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Acylation of a Transient Ti(IV)-enolate by Acyl Halides and Anhydrides. Facile Synthesis of α-Hydroxy-β-ketoesters.*

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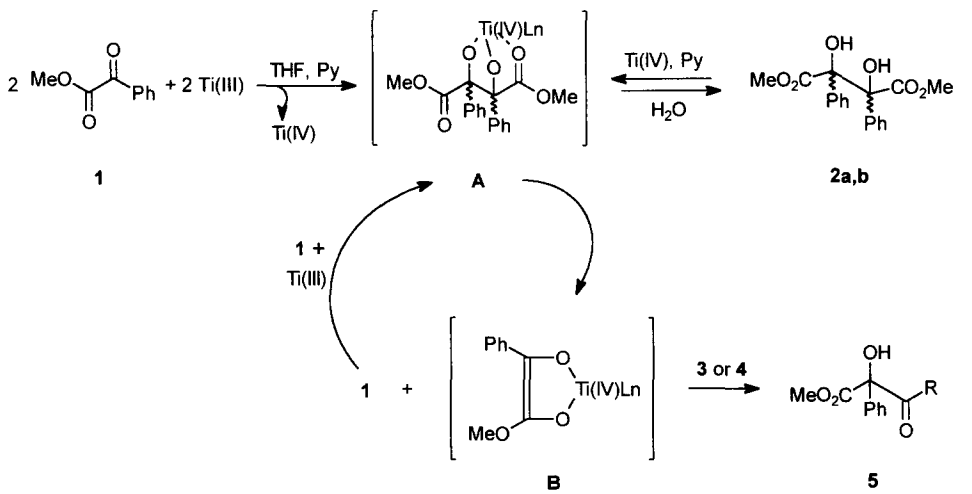
Abstract: Regioselective C-acylation at the carbonyl carbon of methyl phenylglyoxylate **1** occurs by reaction with a variety of acyl halides **3** and anhydrides **4** in the presence of $TiCl_3$/py system in THF at room temperature. α-Hydroxy-β-ketoesters **5** are the only reaction products and pyridine is essential to obtain useful yields (50-90%). The mechanism of acylation involves the intermediacy of a nucleophilic a Ti(IV)-ene diolate **B**. Copyright © 1996 Elsevier Science Ltd

Introduction

α-Ketoesters have been widely used as versatile and efficient substrates in condensation reactions with carbon nucleophiles, like in Knoevenagel,[1] Wittig,[2] Grignard[3] and ene-type reactions.[4] To our knowledge, there have been no examples in which they worked as nucleophiles.

Recently[5] we reported that *meso* and *dl* dimethyl diphenyltartrates **2a,b**, formed by reductive coupling of methyl phenylglyoxylate **1**, undergo a Ti(IV)-catalyzed heterolytic cleavage, *via* the Ti(IV)-chelate complex **A**, to give rise the stabilized Ti(IV)ene-diolate **B** (Scheme 1).

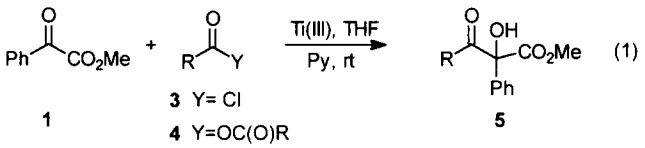
Scheme 1



Since this sequential combination of one- and two-electron reactions changes the polarity of the carbonyl carbon of **1** from electrophilic to nucleophilic, the reaction intermediate **B** might serve as a "methyl mandelanion" synthon to be quenched *in situ* with a variety of electrophiles.

This concept has been successfully applied to the *syn*-diastereoselective synthesis of α,β-dihydroxyesters in an aldol condensation with aldehydes[6] and of β-amino-α-hydroxyesters in a three component Mannich type reaction[7] (Scheme 1).

