Synthesis of 3-Alkoxyalkanoic Esters from Acetals. A Novel Application of Reformatsky Reagents in Asymmetric Synthesis

Tiziana Basile, Emilio Tagliavini,* Claudio Trombini, Achille Umani-Ronchi*
Dipartimento di Chimica "G. Ciamician", Università di Bologna, via Selmi, 2, I-40126 Bologna, Italy

3-Alkoxyalkanoic esters are directly obtained in high yield from the reaction of acetals with Reformatsky reagents in the presence of titanium(IV) chloride or diethyl ether-boron trifluoride complex in dichloromethane. The reaction of ethyl 4-bromo-2-butenoate is regioselective, affording the product formed by attack on the 4-position. With chiral acetals as substrates, up to 84% enantiomerically enriched 3-hydroxyalkanoic esters can be prepared.

The main route to 1,3-difunctional compounds is the condensation of enolate anions or their synthetic equivalents with carbonyl compounds.

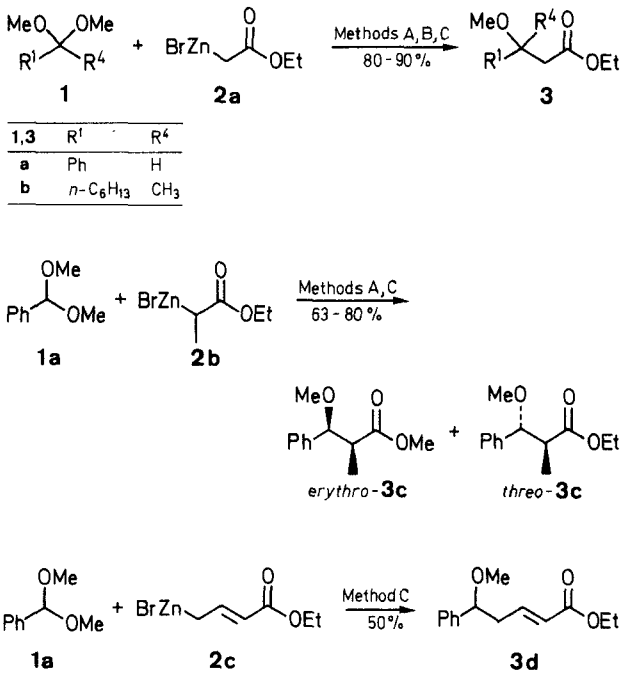
The Lewis acid promoted reaction of acetals with silicon nucleophiles[1] (the Mukaiyama reaction) offers a useful alternative to the traditional base-promoted condensation. The nucleophilic partners are, e. g. allylsilanes silyl enol ethers, ketene silyl acetals,[2] cyanotrimethylsilane,[3] and also cuprates.[4]

The interest in condensations involving acetals is based on the possibility of exploiting these reactions for asymmetric transformations. Prochiral aldehydes can be converted into chiral acetals by means of chiral diols, and their condensation leads, after removal of the chiral auxiliary, to enantiomerically enriched β-hydroxy compounds.[5]

Further, the availability of natural chiral acetals, in particular sugar derivatives, allows chemical transformations to be performed with high control of the stereochemistry of the newly formed stereocenters. We have earlier reported the preparation of chiral synthetic equivalents of protected tartaric aldehydes and regio- and stereocontrolled condensations thereof.[6]

From previous experience with Reformatsky reagents[7,8] we derived the hypothesis that this type of nucleophile should be compatible with the presence of the Lewis acids employed in the Mukaiyama reaction, correct choice of solvent provided;[9] we recently reported some preliminary results.[10]

