Synthesis and Enantioselective Hydrogenation of α-Acyloxyacrylates

Ulrich Schmidt,* Jörg Langner, Bettina Kirschbaum, Christine Braun

Institut für Organische Chemie und Isotopenforschung der Universität Stuttgart, Pfaffenwaldring 55, D-70569 Stuttgart, Germany

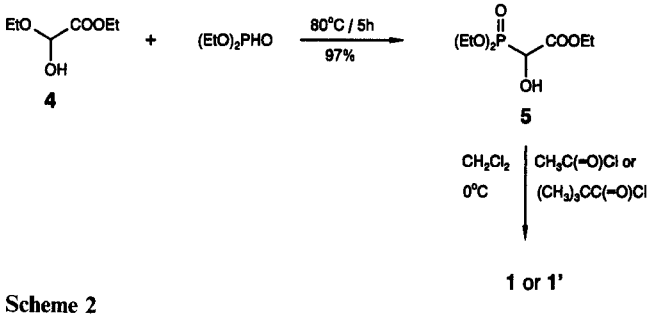
Received 18 March 1994; revised 6 June 1994

Numerous α-acyloxyacrylates have been prepared by Wittig–Horner reaction of aldehydes and ethyl 2-acyloxy-2-(diethoxyphosphoryl)acetates which were easily obtained from glyoxylic acid hydrate. The formed α-acyloxyacrylates were subsequently hydrogenated enantioselectively using Rh–DIPAMP and Ru–BINAP (ee = 82–98%) to furnish the corresponding α-acyloxycarboxylates.

In the past few years, α-acyloxyacrylates have been prepared by acylation of α-ketocarboxylates[1] or their cyanhydrin silyl ethers.[2] Nakamura developed a new synthesis of (tetrahydropyranyloxy)acrylates which involved condensation of a compound analogous to the phosphorylacetate **1** (but carrying R = tetrahydropyranyl) with various aldehydes.[3] Unfortunately, the Japanese authors did not report on the hydrogenation of their products. However, our investigations have shown that hydrogenation with Rh–DIPAMP does not proceed enantioselectively.

In the course of our syntheses of cyclodepsipeptides, we required a method to prepare optically pure α-hydroxycarboxylic acids. For this purpose, we examined the reaction of the protected phosphonates **1** and **1'** with some aldehydes to furnish the protected α-acyloxyacrylates **2** and **2'**. Hydrogenation of the latter products took place enantioselectively to form the protected α-acyloxycarboxylates **3** and **3'**.[4]

However, the preparation of the phosphonate **1** was more difficult than expected.[5] The conversion of **4** into **5** proceeded in good yield, but the starting semiacetal **4** could only be obtained in poor yield from glyoxylic acid hydrate. The known route using the water-free glyoxylate prepared by Pb^{4+} or periodate-mediated cleavage of succinates seemed to be too expensive.[6] We have, however, been able to increase the yield of **5** to 70% by optimizing the reaction conditions, and to acylate it to **1**.

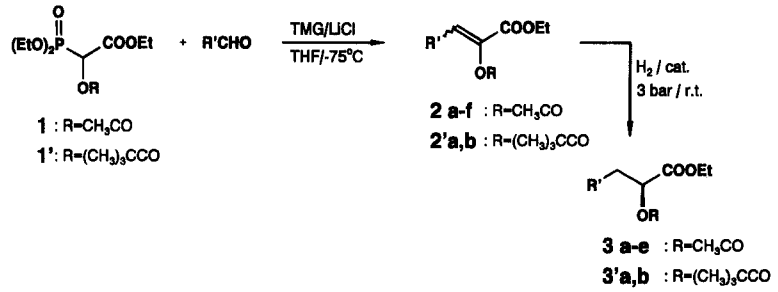


Scheme 2

A thorough investigation of the condensation reaction between **1** and isobutyraldehyde employing various bases revealed that tetramethylguanidine (TMG) in the presence of LiCl gave the highest yields. Table 1 summarizes the yields of aliphatic and aromatic α-acyloxyacrylates prepared by this route.

The products of the condensation reactions are *E*/*Z* diastereomeric mixtures with *E*/*Z* ratios of 2:1 to 4:1.[7] The diastereomers were easily separated by MPLC. It is noteworthy, however, that, in contrast to the formation of α-acylaminoacrylates from the corresponding phosphonate esters (mainly *Z*), one isomer was not preferentially formed. On the other hand, these *E*/*Z* mixtures were transformed into the pure *Z*-isomer by heating in the presence of thiophenol and α,α'-azoisobutyronitrile (AIBN).