In surveying the reactivity of the Ti(IV)ene-diolate **B** towards electrophiles we have extended our investigation to acyl halides **3** and anhydrides **4**, and we report here on a very simple new methodology for constructing α-hydroxy-β-ketoesters **5**[8] starting from equimolar amount of **1** and **3** (or **4**) with two molar amount of $TiCl_3$ in THF-pyridine at room temperature (eq 1).



α-Hydroxy-β-ketoesters **5** are formed from moderate to excellent yields as the sole reaction products, being the acylation reaction completely C-regioselective (eq 1). The type of ligand (Ln = Py) at the titanium ion is ultimately responsible of the yields obtained.

Results and Discussion

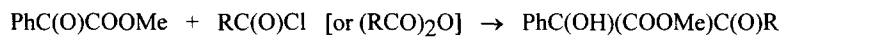
When a 5 mmol of $TiCl_3$ solution in THF/CH_2Cl_2 (2:1)[9] was added, at once, at room temperature under N_2 to an equimolar amount (2.5 mmol) of **1** and **3** (or **4**) in anhydrous THF (10 mL) and pyridine (3 mmol), the blue color of $TiCl_3$ immediately disappeared and the reaction mixture turned green with formation of a yellow precipitate.[10] The reaction mixture, quenched with H_2O after 20 min, afforded **5** after the usual work up.

As it is apparent from the Table I, the yields of **5a-r** range from 45 to 90%, based on the starting **1**, and are always quantitative, based on the converted **1**. The reaction with anhydrides gives yields of **5** comparable to those obtained with acyl halides and it is advantageous only in the case it is undesirable to prepare the acyl halide.

To evaluate the scope and limitation of this process, we have tested acyl halides and anhydrides with different steric environment around the reaction centre or bearing an additional functional group.

As for steric factors are concerned, the yields of **5** decrease upon increasing the steric congestion around the acyl group of **3** or **4** (*cfr* entries 3 with 4, and 16 with 17). This effect becomes manifest in the series *n*-butyryl, *iso*-butyryl and pivaloyl anhydride: as the alkyl chain becomes more branched, the yields of **5** drop from 81, 55 to 0% (entries 13-15).

Table I. Yields of Products Isolated from the Ti(III)-Pyridine Mediated Reaction



entry	R in **3**	R in **4**	yield (%) of **5**[a]
1	Ph-		86 (**5a**)
2		Ph	75 (**5a**)
3	*p*-$CH_3C_6H_4$-		90 (**5b**)
4	*o*-$CH_3C_6H_4$-		55 (**5c**)
5	*p*-$OCH_3C_6H_4$-		74 (**5d**)
6	*p*-ClC_6H_4-		70 (**5e**)
7	*p*-BrC_6H_4-		55 (**5f**)
8	CH_3-		72 (**5g**)
9		CH_3-	71 (**5g**)
10	CH_3CH_2-		75 (**5h**)
11		CH_3CH_2-	74 (**5h**)
12	$CH_3(CH_2)_2$-		80 (**5i**)
13		$CH_3(CH_2)_2$-	81 (**5i**)
14		$(CH_3)_2CH$-	55 (**5j**)
15		$(CH_3)_3C$-	no reaction
16	$PhCH_2$-		60 (**5k**)
17	$PhCH_2CH_2$-		83 (**5l**)
18	PhCH=CH-		77 (**5m**)
19	$ClCH_2$-		70 (**5n**)
20	Cl_2CH-		88 (**5o**)
21	EtO-		60 (**5p**)
22	$EtO_2C(CH_2)_2$-		47 (**5q**)
23	-$(CH_2)_3$-		45 (**5r**)

[a]Isolated yields based on the starting **1**.

With regard to the chemoselectivity, ester, alkoxy, halogen, chloromethyl and dichloromethyl groups and conjugated double bonds do not interfere with the acylation reaction. Interestingly, cinnamoyl chloride (entry 18) afforded the γ-unsaturated α-hydroxy-β-ketoester **5m** in 77% yield with no traces of addition product to the double bond.

