml, 1.09 mmol). After stirring at 0°C for 18 h, the mixture was treated with water and extracted with EtOAc. The combined organic extracts were dried (Na_2SO_4) and evaporated. The crude compound was purified by flash chromatography (n-hexane-EtOAc 1:1) to give β-lactone (**11**) in 78% yield. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.88 (t, 3H, J= 6.5 Hz, CH_3CH_2C), 1.11 (t, 3H, J=6.9 Hz, CH_3CH_2N), 1.17 (t, 3H, J=6.9 Hz, CH_3CH_2N), 1.25-1.55 (m, 10H), 1.55-1.85 (m, 6H), 2.30 (t, 2H, J=7.4 Hz, CH_2CON), 3.17 (ddd, 1H, $J_1=8.5$, $J_2=7.0$ Hz, $J_3=3.9$ Hz, C*H*CO), 3.30 (q, 2H, J=6.9 Hz, CH_2N), 3.38 (q, 2H, J=6.9 Hz, CH_2N), 4.24 (ddd, 1H, $J_1=7.0$ Hz, $J_2=6.5$ Hz, $J_3=3.9$ Hz, C*H*O). ^{13}C-NMR ($CDCl_3$, 200 MHz): δ 171.44, 171.39, 77.75, 56.03, 41.79, 40.01, 34.27, 32.53, 31.36, 28.81, 27.73, 26.78, 24.81, 24.76, 22.38, 14.26, 13.89, 12.99. $[\alpha]_D^{25}$= -26.2° (c 1.14, $CHCl_3$). IR ($CHCl_3$) selected data: 1815, 1620 cm^{-1}. MS (FAB): 312 (M+1).

***Anti* α-alkyl-β-hydroxy ester (13).** Flash chromatography: n-hexane-EtOAc 1:1. Yield: 50%. ^{1}H-NMR ($CDCl_3$ + D_2O, 200 MHz): δ 0.10 (s, 6H, CH_3Si), 0.75-0.95 (m, 12H, $(CH_3)_3C$, CH_3CH_2), 1.00 (d, 3H, J=6.5 Hz, CH_3CH), 1.10-1.40 (m, 10H), 2.35 (s, 6H, NMe_2), 2.4-2.7 (m, 3H, OCOC*H*, C=CCH_2), 2.85-3.00 (m, 1H, $CHNMe_2$), 3.65 (t, 2H, J=7.0 Hz, CH_2OSi), 4.20 (dd, 1H, $J_1=J_2=8.1$ Hz, C*H*OH), 5.50 (dd, 1H, $J_1=16.0$, $J_2=8.1$ Hz, HOCH-C*H*=C), 5.75 (ddd, 1H, $J_1=16.0$ Hz, $J_2=J_3=7.0$ Hz, C=C*H*-CH_2), 6.40 (d, 1H, J=2.4 Hz, C*H*Ph), 7.2-7.4 (m, 5H, Ar*H*).

***Anti* α-alkyl-β-hydroxy acid (14).** A solution of *anti* α-alkyl-β-hydroxy ester (**13**) (550 mg, 1.06 mmol) in MeOH (11.0 ml) was treated with 10% Pd/C (220 mg) under hydrogen (1 atm). After stirring for 3 h at room temperature, the mixture was filtered and the solvent evaporated. The crude product was dissolved in EtOAc, and the organic phase was washed twice with 5% aqueous HCl and once with water. The organic phase was then dried (Na_2SO_4) and evaporated. The crude compound was purified by flash chromatography (n-hexane-EtOAc-MeOH 48:47:5) to give *anti* α-alkyl-β-hydroxy acid (**14**) in >95% yield. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.15 (s, 6H, CH_3Si), 0.90 (s, 9H, $(CH_3)_3C$), 1.10-1.80 (m, 20H), 2.15-2.40 (m, 1H, OCOC*H*), 3.45-3.70 (m, 3H, C*H*OH, CH_2OSi), 5.0-6.0 (br.s, 1H, COO*H*).