Until now only the hydrogenation of α-acetoxyacrylate with Rh–PROPHOS [PROPHOS = (*R*)-1,2-bis(diphenylphosphino)propane] was reported by Bosnich and coworkers (ee = 80%)[8] and in excellent optical yield by Burk[9] using Rh–Et-DuPHOS[Et-DuPHOS = (*R*,*R*)-1,2-bis(phospholano)benzene]. We used the following catalysts in the present work:



	a	b	c	d	e	f
R'	i-C_3H_7	n-C_4H_9	n-C_6H_{13}	n-C_9H_{19}	C_6H_5	

Scheme 1

Downloaded by: York University libraries. Copyrighted material.

Rh–DIPAMP[10] = $[Rh(COD)(R,R\text{-DIPAMP})]^+[BF_4]^-$; Ru–BINAP[11] = $[RuCl(p\text{-cumene})(R\text{-BINAP})]^+Cl^-$; and Rh–BPPM[12] = $[Rh(COD)(S,S\text{-BPPM})]^+Cl^-$, where COD = cycloocta-1,5-diene; DIPAMP = (*R,R*)-1,2-bis[(2-methoxyphenyl)phenylphosphino]ethane; BINAP = (*R*)-2,2-bis(diphenylphosphino)-1,1-binaphthyl; and BPPM = (*S,S*)-*N*-(*tert*-butoxycarbonyl)-4-[(diphenylphosphino)methyl]pyrrolidine.

These catalysts have previously been widely and successfully employed for the hydrogenation of didehydroamino acids. The hydrogenation of α-acyloxyacrylates proceeded with enantioselectivities of up to 98% ee (see Table 2). An examination of the hydrogenations of the aliphatic compounds **2a–d** revealed that the enantioselectivity does not depend on the olefin configuration. In the case of the aromatic compound **2e**, only the *Z*-isomer could be hydrogenated.

The ee-values were determined as follows: For **3a,b** and **3'a**, the enantiomers could be separated by GC on a chiral column; for **3c–e**, the α-acyloxycarboxylates were converted into the corresponding α-hydroxycarboxylates (EtOH/HCl, 20 h, r.t.) which could be separated by GC on a chiral column; for **3'b** the optical rotation was compared with the rotation of **3b**, which was converted into the α-hydroxycarboxylate and subsequently protected with pivaloyl chloride to form **3'b** with a known ee-value.

The absolute configuration of **3** was established as *S* by comparing the sign of rotation with those reported for analogous *S*-compounds.[13,14] In all cases, the sign of rotation was negative.

Accordingly, the optical induction in the hydrogenation of α-acyloxyacrylates and α-acylaminoacrylates with Rh–(*R,R*)-DIPAMP follows the same path.

^{1}H NMR spectra were recorded on a Bruker AC-F (250 MHz). Optical rotation values were determined with a Perkin-Elmer 241 polarimeter. TLC was performed on silica gel plates (Merck Silica 60 F_{254} sheets) and MPLC used Merck LiChroprep Si 60 (15–25 μ).

Table 1. α-Acyloxyacrylates **2** by Condensation of **1** or **1'** with Various Aldehydes

Product	Base/Solvent	E/Z-Ratio	Yield (%)[a]
2a	KOtBu/CH_2Cl_2	70 : 30	28
	BuLi/THF	92 : 8	31
	TMG/THF	35 : 65	72
	TMG/LiCl/THF	94 : 6	84
2'a	BuLi/THF	86 : 14	40
	TMG/THF	45 : 55	55
	TMG/LiCl/THF	80 : 20	87
2b[b]	TMG/THF	25 : 75	61
	TMG/LiCl/THF	92 : 8	91
2'b	TMG/LiCl/THF	82 : 18	56
2c	TMG/LiCl/THF	81 : 19	75
2d	TMG/LiCl/THF	80 : 20	71
2e[b]	TMG/LiCl/THF	75 : 25	60
2f (unstable)	TMG/LiCl/THF	90 : 10	48

[a] Satisfactory microanalyses were obtained for these compounds and compounds **1**, **1'**, **4** and **5**: C ± 0.27, H ± 0.18.
[b] These products were isomerized to the pure *Z*-isomers.