Therefore, in the present reaction, Ti(IV)ene-diolate **B** behaves as a chemoselective and sterically demanding nucleophile. The correctness of the mechanism, reported in Scheme 1 and postulated in earlier papers,[5-7] is evidenced and supported by the following two experiments.

a) When the addition of $TiCl_3$ (5 mmol) to **1** (2.5 mmol), dissolved in THF (10 mL) and pyridine (3 mmol), was followed by addition of benzoylchloride (**3a**, 2.5 mmol) after 10 min and quenching with water after additional 20 min, **5a** was formed in yield comparable to that obtained in the reaction in which **3a** was present from the beginning (entry 1). Considering that, at the time **3a** was added, the Ti(III) reductive dimerization of **1** had already taken place,[11] formation of **5a** should follow the Ti(IV)-catalyzed heterolytic cleavage of the dimer (**A** → **B**).[12]

b) When $TiCl_4$ (0.6 mmol of a 1.0 M CH_2Cl_2 solution) was added to a solution of the *meso* dimer **2a** (0.3 mmol) and benzoylchloride **3a** (0.6 mmol) in THF (3 mL) and pyridine (0.8 mmol), **5a** was obtained in 40% yield along with **1** (60%). This result further on stresses the reaction sequence (**A** → **B** → **5**) postulated in the former experiment.

An important point to consider is the role played by pyridine in this acylation reaction: as reported in a preliminary note,[13] and confirmed by additional experiments, the reaction has no synthetic interest in the absence of pyridine since methylmandelate is formed in high yield (34-45%) to detriment of **5**.

The efficient nucleophilic catalysis of acylation reactions promoted by pyridine has long been known, and the mechanism involves the formation of an intermediate N-acylpyridinium ion (RCOCl + Py → $RCOPy^+$ Cl^-) highly reactive towards nucleophiles.[14] However, we do not believe that the high yield of **5** obtained in the presence of pyridine are to be ascribed to the formation of this intermediate since the aldol condensation of **B** with aldehydes affords α,β-dihydroxyesters in useful yield only when pyridine is present.[6]

We rather believe that pyridine acts as a proper ligand at the metal ion: in fact, being a better donor ligand than THF, it would complex with Ti(IV) and displace THF from the coordinative sphere of the metal ion.[15] In this fashion pyridine increases the nucleophilic reactivity of **B** by increasing the electron density at Ti(IV), and decreases the inherent stability of **B** by decreasing the Lewis acidity (*eg* the chelating properties) of the metal.[16] Both factors favorably contribute to enhance the rate of addition of **B** to the acyl carbon.

In the absence of pyridine, the more stable and less nucleophilic analogue **B** (Ln = THF) is not so efficiently consumed and partially survives until aqueous work-up affording methylmandelate as the main reaction product.[6]

Finally, the high yield of dimer **2a** (63%), obtained when *t*-BuOH was used as an additive instead of pyridine,[13] is in line with the mechanism proposed. Coordination of the bulky *t*-BuOH ligand at Ti(IV) inhibits the formation of the chelate complex **A** (a prerequisite for the cleavage to occur) and/or increases the hydrogen ion concentration (n *t*-BuOH + Ti(IV) → $Ti(IV)(t\text{-}BuO)_n$ + n H^+) thereby shifting the whole equilibrium towards the formation of the dimer.

Conclusions

We have shown the facile Ti(III)-promoted cross-coupling reaction of methyl phenylglyoxylate **1** with a variety of electrophiles, which constitutes a new example of carbonyl umpolung and its use in organic synthetic chemistry.

The procedure leading to α-hydroxy-β-ketoesters **5**, here described, offers several advantages over previous available methods:[8] it combines simple experimental conditions (titration at room temperature) and high product yields with generality in the acylating agent and selectivity for C-acylation.

