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ETHYL-(R)-(4-METHYLPHENYLSULFINYL)-N-METHOXY ACETIMIDATE, A USEFUL CHIRAL ACETATE EQUIVALENT IN ALDOL TYPE CONDENSATIONS.

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Abstract -Ethyl N-methoxyacetimidate was metallated by lithium amides and reacted with (-)-(S)-menthyl p-toluenesulfinate to afford, in excellent yield, (R) - (4-methylphenylsulfinyl)-ethyl-N-methoxy acetimidate (2). Compound (2) was tested in aldol-type condensations with various aldehydes, and the adducts, after desulfurization, were converted into optically active ß-hydroxyesters with good (≥80%) e.e. The stereochemical outcome of the reaction of benzaldehyde was found to be dramatically affected by changing either the counterion of the enolate from lithium to zirconium or by going from kinetic to thermodynamic control.

Optically active α-sulfinyl-esters[1] and -oxazolines[2] have been shown to be effective in asymmetric synthesis of ß-hydroxy acids and esters by aldol type reactions.

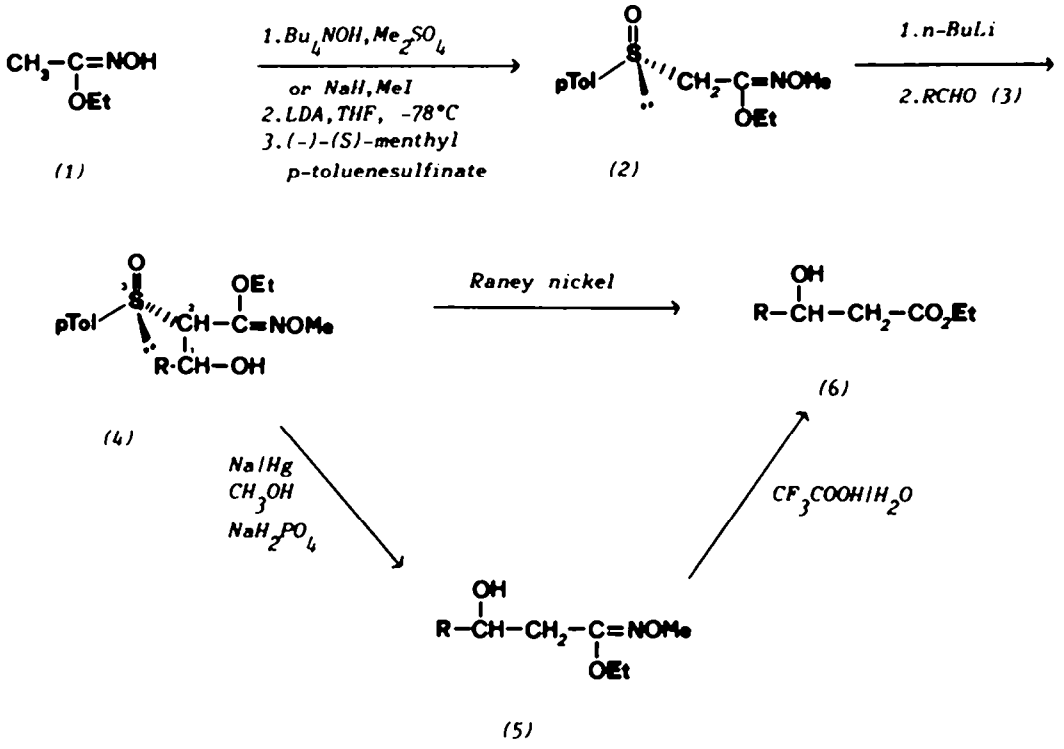
We now report the preparation of stereochemically homogeneous (R)-(4-methylphenyl sulfinyl)-ethyl N-methoxyacetimidate (2) and its effectivness as a chiral acetate equivalent in asymmetric condensations with aldehydes. The choice of the unusual ethyl N-methoxyimidate function was made on the basis of the fact that this functional group could be directly converted into both ester and aldehyde derivatives by acidic hydrolysis[3] or reductive treatment, respectively. Furthermore the feasibility of cleaving N-O bonds by Raney nickel[4] allows the one pot reductive desulfurization accompanied by conversion of the N-methoxy imidate into the ester function.