We now describe the reaction of ethyl α-(bromozinco)carboxylates (Reformatsky reagents **2**) with acetals **1** as a general route to 3-alkoxyalkanoic esters **3**. Our synthesis is carried out in halogenated solvents (dichloromethane or chloroform) in the presence of Lewis acids such as $TiCl_4$ or $Et_2O \cdot BF_3$ under mild conditions (Scheme **A**). The preparation and use of Reformatsky reagents in the above solvents has not been previously reported.[11] We prepared $BrZnCH_2CO_2Et$ in > 90% yield by stirring Zn-Cu couple and ethyl bromoacetate in dichloromethane at room temperature (2 h). The resultant solution (~ 0.2 M), filtered under argon, was analyzed by ^{1}H-NMR spectroscopy; it showed a peak at $\delta = 2.05$ attributed to CH_2 bonded to the metal, while the signal at $\delta = 3.85$ of the starting bromide was absent.[12] Concentrations higher than 0.2 M give a liquid/liquid biphasic system. We did not analyze such mixtures, which anyhow proved to be appropriate for the succeeding condensation reaction, if efficient stirring is mantained. Clear 1 M solutions of $BrZnCH_2CO_2Et$ can be prepared by heating Zn–Cu couple and ethyl bromoacetate in



Method A: $TiCl_4/CH_2Cl_2$, −78 °C, 2 h
Method B: $TiCl_4/CHCl_3/CH_2Cl_2$, −78 °C, 2 h
Method C: $Et_2O \cdot BF_3/CH_2Cl_2$, −60 °C, 2 h
Scheme A

Table 1. Synthesis of Ethyl 3-Methoxyalkanoates **3**

Product	Method	Yield[a] (%)	Ratio[b] *erythro/threo*
3a	A	90	
	B	87	
	C	88	
3b	A	80	
3c	A	80	2:1
	C	63	3:1
3d[c]	C	50[d]	

[a] Yields of the esters purified by flash chromatography on silica gel.
[b] Diastereoisomeric ratios were determined by GC.
[c] There was no trace of the *Z* isomer.
[d] In addition, 10% of a mixture of diastereoisomers of ethyl α-ethenyl-β-methoxybenzenepropanoates in a 2:1 ratio (GC) was formed.
^{1}H-NMR ($CDCl_3$/TMS); major isomer: $\delta = 1.32$ (t, 3H, $OCH_2C\underline{H}_3$), 3.18 (s, 3H, OCH_3), 3.28–3.41 (m, 1H, H-2), 4.24 (complex $A\underline{B}X_3$ pattern, 2H, $OC\underline{H}_2CH_3$), 4.42 (d, 1H, J = 10.2 Hz, H-3), 4.84–5.0 (m, 2H, H_2C=), 5.54 (ddd, 1H, J = 8.7, 10.2, 19.0 Hz, CH=), 7.32, (m, 5H_{arom}), minor isomer: δ = 1.05 (t, 3H, $OCCH_2C\underline{H}_3$), 3.21 (s, 3H, OCH_3), 3.26–3.91 (m, 1H, H-2), 3.97 (complex ABX_3 pattern, 2H, $OC\underline{H}_2CH_3$), 4.51 (d, 1H, J = 8.0 Hz, H-3), 5.06–5.25 (m, 2H, H_2C=), 6.02 (ddd, 1H, J = 8.8, 10.3, 17.2 Hz), 7.32 (m, 5H_{arom}).

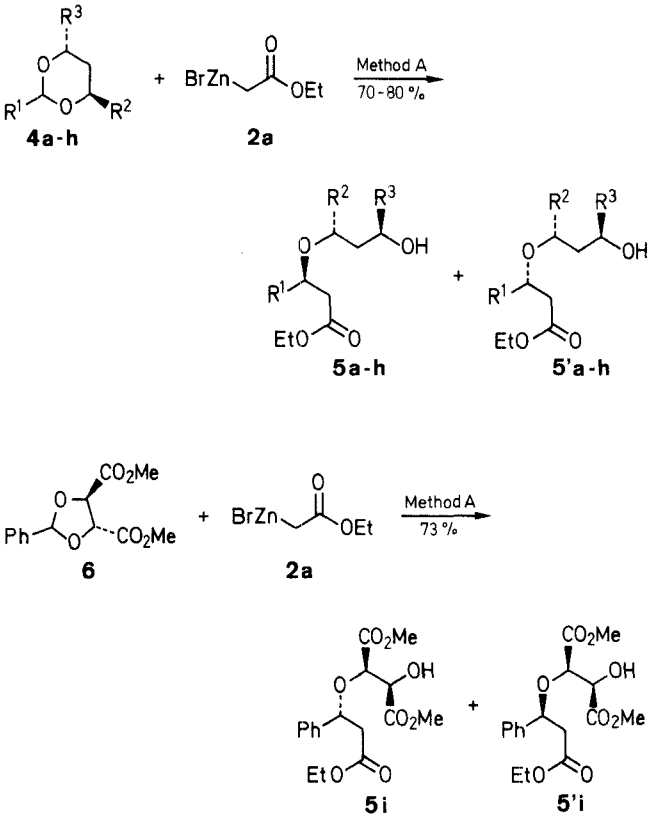
chloroform at 40 °C for 3 h. On storage of such solutions in a Schlenk tube under argon for one month, no change in the NMR spectrum was observed.