Experimental Section

General. All reagents were purchased from commercial suppliers and used as received. THF was distilled from sodium-benzophenone ketyl prior to use. Flash column chromatography was performed by using Merck silica gel 60 (particle size 0.004-0.063). All reactions were carried out under a nitrogen atmosphere. ^1H NMR spectra were recorded in $CDCl_3$ solution on a Bruker AC-250 MHz instrument with Me_4Si as an internal standard. Mass spectra were taken on a Hitachi-Perkin-Elmer RMU-6d spectrometer at 70 eV with an IS temperature of 100°C. Melting points were taken on a Kofler apparatus (uncorrected). Recrystallization solvents for solid products are given in parentheses next to the melting points. Microanalyses were performed by the Analytical Section of REDOX Laboratories, Cologno Monzese (MI).

General Procedure. Equimolar amount (2.5 mmol) of methyl phenylglyoxylate **1** and acyl halide **3** (or anhydride **4**) were dissolved in anhydrous THF (5 mL) and anhydrous pyridine (3 mmol) under N_2 at room temperature.To the well stirred solution, 5 mL (5 mmol) of a 1M anhydrous $TiCl_3$ solution[9] were added, in one portion, with a syringe. The blue color of $TiCl_3$ turned to green within few minutes with formation of a yellow precipitate.[10] Upon additional stirring (30 min.), the reaction mixture was quenched with H_2O (15 mL) and extracted with EtOAc (3x50 mL). The combined organic layers were washed with H_2O, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification of the crude residue by flash column chromatography afforded **5** in the yields collected in Table I.

Spectroscopic Data. Structural assignments of compounds **5a-r** of Table I were deduced from the following data.

Methyl-2,3-diphenyl-2-hydroxy-3-oxopropanoate (5a). Isolated as a colorless solid by flash column chromatography (hexane/Et_2O, 9:1); mp 94°C (hexane/Et_2O,)(lit. mp 91-2°C);[8] IR (nujol) ν_{max} 3470 (OH), 1730 and 1680 (CO) cm^{-1}; ^1H NMR δ 3.84 (s, 3H), 4.85 (s, 1H, D_2O exchangeable), 7.2-7.5 (m, 6H), 7.55 (m, 2H), 7.88 (m, 2H); MS *m/z* 270 (M^+<1), 238, 211, 105 (100), 77.

Methyl-2-hydroxy-3-(4-methylphenyl)-3-oxo-2-phenylpropanoate (5b). The solid product crystallized on standing from the crude reaction mixture (Et_2O); mp 105°C (Et_2O); IR (nujol) υ_{max} 3490 (OH), 1730 and 1680 (CO) cm^{-1}; ^1H NMR δ 2.30 (s, 3H), 3.82 (s, 3H), 4.86 (s, 1H, D_2O exchangeable), 7.10 (d, 2H, J= 7.5

Hz), 7.35 (m, 3H), 7.55 (m, 2H), 7.78 (d, 2H, J= 7.5 Hz); MS *m/z* 284 (M^+<1), 225, 119 (100), 105, 91, 77. Anal. Calcd for $C_{17}H_{16}O_4$: C, 72.96; H, 5.44; O, 21.60. Found: C, 72.88; H, 5.48.

Methyl-2-hydroxy-3-(2-methylphenyl)-3-oxo-2-phenylpropanoate (5c). Isolated as a thick oil by flash column chromatography (hexane/EtOAc, 9:1); IR (nujol) ν_{max} 3460 (OH), 1730 and 1685 (CO) cm^{-1}; ^1H NMR δ 2.38 (s, 3H), 3.85 (s, 3H), 4.78 (s, 1H, D_2O exchangeable), 7.04 (m, 1H), 7.20 (m, 1H), 7.26 (m, 1H), 7.35 8m, 4H), 7.59 8m, 2H); MS *m/z* 284 (M^+<1), 266, 252, 225, 119 (100), 105, 91, 77, 65, 51.