Table 2. Catalytic Hydrogenation of α-Acyloxyacrylates **2**.

α-Acyloxyacrylate (*E/Z*-ratio)	Catalyst	α-Acyloxycarboxylate (ee in %)[a]	$[\alpha]_D^{20}$ in MeOH (*c*)
2a (70 : 30)	Rh–DIPAMP	**3a** (92)	
2a (100 : 0)	Rh–DIPAMP	**3a** (92)	
2a (0 : 100)	Rh–DIPAMP	**3a** (92)	
2a (70 : 30)	Ru–BINAP	**3a** (98)	−37.2 (0.92)
2'a (0 : 100)	Rh–DIPAMP	**3'a** (90)	
2'a (100 : 0)	Ru–BINAP	**3'a** (82)	
2'a (80 : 20)	Ru–BINAP	**3'a** (80)	
2b (75 : 25)	Rh–DIPAMP	**3b** (92)	−25.1 (1.21)
2b (75 : 25)	Rh–BPPM	**3b** (24)[b]	
2'b (82 : 18)	Rh–DIPAMP	**3'b** (87)	−24.9 (0.99)
2c (81 : 19)	Rh–DIPAMP	**3c** (88)	−1.9 (1.06)
2d (80 : 20)	Rh–DIPAMP	**3d** (94)	−1.1 (0.37)
2e (0 : 100)	Rh–DIPAMP	**3e** (88)	−2.0 (1.05)

[a] The yield of the hydrogenation was always > 95%.
[b] The hydrogenation was incomplete. The ee-value refers to the hydrogenated part.

Table 3. NMR-Data of α-Acyloxyacrylates **2** (*E/Z*-mixtures)

Compound	^{1}H NMR ($CDCl_3$/TMS, 250 MHz) δ, *J* (Hz)
2a	6.37 (d, *Z*-1 H, *J* = 10.0), 5.73 (d, *E*-1 H, *J* = 10.3), 4.28–4.19 (m, 2 H), 3.74–3.32 (m, 1 H), 2.25 (s, *Z*-3 H), 2.18 (s, *E*-3 H), 1.30 (t, 3 H, *J* = 7.1), 1.07 (d, 9 H, *J* = 6.6)
2'a	6.38 (d, *Z*-1 H, *J* = 9.8 Hz), 5.67 (d, *E*-1 H, *J* = 10.3), 4.26–4.16 (m, 2 H), 3.50–3.35 (m, *E*-1 H), 2.63–2.54 (m, *Z*-1 H), 1.32–1.24 (m, 3 H), 1.28 (s, 9 H), 1.07 (d, 6 H, *J* = 6.7)
2b	6.55 (t, *Z*-1 H, *J* = 7.7), 5.93 (t, *E*-1 H, *J* = 8.0), 4.24 (q, *E*-2 H, *J* = 7.2), 4.23 (q, *Z*-2 H, *J* = 7.1), 2.59 (dt, *E*-2 H, *J* = 2 × 7.5), 2.25 (s, *Z*-3 H), 2.18 (s, *E*-3 H), 2.14 (dt, *Z*-2 H, *J* = 2 × 7.5), 1.49–1.35 (m, 4 H), 1.30 (t, 3 H, *J* = 7.2), 0.94–0.88 (m, 3 H)
2'b	6.54 (t, *Z*-1 H, *J* = 7.7), 5.88 (t, *E*-1 H, *J* = 8.0), 4.21 (q, 2 H, *J* = 7.0), 2.60 (dt, *E*-2 H, J = 2 × 7.5), 2.11 (dt, *Z*-2 H, *J* = 2 × 7.4), 1.49–1.18 (m, 7 H), 1.28 (s, 9 H), 0.91 (t, 3 H, *J* = 7.0)
2c	6.55 (t, *Z*-1 H, *J* = 7.7), 5.93 (t, *E*-1 H, *J* = 8.0), 4.24 (q, *E*-2 H, *J* = 7.2), 4.23 (q, *Z*-2 H, *J* = 7.2), 2.58 (dt, *E*-2 H, *J* = 2 × 7.4), 2.45 (s, *Z*-3 H), 2.18 (s, *E*-3 H), 2.13 (dt, *Z*-2 H, *J* = 2 × 7.4), 1.60–1.34 (m, 8 H), 1.30 (t, 3 H, 7.1), 0.91–0.86 (m, 3 H)
2d	6.55 (t, *Z*-1 H, *J* = 7.7), 5.93 (t, *E*-1 H, *J* = 8.0), 4.24 (q, *E*-2 H, *J* = 7.2), 4.23 (q, *Z*-2 H, *J* = 7.1), 2.58 (dt, *E*-2 H, *J* = 2 × 7.4), 2.45 (s, *Z*-3 H), 2.18 (s, *E*-3 H), 2.13 (dt, *Z*-2 H, *J* = 2 × 7.4), 1.45–1.26 (m, 17 H), 0.91–0.85 (m, 3 H)
2e	7.60–7.31 (m, 5 H), 7.26 (s, *Z*-1 H), 6.86 (s, *E*-1 H), 4.30 (q, *Z*-2 H, *J* = 7.1), 4.16 (q, E-2 H, *J* = 7.2), 2.33 (s, *Z*-3 H), 2.25 (s, *E*-3 H), 1.35 (t, *Z*-3 H, *J* = 7.1), 1.13 (t, *E*-3 H, *J* = 7.2)
2f	7.47 (m, 2 H), 7.27 (s, *Z*-1 H), 6.70 (s, *E*-1 H), 6.50 (m, 1 H), 4.29 (q, 2 H, *J* = 7.1), 2.24 (s, *E*-3 H), 2.04 (s, *Z*-3 H), 1.32 (t, 3 H, *J* = 7.1)