Benzaldehyde dimethyl acetal (**1a**) was chosen as a model substrate and comparative runs were carried out to test the solvent system, the Lewis acid, and the long-term stability of the Reformatsky reagent solution: the freshly prepared reagent in CH_2Cl_2 or $CHCl_3$ and the stored chloroform solution gave essentially the same yield using $TiCl_4$ at −78 °C; a higher temperature (−60 °C) was required to obtain **3a** in the presence of $Et_2O \cdot BF_3$.

The reaction was easily extended to acetal **1b** with good results, while ethyl bromozincopropanoate (**2b**) afforded moderate diastereoselectivity in the reaction with **1a** in the presence of $TiCl_4$; when $Et_2O \cdot BF_3$ is used as Lewis acid a 3:1 ratio of *erythro*-**3c** to *threo*-**3c** was obtained. The *erythro* configuration was attributed to the major isomer on the basis of ^{1}H-NMR coupling constants. The measured values (see Table 4) were compared with those calculated according to Haasnoot[13] on structures obtained from molecular mechanics calculations (PCMODEL program).[14] The corresponding reaction with unprotected aldehydes gives the *erythro* diastereoisomer with lower selectivity.[15]

An interesting result was observed when ethyl (*E*)-4-bromo-2-butenoate was used as starting material for the preparation of the zinc derivative **2c**. The chemistry of dienolate anions is well established: alkylation or condensation of these reagents under kinetic-control conditions mainly occurs at C-α to afford γ,δ-unsaturated esters, and also zinc dienolates react in accord with this rule;[7] however, the attack can be directed to the γ-position in certain solvents if equilibrating conditions are used.[16] From the reaction of **2c** with **1a** at −60 °C in the presence of diethyl ether boron trifluoride complex we obtained the (*E*)-α,β-unsaturated ester **3d** in 50% yield, the regioisomeric product being formed in negligible yield.

We also studied the asymmetric synthesis of 3-hydroxyalkanoic esters by using chiral cyclic acetals as substrates. Table 2 shows the results obtained from the reactions of ethyl bromozincoacetate (**2a**) with chiral dioxanes **4a–h** and dioxolanes **6** in the presence of $TiCl_4$ (Scheme **B**). The diastereoisomeric products **5** and **5′** are generally obtained in good yields, the stereoselectivity depending on both the chiral auxiliary and the substrate side chain. In the case of the benzaldehyde derivatives **4a**, **4b**, and **6**, the acetal **6** derived from a *vic*-diol reacts with the lowest stereoselectivity and the acetal **4b** derived from 2,4-pentanediol with the highest (Table 2). The acetals **4d** and **4f** formed from linear alkanals and 2,4-pentanediol react with ethyl bromozincoacetate to give the esters **5d** + **5′d** or **5f** + **5′f**, respectively, in an isomer ratio of 6:1 in both cases, whereas the acetals **4c** and **4e** formed from the same aldehydes and 1,3-butanediol are converted into esters **5c** + **5′c** or **5e** + **5′e**, respectively, in isomer ratios of 4:2. The lowest stereoselectivity is observed in the anologous reaction of the acetal **4g** derived from a branched alkanal.