Methyl-2-hydroxy-3-(4-methoxyphenyl)-3-oxo-2-phenylpropanoate (5d). Isolated as a colorless solid by flash column chromatography (hexane/Et_2O/$CHCl_3$, 6:2:2); mp 110-1°C (hexane/Et_2O, 1:1); IR (nujol) ν_{max} 3430 (OH), 1740 and 1680 (CO) cm^{-1}; ^1H NMR δ 3.78 (s, 3H), 3.85 (s, 3H), 4.88 (s, 1H, D_2O exchangeable), 6.78 (d, 2H, J= 9 Hz), 7.35 (m, 3H), 7.54 (m, 2H), 7.88 (d, 2H, J= 9 Hz); MS *m/z* 300 (M^+<1), 241, 135 (100), 107, 105, 92, 77, 65, 51. Anal. Calcd for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37; O, 26.64. Found: C, 68.04; H, 5.33.

Methyl-3-(4-chlorophenyl)-2-hydroxy-3-oxo-2-phenylpropanoate (5e). Isolated as a colorless solid by flash column chromatography (hexane/EtOAc, 9:1); mp 99-100°C (hexane/Et_2O); IR (nujol) ν_{max} 3490 (OH), 1720 and 1695 (CO) cm^{-1}; ^1H NMR δ 3.85 (s, 3H), 4.82 (s, 1H, D_2O exchangeable), 7.25 (d, 2H, J= 9 Hz), 7.35 (m, 3H), 7.54 (m, 2H), 7.82 (d, 2H, J= 9 Hz); MS *m/z* 306-304 (M^+<1), 374-372, 247-245, 141-139 (90), 113-111, 105 (100), 77, 51. Anal. Calcd for $C_{16}H_{13}O_4Cl$: C, 63.06; H, 4.30; O, 21.00. Found: C, 62.98; H, 4.25.

Methyl-3-(4-bromophenyl)-2-hydroxy-3-oxo-2-phenylpropanoate (5f). Isolated as a colorless solid by flash column chromatography (hexane/Et_2O, 1:1); mp 111-2°C (hexane/Et_2O); IR (nujol) ν_{max} 3470 (OH), 1720 and 1690 (CO) cm^{-1}; ^1H NMR δ 3.85 (s, 3H), 4.80 (s, 1H, D_2O exchangeable), 7.36 (m, 3H), 7.45 (d, 2H, J= 8 Hz), 7.52 (m, 2H), 7.74 (d, 2H, J= 8 Hz); MS *m/z* 350-348 (M^+<1), 318-316 (M^+-MeOH, m^*= 286,9), 291-289, 185-183 (100), 157-155, 105 (70), 77, 51. Anal. Calcd for $C_{16}H_{13}O_4Br$: C, 55.04, H, 3.75; O, 18.33: Found: C, 55.11; H, 3.81.

Methyl-2-hydroxy-3-oxo-2-phenylbutanoate (5g). Isolated as a pale-yellow thick oil by flash column chromatography (hexane/EtOAc, 8:2); IR (neat) ν_{max} 3450 (OH), 1720 (CO) cm^{-1}; ^1H NMR δ 2.22 (s, 3H), 3.85 (s, 3H), 4.82 (s, 1H, D_2O exchangeable), 7.38 (m, 3H), 7.55 (m, 2H); MS *m/z* 208 (M^+<1), 176, 166 (40), 105 (100), 77, 51, 43 (50).