β-Lactone (15). A solution of *anti* α-alkyl-β-hydroxy acid (**14**) (73 mg, 0.202 mmol) in pyridine (2.0 ml) was treated at 0°C with $PhSO_2Cl$ (0.052 ml, 0.405 mmol). After stirring at 0°C for 18 h, the mixture was treated with water and extracted with EtOAc. The combined organic extracts were dried (Na_2SO_4) and evaporated. The crude compound was purified by flash chromatography (n-hexane-EtOAc 95:5) to give β-lactone (**15**) in 70% yield. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.05 (s, 6H, CH_3Si), 0.85-0.95 (m, 12H, $(CH_3)_3C$, CH_3CH_2), 1.2-2.0 (m, 16H), 3.18 (ddd, 1H, $J_1=8.7$ Hz, $J_2=6.3$ Hz, $J_3=3.8$ Hz, C*H*C=O), 3.65 (t, 2H, J=5.9 Hz, CH_2OSi), 4.23 (ddd, 1H, $J_1=J_2=7.0$ Hz, $J_3=3.8$ Hz, C*H*-O). $[\alpha]_D^{25}$= -11.7° (c 1.25, $CHCl_3$). IR ($CHCl_3$) selected data: 1815, 1250, 1100 cm^{-1}.

β-Lactone (16). β-Lactone (**15**) (400 mg, 1.12 mmol) was treated with a 0.5 M solution of HF in CH_3CN-H2O (66:1) (2.8 ml) at 0°C, and stirred at 0°C for 3.5 h. The solvent was then evaporated and the crude product purified by flash chromatography (n-hexane-EtOAc 6:4) to give the desired alcohol in 95% yield. ^{1}H-NMR

($CDCl_3$, 200 MHz): δ 0.90 (t, 3H, J=5.9 Hz, CH_3CH_2), 1.2-2.0 (m, 16H), 2.8 (br.s, 1H, OH), 3.19 (ddd, 1H, J_1=8.5 Hz, J_2=6.5 Hz, J_3=3.8 Hz, CHC=O), 3.69 (t, 2H, J=6.0 Hz, CH_2OH), 4.25 (ddd, 1H, $J_1=J_2$=7.1 Hz, J_3=3.8 Hz, CH-O). $[\alpha]_D^{25}$= -27.3° (c 1.85, $CHCl_3$). IR ($CHCl_3$) selected data: 3620, 1815, 1120, 1055 cm^{-1}. A solution of the above described alcohol (360 mg, 1.6 mmol) in CH_2Cl_2 (31.5 ml) was treated at room temperature with DCC (660 mg, 3.2 mmol), 4-pyrrolidinpyridine (4-PP, 25 mg, 0.16 mmol) and N-formyl leucine (510 mg, 3.3 mmol). After stirring for 2 h at RT, the mixture was filtered and the resulting solution was washed with water, dried (Na_2SO_4), and evaporated. The crude product was purified by flash chromatography (n-hexane-EtOAc 6:4) to give β-lactone (**16**) in 88% yield. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.85-1.00 (m, 9H, CH_3CH_2,CH_3CH), 1.15-2.00 (m, 19H), 3.20 (ddd, 1H, J_1=8.5 Hz, J_2=6.8 Hz, J_3=4.0 Hz, CHC=O), 4.1-4.3 (m, 3H, CH_2O, CH-O), 4.65-4.80 (m, 1H, CO-CHN), 6.05 (br.d, 1H, J=7.50 Hz, NH), 8.20 (s, 1H, N-CHO). ^{13}C-NMR ($CDCl_3$, 200 MHz): δ 172.59, 171.30, 160.65, 77.65, 64.90, 56.20, 49.36, 41.61, 33.96, 31.43, 28.89, 28.08, 27.77, 26.87, 24.80, 22.71, 22.46, 21.88, 21.61, 13.96. $[\alpha]_D^{25}$= -19.5° (c 2.6, $CHCl_3$). IR ($CHCl_3$) selected data: 3420, 1815, 1735, 1685, 1120 cm^{-1}. MS (FAB): 370 (M+1).

References and Notes

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