Compound (2) was prepared by reacting the lithium enolate of ethyl N-methoxyacetimidate (LDA, THF, -78°C), with (-)-(S)-menthyl p-toluenesulfinate[1] in 89% yield.

On the basis of the reasonable assumption that this Andersen-type synthesis proceeds with inversion of chirality at the sulfur atom[1], absolute configuration (R) can be assigned to compound (2). The optical purity was checked by ^{1}H n.m.r. analysis with the aid of the chiral shift reagent Eu(hfc)$_3$ and proved to be ≥98%.

The starting N-methoxy derivative could be either isolated by distillation after treatment of the commercially available ethyl N-hydroxyacetimidate (1) with dimethyl sulphate in phase transfer conditions or prepared by alkylation with methyl iodide and sodium hydride. In the latter case the crude solution was directly added to the LDA solution for metallation. Addition of n-BuLi to (2) followed by treatment with aldehydes (3a-d), afforded adducts (4a-d) which in turn using Raney nickel[5] gave directly

SCHEME 1



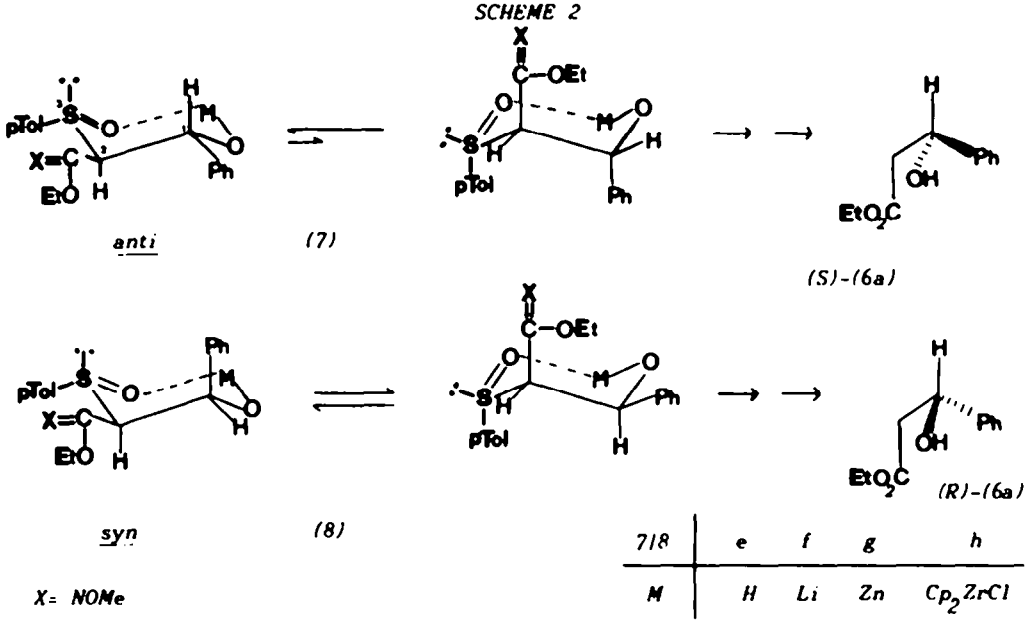
3-6	a	b	c	d
R	C_6H_5	$i\text{-}C_3H_7$	$n\text{-}C_5H_{11}$	cyclohexyl

ß-hydroxy esters (6a-d). The latter transformation, however, was achieved with a yield of less than 40% and we preferred to perform it in two separate steps, first by desulfurization[6] of compounds (4a-d) and then by acidic hydrolysis of ß-hydroxy alkylimidates (5a-d).

In order to check the extent of 1,3-asymmetric induction, ethyl ß-hydroxy esters (6a-d) were hydrolyzed (aq. NaOH) and then converted into the corresponding methyl esters (CH_2N_2, Et_2O), whose optical purity was easily tested by ^1H n.m.r. spectroscopy using $Eu(hfc)_3$ complex. The sense of enantioface differentiation was demonstrated in some instances referring to ß-hydroxy acids or esters of known optical purity and absolute configuration.