Methyl-2-hydroxy-3-oxo-2-phenyl-pentanoate (5h). Isolated as a colorless thick oil by flash column chromatography (hexane/EtOAc, 9:1); IR (neat) ν_{max} 3460 (OH), 1725 (CO) cm^{-1}; ^1H NMR δ 1.0 (t, 3H, J= 7.2 Hz), 2.52 (dq, 1H, J= 7.2, 18.4 Hz), 2.68 (dq, 1H, J= 7.2, 18.4 Hz), 3.8 (s, 3H), 4.8 (s, 1H, D_2O exchangeable), 7.38 (m, 3H), 7.55 (m, 2H); MS *m/z* 222 (M^+<1), 190, 166 (30), 105 (100), 77, 57 (63), 51, 29.

Methyl-2-hydroxy-3-oxo-2-phenylhexanoate (5i). Isolated as a colorless thick oil by flash column chromatography (hexane/Et_2O/$CHCl_3$, 7:1:2); IR (neat) ν_{max} 3460 (OH), 1725 (CO) cm^{-1}; ^1H NMR δ 0.82 (t, 3H, J= 7.4 Hz), 1.53 (dddq, 1H, J= 14.0, 7.6, 6.8, 7.4 Hz), 1.56 (dddq, 1H, J= 14.0, 7.4, 6.8, 7.4 Hz), 2.50 (ddd, 1H, J= 17.6, 7.4, 6.8 Hz), 2.60 (ddd, 1H, J= 17.6, 7.4, 6.8 Hz), 4,75 (s, 1H, D_2O exchangeable);7.38 (m, 3H), 7.54 (m, 2H); MS *m/z* 236 (M^+<1), 219, 204, 177, 165 (35), 105 (100), 77, 71 (85), 51, 43 (60).

Methyl-2-hydroxy-4-methyl-3-oxopentanoate (5j). Isolated as a colorless thick oil by flash column chromatography (hexane/Et_2O/$CHCl_3$, 7:1:2); IR (neat) ν_{max} 3460 (OH), 1725 (CO) cm^{-1}; ^1H NMR δ 0.83 (d, 3H, J= 6.8 Hz), 1.04 (d, 3H, J= 6.8 Hz), 3.15 (sep, 1H, J= 6.8 Hz), 3.86 (s, 3H), 4.8 (s, 1H, D_2O exchangeable), 7.36 (m, 3H), 7.55 (m, 2H); MS *m/z* 236 (M^+<1), 204, 177, 166 (13), 105 (90), 77, 71 (93), 51, 43 (100).

Methyl-2,4-diphenyl-2-hydroxy-3-oxobutanoate (5k). Isolated as a colorless thick oil by flash column chromatography (hexane/EtOAc, 8:2); IR (neat) ν_{max} 3450 (OH), 1725 (CO) cm^{-1}; ^1H NMR δ 3.80 (s, 3H), 3.86 (s, 2H), 4.75 (s, 1H, D_2O exchangeable), 7.02 (m. 2H), 7.24 (m, 3H), 7.38 (m, 3H), 7.58 (m, 2H); MS *m/z* 284 (M^+, 2), 252, 225, 166 (45), 105 (100), 91 (70), 77, 65 51.

Methyl-2,5-diphenyl-2-hydroxy-3-oxopentanoate (5l). Isolated as a colorless thick oil by flash column chromatography (hexane/Et_2O/$CHCl_3$, 7:1:2); IR (neat) ν_{max} 3450 (OH), 1725 (CO) cm^{-1}; ^1H NMR δ 2.75-3.0 (m, 4H), 3.71 (s, 3H), 4.75 (s, 1H, D_2O exchangeable), 7.06 (m, 2H), 7.20 (m, 3H), 7.35 (m, 3H), 7.46 (m, 2H); MS *m/z* 298 (M^+<1), 266, 239, 133 (42), 107 (40), 105 (100), 91 (80), 77.