HPLC was performed on an LKB instrument and a silica gel column (Merck Hibar LiChrosorb Si 60 7 μ). Gas chromatograms were run with a Carlo Erba HRGC 5300 MEGA on glass capillary columns (PS 086 + 10% permethyl-β-cyclodextrine, 20 m, prepared in the GC department of our institute. After an initial hold of 10 min at

Downloaded by: York University libraries. Copyrighted material.

80 °C the column was temperature programmed at 0.5 °C/min to 200 °C. Hydrogen was employed as the carrier gas).

Ethyl 2-Ethoxy-2-hydroxyacetate (4):
The solution of glyoxylic acid monohydrate (4.6 g, 50 mmol) in EtOH (50 mL) was heated for 114 h at 80 °C. The semiacetal ester **4** and excess EtOH were distilled from the reaction mixture at r.t. and 2 Torr into a cooling trap cooled with liquid nitrogen. Afterwards the excess EtOH was evaporated. The colourless oil **4** (5.2 g, 70%) was used without further purification.

^{1}H NMR (250 MHz/$CDCl_3$): $\delta = 4.33–4.21$ (m, 3H), 3.90–3.62 (m, 2H), 1.40–1.22 (m, 6H).

Ethyl 2-(Diethoxyphosphoryl)-2-hydroxyacetate (5):
Compound **4** (10.4 g, 70 mmol) and diethyl phosphite (9.7 g, 70 mmol) were heated for 5 h at 80 °C. Volatile compounds were evaporated and the product was purified by bulb-to-bulb distillation to give **5** (15.4 g, 97%). Bp: 120 °C/10^{-3} Torr.

^{1}H NMR (250 MHz/$CDCl_3$): $\delta = 4.56$ (d, 1H, $J = 15.8$ Hz), 4.33–4.15 (m, 6H), 3.72 (s, 1H), 1.40–1.27 (m, 9H).

Ethyl 2-Acetoxy-2-(diethoxyphosphoryl)acetate (1):
The phosphonate ester **5** (4.56 g, 20 mmol) and anhydr. pyridine (1.63 mL, 20.2 mmol) were dissolved in anhydr. CH_2Cl_2 (40 mL). Acetyl chloride (1.13 mL, 20 mmol) was added at 0 °C. After stirring overnight, the reaction mixture was allowed to warm to r.t. Precipitated pyridine chloride was filtered off. After evaporating the solvent, the residue was dissolved in EtOAc (20 mL) was washed successively with 1 N H_2SO_4, 1 N $NaHCO_3$ and brine. The solution was dried ($MgSO_4$) and the solvent was evaporated. The pure product was obtained by bulb-to-bulb distillation (4.1 g, 72%). Bp: 100 °C/10^{-3} Torr.

^{1}H NMR (250 MHz/$CDCl_3$): $\delta = 5.41$ (d, 1H, $J = 16.8$ Hz), 4.33–4.15 (m, 6H), 2.22 (s, 3H), 1.40–1.27 (m, 9H).