4, 5	R^1	R^2	R^3
a	Ph	CH_3	H
b	Ph	CH_3	CH_3
c	*n*-C_7H_{15}	CH_3	H
d	*n*-C_7H_{15}	CH_3	CH_3
e	C_2H_5	CH_3	H
f	C_2H_5	CH_3	CH_3
g	*i*-C_4H_9	CH_3	H
h	$(C_2H_5)_2CH$	CH_3	H

Scheme **B**

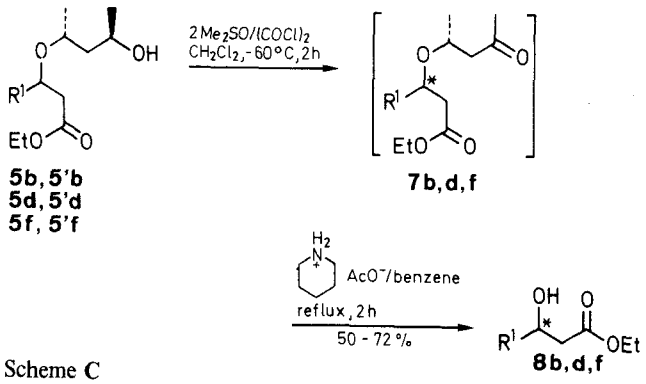
Table 2. Synthesis of Ethyl 3-(3-Hydroxyalkoxy)alkanoates **5** + **5′**[a]

Product **5** + **5′**	Yield %[b]	Ratio **5**/**5′**[c]
a	80	3:1
b	80	6:1
c	70	4.2:1
d	73	11.5:1
e	70	4.2:1
f	73	6.4:1
g	80	4:1
h	72	2.4:1
i[d]	73	1.5:1

[a] All reactions were carried out according to Method A.
[b] Yields of esters **5** + **5′** purified by flash chromatography on silica gel.
[c] Diastereoisomeric ratios were determined by GC.
[d] 1.5 equivalents of $TiCl_4$ were used.

For a few interesting substrates we completed the synthetic sequence to the target 3-hydroxyalkanoic esters **8** via the oxidation-elimination procedure depicted in Scheme **C**. Thus, oxidation of the isomer mixtures **5b**/**5′b**, **5d**/**5′d**, and **5f**/**5′f** with dimethyl sulfoxide/oxalyl

chloride in dichloromethane gave the 3-(3-oxoalkoxy-alkanoic esters **7b,d,f** as mixtures of diastereoisomers which were not purified but immediately cleaved by treatment with piperidinium acetate in boiling benzene to afford the optically active ethyl 3-hydroxyalkanoates **8b**, **8d**, or **8f**, respectively, in satisfactory yield and 71–84% enantiomeric excess.



Scheme C

Table 3. Synthesis of Chiral Ethyl 3-Hydroxyalkanoates **8**

Product	Yield[a] (%)	$[\alpha]_D^{20}$ found	$[\alpha]_D^{20}$ reported	e.e.[b] (%)	Configuration
8b	72	−22.01 ($c = 1.30$, $CHCl_3$)	−25.28 ($c = 1.3$)[17]	71	*S*
8d	64	−10.0 ($c = 1.20$, $CHCl_3$)		84	*R*[c]
8f	50	−7,0 ($c = 0.14$, $CHCl_3$)	−13.4 ($c = 1.2$, $CHCl_3$)[8]	73	*R*

[a] Overall yields of the oxidation and elimination steps (**5/5'** → **7** → **8**). Yields refer to chromatographed esters **8b,d,f**.

[b] Determined by ^{1}H-NMR spectrometry of the corresponding MPTA esters.

[c] Configuration attributed on the basis of the sign of optical rotation of the methyl (*R*)-3-hydroxydecanoate ($[\alpha]_{25}^D$ − 15.7, *c* = 2.06, EtOH).[16]

From the sign of optical rotations of compounds **8b,d,f** it may be concluded that the attack at the acetalic center of **4** occurs from the *Si*-face if (*R*)-1,3-butanediol or (*R,R*)-2,4-pentanediol are used as chiral auxiliaries. This result is in agreement with Johnson's findings, so that we can assume that a parallel mechanism is active in our reaction.