Methyl-2-hydroxy-3-oxo-2-phenyl-*trans*-5-phenylpentenoate (5m). Isolated as a colorless thick oil by flash column chromatography (hexane/EtOAc, 8:2); mp 81-3°C (hexane/Et_2O); IR (nujol) ν_{max} 3450 (OH), 1740 and 1685 (CO) cm^{-1}; ^1H NMR δ 3.85 (s, 3H), 4.94 (s, 1H, D_2O exchangeable), 7.05 (d, 1H, J= 13 Hz), 7.35 (m, 6H), 7.48 (m, 2H), 7.56 (m, 2H), 7.78 (d, 1H, J= 13 Hz); MS *m/z* 296 (M^+<1), 264, 237, 131 (100), 105 (26), 104, 103, 77. Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44; O, 21.60. Found: C, 72.90; H, 5.41.

Methyl-4-chloro-2-hydroxy-3-oxo-2-phenylbutanoate (5n). Isolated as a colorless oil by flash column chromatography (hexane/Et_2O/$CHCl_3$, 5:2.5:2.5); IR (neat) ν_{max} 3460 (OH), 1740 (CO) cm^{-1}; ^1H NMR δ 3.89 (s, 3H), 4.41and 4.51 (AB system, 2H, J= 16 Hz), 4.65 (bs, 1H, D_2O exchangeable), 7.40 (m, 3H), 7.58 (m, 2H); MS *m/z* 244-242 (M^+<1), 212-210, 185-183, 165 (21), 105 (100), 77.

Methyl-4,4-dichloro-2-hydroxy-3-oxo-2-phenylbutanoate (5o). Isolated as a colorless oil by flash column chromatography (hexane/Et_2O/$CHCl_3$, 5:2.5:2.5); IR (neat) ν_{max} 3455 (OH), 1738 (CO) cm^{-1}; ^1H NMR δ 3.90 (s, 3H), 4.65 (bs, 1H, D_2O exchangeable), 6.60 (s, 1H), 7.40 (m, 3H), 7.65 (m, 2H); MS *m/z*280-278-276 (M^+<1), 248-246-244, 221-219-217, 165, 107, 105 (100), 77, 51.

Phenyltartronic acid-methyl, ethylester (5p). Isolated as a colorless oil by flash column chromatography (hexane/Et_2O/$CHCl_3$, 5:2.5:2.5); IR (neat) ν_{max} 3470 (OH), 1740 (CO) cm^{-1}; ^1H NMR δ 1.29 (t, 3H, J= 7.25 Hz), 3.83 (s, 3H), 4.29 (dq, 1H, J= 11, 7.25 Hz), 4.35 (dq, 1H, J= 11, 7.25 Hz), 4.4 (s, 1H, D_2O exchangeable), 7.35 (m, 3H), 7.65 (m, 2H); MS *m/z* 238 (M^+, 2), 206 (M^+- MeOH, m^*= 178.3), 192 (M^+-EtOH, m^*= 154.9), 179, 165, 105 (100), 77.

2-Hydroxy-3-oxo-2-phenyladipic acid-1-methyl, 6-ethylester (5q). Isolated as a colorless oil by flash column chromatography (hexane/Et_2O/$CHCl_3$, 5:2.5:2.5); IR (neat) ν_{max} 3480 (OH), 1730 (CO) cm^{-1}; ^1H NMR δ 1.22 (t, 3H, J= 7.5 Hz), 2.53 (dt, 1H, J= 17.2, 6.8 Hz), 2.54 (dt, 1H, J= 17.2, 6.8 Hz), 2.91 (dt, 1H, J= 18.8, 6.8 Hz), 2.93 (dt, 1H, J= 18.8, 6.8 Hz), 3.84 (s, 3H), 4.10 (q, 2H, J= 7.5 Hz), 4.76 (s, 1H, D_2O exchangeable), 7.38 (m, 3H), 7.58 (m, 2H); MS *m/z* 294 (M^+<1), 189, 166, 129 (50), 105 (77), 101 (100), 77.