First we examined in detail the reaction between (2) and benzaldehyde in order to establish its stereochemical course. Kinetically controlled conditions (-78°C, THF) led to a mixture of three diastereoisomers in a relative ratio of 45:50:5[7]. The two major components of the mixture must have opposite configuration at the carbinolic C1 centre as the ß-hydroxy ester (6a), obtained according to Scheme 1, was nearly racemic. Furthermore these two stereoisomers have been shown to have the same absolute configuration at C2. They were separated by flash chromatography and each of them oxidized to the corresponding sulfonyl derivative, affording two distinct

SCHEME 2



7/8	e	f	g	h
M	H	Li	Zn	Cp_2ZrCl

diastereoisomers characterized by ^{1}H and ^{13}C n.m.r.. On the basis of the reasonable assumption that compounds (7-8e) are six membered hydrogen-bonded cyclic structures[8], as depicted in Scheme 2, then their J_{CH-CH} values in $CDCl_3$ (8.3 and 3.9 Hz.)[8,9] and δ values for benzylic carbon (74.2 and 71.3 p.p.m.)[10] suggest that they have respectively the anti and syn configuration at centres C1 and C2[11].

The pure anti stereoisomer (7e) gave the optically active(S)-ß-hydroxy ester (6a, ⩾96% e.e.) while the syn gave (R)-(6a), so that the configuration of compound (7e) was automatically assigned as 1S,2S,3R and that of compound (8e) as 1R,2S,3R.

We then turned our attention to thermodynamically controlled conditions, taking advantage of the supposed higher stability of the intermediate (7f)[8].

When the reaction mixture was allowed to rise to 0°C, an equilibrium was reached where the anti stereoisomer (7f) greatly exceeded the others, bringing about, as a final result, a considerable improvement with respect to the extent of 1,3 induction (see Table, entry 2).

It is the equilibration between (7f) and (8f) and not between the two isomeric lithium azaenolates of (2) that causes such a variation in the diastereoisomeric ratio. In this way, if the lithium azaenolate of (2) is warmed to 0°C, made to react with benzaldehyde at -78°C and in turn followed by quenching at this temperature, the (7/8e) ratio is similar to that obtained without equilibration of the lithium enolate.

Moreover the syn isomer (8e) is partially converted into the anti compound (7e) and the starting sulfinyl derivative (2) by treatment with n-BuLi in THF at 0°C. This conversion was raised to an extent of 88% using Me_2CuLi as a base (4 eq.) at 0°C for 2 hrs.

Higher diastereoselectivity was achieved by changing the counterion from lithium to a more chelating one, such as zinc (see Table, entry 3). In fact the tighter the structures like those depicted in Scheme 2, the more the equilibrium involving intermediates (7) and (8) favours the former.

On the contrary,in order to obtain diastereoselection under kinetic control we utilized the knowledge that zirconium enolates exhibit good to excellent kinetic

Table- Optically active ß-hydroxyesters (6) prepared by asymmetric synthesis according to Scheme (1).

Entry	Aldehyde	Metallation conditions	Condensation cond.	Product	Abs. Config.	e.e.
1	3a	n-BuLi, -78°C, 15'	-78°C, 15'	6a	-	-
2	3a	n-BuLi, -78°C, 15'	-78°→ 0°C (4 h)	6a	S	75%
3	3a	n-BuLi, -78°C, 15' 1 eq. $ZnCl_2$, -78°C, 30'	-78°→ 20°C (4h) 20°C, 30'	6a	S	86%
4	3a	n-BuLi, -78°C, 15' 2 eq. Cp_2ZrCl_2 -78°C, 30'	-78°C, 2.5 h	6a	R	88%
5	3b	n-BuLi, -78°C, 15'	-78°C, 1 h	6b	S	72%
6	3b	n-BuLi, -78°C, 15'	-78°→ 20°C (4 h) 20°C, 30'	6b	S	84%
7	3b	n-BuLi, -78°C, 15' 1 eq. $ZnCl_2$, -78°C, 30'	-78°→ 0°C (2 h) 0°C, overnight	6b	S	76%
8	3b	n-BuLi, -78°C, 15' 2 eq. Cp_2ZrCl_2, -78°C, 30'	-78°→ -30°C (3 h) -30°C,30'	6b	R	79%
9	3c	n-BuLi, -78°C, 15'	-78°→ 0°C (2.5 h) 0°C, overnight	6c	-	94%
10	3d	n-BuLi, -78°C, 15'	-78°→ 0°C (1 h) 0°C, 2h	6d	-	91%