In conclusion, we believe that the reaction of α-bromozincocarboxylic esters with acetals represents something more than a simple variation of the classical Reformatsky protocol. Not only a novel reactivity of an old reagent has been discovered and *O*-protected 3-hydroxyalkanoic esters are prepared in one step, but there are also some other new interesting facts and improvements, in particular, the synthetically attractive possibility of γ-alkylation of dienolates as well as the preparation and use of Reformatsky reagents in halogenated solvents and the possibility of storing these solutions. The enantiomeric excesses obtained by our method are somewhat lower those achieved by the use of ketene silyl acetals,[5] but it is worthy of note that in our case inexpensive starting materials and simple procedures are used.

Optical rotations were measured on a Perkin-Elmer 241 polarimeter. TLC analyses were performed on Kieselgel 60 F_{254} plates and flash column chromatography with Kieselgel 60 (230–400 mesh) purchased from Merck using cyclohexane/EtOAc mixtures as eluents. GC analyses were performed on a Carlo Erba HRGC 5160 Mega Series chromatograph equipped with a fused-silica capillary Supelcowax column (30 m length, 0.32 mm i.d., 0.25 μm film thickness) with H_2 flow of 2 mL/min. GC-MS analyses were performed with a Hewlett-Pakard 5970 mass detector connected to a 5890 gas chromatograph equipped with a HP-1 (12 m length, 0.2 mm i.d., 0.33 μm film thickness) capillary column. IR spectra recorded on a Perkin-Elmer 682 spectrophotometer. ^{1}H-NMR spectra were recorded at 200 MHz and ^{13}C-NMR spectra at 50.8 MHz on a Varian Gemini 200 spectrometer.

All solvents were distilled before use: benzene from $LiAlH_4$, and CH_2Cl_2 and $CHCl_3$ from P_2O_5. Most of the commercially available reagents were purchased from Aldrich or Fluka at a purity of 98% or better and were used without further purification. Ethyl bromoacetate, ethyl 2-bromopropanoate, and ethyl (*E*)-4-bromo-2-butenoate were distilled and stored under argon.
Benzaldehyde dimethyl acetal (**1a**) was obtained from Aldrich; 2,2-dimethoxyoctane (**1b**) was prepared from 2-octanone and trimethyl orthoformate. Dioxanes and dioxolanes **4a–h** and **6** were prepared from the corresponding aldehydes and (*R*)-1,3-butanediol, (*R,R*)-2,4-pentanediol, and diethyl (*R,R*)-tartrate, respectively, according to standard procedures.

Zn-Cu couple was prepared from Zn and $Cu(OAc)_2$ in AcOH according to Lit.[17] and washed 4 times with CH_2Cl_2 or $CHCl_3$ under argon.

All reactions were carried out under dry argon in oven-dried (120 °C) or flame-dried glassware.

Standard Solution of Ethyl Bromozincoacetate (2a) in Chloroform:
In a 250 mL flask filled with argon and equipped with a sintered-glass filter and a stopcock on a side arm, Zn–Cu couple (200 mmol) is suspended in $CHCl_3$ (80 mL). Ethyl bromoacetate (12.0 mL, 100 mmol), dissolved in $CHCl_3$ (20 mL), is added dropwise with vigorous stirring. The mixture is heated at 40 °C for 3 h; then, the pale yellow solution is filtered, to remove unreacted metal, through the side arm filter into a dry argon-flushed ampoule. Titration with 1 N aqueous HCl shows a 0.97 M concentration of **2a**.

^{1}H-NMR ($CDCl_3$/TMS) of **2a** after concentration of the solution to remove $CHCl_3$: δ = 4.17 (q, 2H, OCH_2), 2.05 (s, 2H, $ZnCH_2$), 1.30 (t, 3H, CH_3).