2-Hydroxy-3-oxo-2-phenylpimelic acid-1-methylester (5r). Isolated as a colorless oil by flash column chromatography (hexane/EtOAc, 6:4); IR (neat) ν_{max} 3500-2500 (OH), 1720 (CO) cm^{-1}; ^1H NMR δ 1.85 (quint, 2H, J= 7.3 Hz), 2.29 (t, 2H, J= 7.3 Hz), 2.64 (dt, 1H, AB system, J= 18.4, 7.3 Hz), 2.68 (dt, 1H, AB

system, J= 18.4, 7.3 Hz), 3.85 (s, 3H), 4.80 (bs, 1H, D_2O exchangeable), 7.35 (m, 3H), 7.5 (m, 2H); MS *m/e* 281 M^++1, 40), 263 (38), 245 (45), 231 (60), 166 (90), 105 (100), 77.

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References and Notes

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1. Yamada, Y.; Iguchi, K.; Hosaka, K.; Hagiwara, K. *Synthesis* **1974**, 669. (b) Hori, T.; Nakanishi, K. *J. Chem. Soc. Chem. Comm.* **1969**, 528.
2. March, J. *Advanced Organic Chemistry*, 3rd ed., J. Wiley and Sons: New York, 1985; p 850 and references cited herein.
3. (a) Morrison, J. D.; Mosher, H. S. *Asymmetric Organic Reactions*, Prentice Hall: New Jersey, 1971, pp 50-83. (b) Tatibouet, F.; Fréon, P. *Bull. Soc. Chim. French Ed.* **1963**, 1496.
4. Mikami, K.; Shimizu, S. *Chem. Rev.* **1992**, 1021.
5. Clerici, A.; Clerici, L.; Porta, O. *J. Org. Chem.* **1995**, *60*, 480.
6. Clerici, A.; Clerici, L.; Malpezzi, L.; Porta, O. *Tetrahedron* **1995**, *51*, 13385.
7. Clerici, A.; Clerici, L.; Porta, O. *Tetrahedron Lett.* **1995**, *36*, 5955.
8. The few literature methods, available for the synthesis of **5**, require multi-step and low-yielding reactions: (a) Le Dao, H.; Dayer, F.; Duc, L.; Rodè-Gowal, H.; Dahn, H. *Helv. Chim. Acta* **1974**, *57*, 2215. (b) Beccalli, E. M.; Marchesini, A. *Gazz. Chim. Ital.* **1984**, *114*, 389.
9. Solutions of $TiCl_3$ in THF/CH_2Cl_2 (2.1) are now commercially available from Aldrich.
10. The yellow precipitate is an adduct of Ti(IV). Its ^1H NMR (DMSO) spectrum evidences the presence of THF and pyridine in the ratio 1:4. It is very sensitive to moisture and is completely destroyed when the reaction is quenched with water.
11. A control experiment revealed that the reduction of **1** by $TiCl_3$ was over in less than 5 min and afforded dimer **2a** (59% yield) as the almost exclusive product.
12. In the absence of electrophiles, which drive **B** from the equilibrium, both **B** and **1** may regenerate **A**, the former by oxidative and the latter by reductive dimerization (see ref 5).
13. Araneo, S.; Clerici, A.; Porta, O. *Tetrahedron Lett.* **1994**, *35*, 2213.
14. (a) Fersht, A. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1970**, *92*, 5432. (b) Deady, L. W.; Finlayson, W. L. *Aust. J. Chem.* **1983**, *36*, 1951. (c) March, J. *Advanced Organic Chemistry*, 3rd ed., J. Wiley and Sons: New York, 1985; p 333.
15. When $TiCl_4$ was used to titrate pyridine in an acyl halide solvent, the maisequencinvolves the formation of both 1:1 and 2:1 pyridine-$TiCl_4$ complexes rather than the formation of a N-acyl pyridinium ion: Patay, S. *The Chemistry of Acyl Halides* chapt 4, p 131 and references cited herein.
16. Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*, Springer-Verlag: Berlin, 1986, chapts 1 and 5.

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