All condensations were performed in THF. The absolute configurations were determined by conversion to the corresponding acid or methyl ester.

diastereoselection in aldol condensations independent of enolate geometry[12]. Actually the zirconium enolate of (2),obtained treating the lithium enolate with Cp_2ZrCl_2,gave selectively (-78°C, THF) the syn isomer (8h) and consequently the (R)-ß-hydroxy ester (6) in 88%e.e.. The only limitation affecting the use of zirconium enolates rested in the condensation yields not exceeding 60%. Therefore we synthesized ß-hydroxy ester (6a) of opposite absolute configuration, starting from the same chiral acetate equivalent but varying the counterion and the reaction conditions.

Lithium azaenolates deriving from R-(2) generally gave good enantioselectivities, independent of the nature of the aldheyde R group. The best optical yields achieved in each case were under thermodynamic control (see table).

All attempts to reduce to an aldehyde the N-methoxy imidate function failed. Treatment with the usual reducing agents such as $NaBH_4$, $LiAlH_4$, DIBAH, $NaAlH_2(OCH_2CH_2OCH_3)_2$ were ineffective and only by-products were obtained. The reaction with $MeOSO_2F$ or BF_4OEt_3 followed by reduction with $NaBH_4$ (THF, r.t.) gave low yields of the corresponding alcohol.

EXPERIMENTAL

^1H n.m.r. spectra were recorded with Varian XL-200 or Bruker WP-80, while ^{13}C n.m.r. spectra with Varian XL-100 instruments, in the F.T. mode, using tetramethylsilane as internal standard. I.R. spectra were recorded with a Perkin-Elmer 457 spectrophotometer. Optical rotations were measured in 1dm cells of 1ml capacity using a Perkin-Elmer 141 polarimeter. Mass spectra were recorded with a Varian MAT 112 spectrometer. Elemental analysis were performed with a Perkin-Elmer 240 instrument. 70-230 mesh or 270-400 mesh (for "flash chromatography"[13]) silica gel (Merck) were used for column chromatography.

"Dry" solvents were distilled under dry N_2 just before use: THF from sodium metal in the presence of benzophenone as indicator; MeOH from magnesium methoxyde; diisopropylamine from CaH_2. All reactions employing "dry" solvents were run under a nitrogen (from liquid N_2) atmosphere.

Ethyl-N-methoxy-acetimidate Ethyl-N-hydroxy acetimidate (6.7g, 65mmol) was added to 40% aqueous NaOH (32.5ml); Bu_4NHSO_4 (22.5g, 66mmol) and Me_2SO_4 (7.5ml, 78mmol) were then added and the mixture stirred for 1.5hr. The organic phase was separated and the aqueous layer extracted with ether. The organic extracts were washed with water, dried (Na_2SO_4) and evaporated. The residue was distilled at room pressure (90°C). (4.5g, 57%). (Found: C 51.31%; H9.35%; N 12.01%. $C_5H_{11}O_2N$ requires C 51.26; H 9.46; N 11.96%); δ ($CDCl_3$): 1.30 (3H, t, J=7.0Hz), 1.97 (3H,s), 3.80 (3H,s), 4.09 (2H,q,J=7.0Hz).