Ethyl 3-Alkoxyalkanoates 3a,b and 5/5'; General Procedures:
Method A: To a stirred suspension of Zn-Cu couple (20 mmol) in CH_2Cl_2 (30 mL) is added a solution of ethyl bromoacetate (1.2 mL, 10 mmol) in CH_2Cl_2 (5 mL), dropwise at r.t. The suspension is stirred for 2 h (disappearence of the GC peak of the bromoester), then filtered into the reaction flask through a side arm filter. At this point, the system is a biphasic mixture formed by an upper clear mobile liquid and a lower pale green, viscous liquid. This mixture is cooled at − 78 °C and the acetal **1**, **4**, or **6** (2.5 mmol) and then a solution of $TiCl_4$ (0.8 mL, 7.5 mmol) in CH_2Cl_2 (5 mL) are slowly added dropwise (10 min). The mixture is stirred at − 78 °C for 2 h, then quenched with sat. $NaHCO_3$ solution (10 mL), and extracted with EtOAc (3 × 30 mL). The combined organic layers are dried (Na_2SO_4) and concentrated under reduced pressure. The residue is column chromatographed eluting with cyclohexane/EtOAc (8:2) to give products **3a,b** as pure compounds or inseparable mixtures of products **5** and **5'**.

Table 4. Physical and Spectroscopic Data of the Products Prepared

Product	bp[a] (°C/Torr)	Molecular Formula[b]	MS[c](70 eV) *m/z* (%)	IR (neat) ν (cm^{-1})	^{1}H-NMR[d] ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C-NMR[d] ($CDCl_3$/TMS) δ
3a	69–71/ 0.32	$C_{12}H_{16}O_3$ (208.25)	208 (M^+, 2.6), 193 (36), 177 (5), 147 (8), 135 (3), 133 (5), 121 (100), 105 (18), 91 (15), 77 (20), 51 (5)	1735, 1450, 1155, 1100, 700	1.25 (t, 3H, $OCH_2C\underline{H}_3$), 2.56 (dd, 1H, *J* = 4.7, 15.3, H-2), 2.80 (dd, 1H, *J* = 9.2, 15.3, H-2), 3.23 (s, 3H, OCH_3), 4.15 (q, 2H, OCH_2), 4.65 (dd, 1H, *J* = 4.7, 9.2, H-3), 7.35 (m, $5H_{arom}$)	170.8 (C-1), 141.8, 128.6, 128.0, 126.7 (C_{arom}), 80.2 (C-3), 60.5 (OCH_2), 56.8 (OCH_3), 46.6 (C-2), 14.2 ($OCH_2\underline{C}H_3$)
3b	60/0.12	$C_{13}H_{26}O_3$ (230.3)	215 (M^+-CH_3, 8), 199 (2.6), 185 (5), 153 (8), 146 (17), 145 (100), 143 (26), 117 (23), 103 (21), 85 (13), 69 (21), 43 (21)	1730, 1460, 1360, 1080	0.9 (t, 3H, H-8), 1.15–1.40 (m, 16H, $OCH_2C\underline{H}_3$, $C\underline{H}_3C$, H-5, H-6, H-7, H-8), 1.55 (m, 2H, H-4), 2.48 (d, 1H, *J* = 12.2, H-2), 2.49 (d, 1H, *J* = 12.2, H-2), 3.21 (s, 3H, OCH_3), 4.15 (q, 2H, OCH_2)	170.9 (C-1), 76.0 (C-3), 60.0 (OCH_2), 49.0 (OCH_3), 42.8 (C-2), 37.6, 31.7, 29.6, 23.2 (CH_2), 22.8 (3-CH_3), 22.5 (CH_2), 14.0, 13.9 (CH_3)