Ethyl 2-(Diethoxyphosphoryl)2-pivaloyloxyacetate (1′):
The phosphonate ester **5** (2.26 g, 10 mmol) and anhydr. pyridine (0.89 mL, 11 mmol) were dissolved in anhydr. CH_2Cl_2 (20 mL). Pivaloyl chloride (1.35 mL, 11 mmol) was added at 0 °C. After stirring overnight, the reaction mixture was allowed to warm to r.t. Precipitated pyridine chloride was filtered off. After evaporating the solvent, the residue was dissolved in EtOAc (15 mL) and washed successively with 1 N H_2SO_4, 1 N $NaHCO_3$ and brine. The solution was dried ($MgSO_4$) and the solvent was evaported. The pure product (2.8 g, 89%) was obtained by flash chromatography (hexane/EtOAc, 1:1).

^{1}H NMR (250 MHz/$CDCl_3$): $\delta = 5.40$ (d, 1H, $J = 16.9$ Hz), 4.28–4.18 (m, 6H), 1.39–1.26 (m, 18H).

2-Acyloxyacrylates 2 and 2′; General Procedure:
Compound **1** or **1′** (5 mmol) and LiCl (210 mg, 5 mmol) were dissolved in THF (6 mL) and the solution was cooled to − 75 °C. After the addition of TMG (690 µL, 5.5 mmol), the reaction mixture was stirred for 15 min. The corresponding aldehyde (6 mmol) was added slowly. After warming up to r.t. overnight, the reaction mixture was dissolved in EtOAc and water (10 mL, 1:1). The solution was successively washed with 1 N H_2SO_4, 1 N $NaHCO_3$ and brine, and dried ($MgSO_4$). After evaporation, the crude product was purified by flash chromatography (hexane/EtOAc, 1:1).

(*S*)-1-Acyloxyalkanoates 3; General Procedure:
The corresponding alkene (1 mmol) and the catalyst (10 mg) were dissolved in MeOH p.a. (10 mL) under Ar atmosphere. For DIPAMP the hydrogenation was carried out at r.t. under a hydrogen pressure of 3 bar. For BINAP the hydrogenation was carried out at 50 °C under a hydrogen pressure of 50 bar. After 4 d, the solvent was evaporated and the catalyst was filtered off with silica gel (hexane/EtOAc, 1:1).

Isomerization of 2a and 2e; General Procedure:
The *E*/*Z*-mixture of **2a** or **2e** (1 mmol), AIBN (20 mg) and thiophenol (10 mg) were dissolved in benzene (2 mL) and heated for 4 h at 70 °C. After evaporation of the solvent, the product was purified by flash chromatography (yield > 98%).

(1) Monnin, J. *Helv. Chim. Acta* **1956**, *39*, 1721.
(2) Mukaiyama, T.; Oriyama,, T.; Murakami, M. *Chem. Lett.* **1983**, 985.
(3) Nakamura, E. *Tetrahedron Lett.* **1981**, *22*, 663.
(4) We also synthesized several other phosphonate esters (**1**: R = $MeSO_2$, $PhSO_2$, $PhSO_2NHCO$, PhNHCO, $PhCH_2CO$). However, these phosphonate esters either did not undergo the Wittig–Horner reaction or the alkenes could not be hydrogenated enantioselectively.
(5) The readily available methyl analogue semiacetal (**4**, Me instead of Et) led to the methyl analogue phosphonate (**5**, Me instead of Et) only in low yield.
(6) Kelly, T. R.; Schmidt, T. E.; Haggerty, J. G. *Synthesis* **1973**, 416.
(7) With regard to the determination of the configuration see: Fischer, P.; Schweizer, E.; Langner, J.; Schmidt, U. *Magnetic Resonance in Chemistry*, in press.
(8) Fryzuk, M. D.; Bosnich, B. *J. Am. Chem. Soc.* **1978**, *100*, 5491.
(9) Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518.
(10) Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 5946.
(11) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932.
(12) Achiwa, K. *J. Am. Chem. Soc.* **1976**, *98*, 8265.
(13) Larchevêque, M.; Petit, Y. *Tetrahedron Lett.* **1987**, *28*, 1993.
(14) Nakamura, K.; Inoue, K.; Ushio, K.; Oka, S.; Ohno, A. *J. Org. Chem.* **1988**, *53*, 2589.

Downloaded by: York University libraries. Copyrighted material.