Ethyl-(R)-(+)-(p-toluenesulfinyl)-N-methoxy-acetimidate (2). Ethyl-N-methoxyacetimidate (3.3ml, 28.2mmol) was added dropwise to a solution of LDA (30.7mmol) in dry THF (120ml) under nitrogen at -78°C. After 30' a THF solution (60ml) of (S)-(-)-menthyl-p-toluenesulfinate (3.76g, 12.8mmol) was slowly added and the mixture stirred for 5'. The reaction was quenched with saturated aqueous NH_4Cl, then ether (100ml) was added and the organic phase separated. The aqueous layer was extracted with ether and the combined organic extracts were evaporated to give a crude mixture which was purified by flash chromatography (n-hexane:AcOEt 6:4) (2.9g, 89%). (Found: C 56.53; H 6.64; N 5.52%. $C_{12}H_{17}O_3NS$ requires: C 56.45; H 6.71; N 5.49%); $[\alpha]_D^{20}$ = +28° (c 1.0, $CHCl_3$); ν (cm^{-1}, liquid film): 3440,1650,1050; δ ($CDCl_3$): 1.15 (3H,t,J=6.2Hz), 2.41 (3H,s,), 3.92 (2H,q,J=6.2Hz), 3.65 (1H, d,J=12.5Hz), 4.00 (1H,d,J=12.5Hz), 7.20-7.80 (4H,m).

Ethyl-(R)-(+)-(p-toluenesulfinyl)-N-methoxy acetimidate (2): one pot procedure from (1). A solution of imidate (1) (5.3ml, 52mmol) in dry THF (30ml) was added to NaH (1.7g,80% suspension in mineral oil,57.2mmol) in dry THF (40ml) under nitrogen at 0°C. The mixture was stirred for 15' at room temperature and then treated at 0°C with CH_3I (3.6ml, 57.2mmol) by slow addition (15'). The reaction mixture was allowed to stand at r.t. for 10' and added by syringe to a solution of LDA (57.2mmol) in dry THF (100ml) at -78°C under nitrogen. The same procedure described in the preceding preparation was followed and no valuable variation affected the yield (85.5%).

Ethyl-α-(p-toluenesulfinyl)-β-hydroxy-N-methoxy-alkylimidates (4). General procedures.

Via Lithium enolates. (Method A). To a stirred solution of (2) (1mmol) in dry THF (10ml), kept under nitrogen at -78°C, 1.5M n-BuLi in n-hexane (1mmol) was added. After 20' the appropriate aldehyde (1.1mmol) was added dropwise. The reaction mixture was stirred for the requested time at the appropriate temperature (see Table) and then quenched with acetic acid (10mmol) in THF (5ml). Water was added and the aqueous phase was extracted with ether; the organic extracts were evaporated. The crude final residue can be directly submitted to the subsequent reaction.

Via Zinc enolates. (Method B). A 1M solution of anhydrous $ZnCl_2$ in Et_2O (0.5ml) was added at -78°C to the lithium enolate solution obtained as in method A. After 30' the aldehyde (1mmol) was added and the reaction carried out as described above.

Via Zirconium enolates. (Method C). A 0.16N solution of Cp_2ZrCl_2 in dry THF (6ml) was added at -78°C to the lithium enolate solution (method A). After 30' the appropriate aldehyde (1mmol) was added and the resulting pale yellow solution stirred for the requested time (see Table) and quenched as usual.

Compound (7e): m.p. 80°C (from n-hexane) (Found: C 63.19, H 6.40, N 3.86%. $C_{19}H_{23}O_4NS$ requires: C 63.12, H 6.43, N 3.88%. ν (cm^{-1}, KBr): 3340,1620,1010. δ ($CDCl_3$): 1.1(3H,t, J=7.2Hz), 2.40(3H,s), 3.20(3H,s), 3.65(1H,q, J=7.2Hz), 3.67(1H,q,J=7.2Hz), 4.45(1H,d, J=8.5Hz), 5.00(1H,d,J=2Hz), 5.60(1H,dd,J=2Hz, J=8.5Hz), 7.1-7.7(9H,m).

Compound (8e): m.p. 130°C (from ether-n-hexane).(Found: C 63.15, H 6.45, N 3.91%. $C_{19}H_{23}O_4NS$ requires: C 63.12, H 6.43, N 3.88%. ν (cm^{-1},KBr): 3320,1610,1010. δ ($CDCl_3$): 1.20(3H,t,J=7.2Hz), 2.40(3H,s), 3.15(3H,s), 3.85(2H,q,J=7.2Hz), 4.05(1H,d, J=9.8Hz), 4.50(1H,d,J=3.3Hz), 5.55(1H,dd, J=3.3,J=9.8Hz), 7.10-7.70(9H,m).

Compound (4b): ν (cm^{-1}, $CHCl_3$): 3670,1620, 1010. δ($CDCl_3$): 0.83(3H,d,J=6.7Hz), 1.03(3H, d,J=6.7Hz), 1.20(3H,t,J=7.3Hz), 1.56(2H,bs), 2.40(3H,s), 3.36(3H,s), 3.86(2H,q,J=7.3Hz), 4.16(1H,d,J=9.2Hz), 4.50(1H,dt,J=2,J=9.2Hz), 7.40(4H,m).

Compound (4c): ν (cm-^{1}, liquid film): 3400, 1620,1010. δ ($CDCl_3$): 0.85(3H,bt),1.25(3H,t, J=7.2Hz), 1.00-2.00(8H,m), 2.40(3H,s), 3.40(3H,s), 3.90(2H,q,J=7.2Hz), 3.95(1H,s), 4.16(1H,d,J=8.5Hz), 4.3-4.8(1H),7.3-7.6(4H,m).

Compound (4d): ν (cm^{1},liquid film): 3400, 1620,1010. δ ($CDCl_3$): 0.70-2.00(11H), 1.20(3H,t,J=7.2Hz), 2.40(3H,s), 3.36(3H,s), 3.90(2H,q,J=7.2Hz), 4.20(1H,d,J=8.5Hz), 4.26 (1H,s), 4.45(1H,d,J=8.5Hz), 7.3-7.6(4H,m).

Ethyl-3-hydroxy-3-phenylpropionate (6a): A solution of (4a) (0.9mmol) and H_3BO_3 (167.4mg, 2.7mmol) in MeOH:H_2O 5:1 (6ml) was treated with a catalytic amount of W-2 Raney Nickel under a hydrogen atmosphere. The mixture was vigorously stirred for 4hr. The catalyst was filtered off,washed with MeOH (10ml) and the solvent evaporated to a small volume. The residue was taken up with saturated aqueous NH_4Cl and extracted with ether. The crude final product was purified by flash chromatography (n-hexane: AcOEt 8:2) (76.5mg,43%). The known B-hydroxyester (6a) was identified by comparison of physical and spectral data with those of an authentic sample.

Ethyl-3-hydroxy-N-methoxyalkylimidates (5). General procedure: The crude residue resulting from the reactions indicated as Method A,B and C (1mmol scale reactions), was taken into dry methanol (5ml) and anhydrous NaH_2PO_4 (0.48g). To the resulting slurry,cooled at -15°C, 15% sodium amalgam (1.2g) was added in one portion. The mixture was stirred overnight at -15°C, then diluted with CH_2Cl_2 (20ml) and finally a saturated NH_4Cl solution (30ml) was added. The aqueous layer was extracted with CH_2Cl_2 (3x10ml) and the organic phase was dried (Na_2SO_4) and evaporated to give a crude mixture which was purified by flash chromatography (n-hexane:AcOEt 8:2) (75%).

Compound (5a): ν (cm^{-1}, liquid film): 3400, 1630. δ ($CDCl_3$): 1.23(3H,t,J=7.3Hz), 1.60(1H, bs), 2.7-3.1(2H,m), 3.70(3H,s), 4.05(2H,q, J=7.3Hz), 5.05(1H,m), 7.40(5H,s). m/z (%): 223(39), 192(70),117(88),107(100),105(92).

Compound (5b): ν(cm^{-1}, $CHCl_3$): 3550,1630. δ ($CDCl_3$): 0.83(3H,d,J=8.7Hz), 0.90(3H,d, J=8.7Hz), 1.26(3H,t,J=7.2Hz), 1.60(2H,bs), 2.4-2.7(2H,m), 3.70(3H,s), 4.05(2H,q,J=7.2Hz). m/z (%): 189(6), 117(50), 89(53), 73(56), 71(100).

Compound (5c): ν(cm^{-1}, $CHCl_3$): 3600,1625. δ ($CDCl_3$): 0.86(3H,bt), 1-1.5(8H,m), 1.26 (3H,t,J=7.2Hz), 1.65(1H,bs), 2.3-2.7(2H,m), 3.70(3H,s), 3.8-4.2(1H,m), 4.03(2H,q,J=7.2Hz). m/z (%): 217(10), 171(90), 146(42), 117(100), 89(95).

Compound (5d): ν(cm^{-1}, liq.film): 3420, 1625. δ ($CDCl_3$): 0.9-2.0(11H), 1,26(3H,t, J=7.2Hz), 2.43(1H,d,J=4.6Hz), 2.45-2.60(2H,m), 3.4-3.8(1H,m), 3.70(3H,s), 4.03(2H,q,J=7.2Hz). m/z (%): 229(2), 183(55), 117(68), 89(100), 83(57).

Ethyl-3-hydroxy-3-alkylpropionates (6). General procedure: A solution of (5) (0.5mmol) in CF_3COOH (4ml) was stirred at 0°C for 15', then water (4ml) was added and the solution stirred for 2hr at the same temperature. After 1hr at r.t. water (40ml) was added and the reaction mixture extracted with CH_2Cl_2 (3x20ml). The organic phase was washed with water, 5% aqueous $NaHCO_3$, H_2O and finally dried (Na_2SO_4) and evaporated. The crude residue was purified by flash chromatography (75-80%).

Compound (6a): ν (cm^{-1}, $CHCl_3$): 3600,1720. δ ($CDCl_3$): 1.20(3H,t,J=7.3Hz), 2.6-2.8(2H,m), 3.30(1H,d,J=3.3Hz), 4.20(2H,q,J=7.3Hz), 5.20 (1H,m), 7.40(5H,s). m/z (%): 194(25), 107(100), 105(68).

Compound (6b): ν (cm^{-1}, $CHCl_3$): 3600,1720. δ ($CDCl_3$): 0.93(3H,d,J=6.7Hz), 0.95(3H,d, J=6.7Hz), 1.25(3H,t,J=7.3Hz), 1.65(1H,m), 2.3-2.5(2H,m), 2.85(1H,d,J=4Hz), 3.6-3.9(1H, bs), 4.60(2H,q,J=7.3Hz). m/z (%): 161(72), 117(100), 88(46).

Compound (6c): ν (cm^{-1}, liq.film): 3440,1730 δ ($CDCl_3$): 0.89(3H,bt,J=6.7Hz), 1.0-1.6(8H), 1.25(3H,t,J=7.3Hz), 2.3-2.5(2H,m), 2.70(1H, bs), 4.10(1H,m),4.15(2H,q,J=7.3Hz). m/z (%): 117(100), 99(31), 88(41).

Compound (6d): ν (cm^{-1}, liq.film): 3440, 1710. δ ($CDCl_3$): 0.7-2.0(11H), 1.25(3H,t, J=7.2Hz), 2.3-2.5(2H,m), 2.80(1H,bs), 3.76 5(1H,dt,J=4.6,J=6.6Hz), 4.15(2H,q,J=7.2Hz). m/z (%): 201(8), 137(50), 117(100), 88(57).

Methyl-3-hydroxy-3-alkylpropionates. General procedure: A mixture of ethylester (6) (0.5mmol) and 0.1N aqueous NaOH (6ml) was stirred at r.t. until all the ester was dissolved (1-4hr). The solution was then treated with 1N aqueous HCl to pH 2 and extracted with ether (2x10ml). The organic phase was treated directly with a solution of CH_2N_2 in ether and stirred for 15' at 0°C. After drying (Na_2SO_4) the solvent was evaporated and the crude residue purified by flash chromatography. The known β-hydroxyesters were identified by comparison of physical and spectral data with those of an authentic sample.

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