erythro-**3c**	68/0.11	$C_{13}H_{18}O_3$ (222.3)	222 (M^+, 2.5), 207 (5), 191 (2), 177 (2.5), 161 (5), 149 (3), 121 (100), 105 (8), 92 (13), 77 (13), 51 (5)	1730, 1450, 1175, 1095	0.86 (d, 3H, *J* = 7.4, $C\underline{H}_3CH$), 1.29 (t, 3H, $OCH_2C\underline{H}_3$), 2.74 (dq, 1H, *J* = 7.2, 10.0, H-2), 3.15 (s, 3H, OCH_3), 4.22 (complex $\underline{A}\underline{B}X_3$ pattern, OCH_2), 4.25 (d, 1H, *J* = 10.0, H-3), 7.32 (m, $5H_{arom}$)	175.7 (C-1), 139.6, 128.8, 128.6, 128.1 (C_{arom}), 86.3 (C-3), 60.5 (OCH_2), 59.6 (OCH_3), 47.3 (C-2), 14.3, 14.0 (CH_3)
threo-**3c**	49–52/ 0.11	$C_{13}H_{18}O_3$ (222.3)		1730, 1450, 1175, 1095	1.07 (t, 3H, $OCH_2C\underline{H}_3$), 1.22 (d, 3H, *J* = 7.0, $C\underline{H}_3CH$), 2.73 (quint, 1H, *J* = 7.0, H-2), 3.23 (s, 3H, OCH_3), 3.95 (complex $\underline{A}\underline{B}X_3$ pattern, 2H, OCH_2), 4.41 (d, 1H, *J* = 7.0, H-3), 7.30 (m, $5H_{arom}$)	175.7 (C-1), 139.6, 128.4, 127.9, 127.3 (C_{arom}), 84.6 (C-3), 60.1 (OCH_2), 57.0 (OCH_3), 47.4 (C-2), 13.8, 12.4 (CH_3)
3d	109–112/ 0.26	$C_{14}H_{18}O_3$ (234.3)	189 (M^+-OEt, 5), 157 (5), 145 (5), 129 (2.5), 128 (5), 122 (10), 121 (100), 105 (8), 91 (15), 77 (17), 51 (5)	1720, 1650, 1635, 1180	1.25 (t, 3H, $OCH_2C\underline{H}_3$), 2.52 (dddd, 1H, *J* = 1.5, 5.2, 7.2, 14.2, H-4), 2.68 (dddd, 1H, *J* = 1,5, 7.2, 7.9, 14.2, H-4), 3.2 (s, 3H, OCH_3), 4.17 (q, 2H, OCH_2), 4.24 (dd, 1H, *J* = 5.2, 7.9, H-5), 5.85 (dt, 1H, *J* = 1.5, 15.7, H-2), 6.95 (dt, 1H, *J* = 7.2, 15.7, H-3), 7.25–7.45 (m, $5H_{arom}$)	171.0 (C-1), 145.0 (C-3), 141.0, 128.6, 127.9, 126.6 (C_{arom}), 123.4 (C-2), 82.6 (C-5), 60.2 (OCH_2), 56.7 (OCH_3), 41.0 (C-4), 14.3 ($OCH_2C\underline{H}_3$)
5a	–	$C_{15}H_{22}O_4$ (266.3)	221 (M^+-OEt), 207 (5); 193 (71), 181 (38), 167 (10), 95 (41), 81 (43), 67 (41), 55 (100), 45 (54)	3450, 1730, 1370, 1045	1.2 (t, 3H, $OCH_2C\underline{H}_3$), 1.25 (d, 3H, $OCHC\underline{H}_3$), 1.65 (m, 2H, $OCHC\underline{H}_2CH_2$), 2.53 (dd, 1H, *J* = 5.0, 15.0, H-2), 2.65 (br s, 1H, OH), 2.75 (dd, 1H, *J* = 8.7, 15.0, H-2), 3.4–3.7 (m, 3H, $OC\underline{H}CH_2C\underline{H}_2$), 4.17 (q, 2H, $OC\underline{H}_2CH_3$), 4.85 (dd, 1H, *J* = 5.0, 8.7, H-3), 7.35 (m, $5H_{arom}$)	171.3 (C-1), 141.4, 129.1, 128.9, 127.3 (C_{arom}); 75.5, (C-3), 71.4 ($O\underline{C}HCH_2CH_2$) 60.8, 60.4 (OCH_2), 44.0 (C-2), 39.6 ($OCH\underline{C}H_2CH_2$) 18.7, 14.3 (CH_3)
5'a	–	$C_{15}H_{22}O_4$ (266.3)		3450, 1730, 1370, 1045	0.95 (d, 3H, $OCHC\underline{H}_3$), 1.2 (t, 3H, $OCH_2C\underline{H}_3$), 1.7 (m, 2H, $OCHC\underline{H}_2CH_2$), 2.55 (dd, 1H, *J* = 5.0, 15.0, H-2), 2.65 (br s, 1H, OH), 2.75 (dd, 1H, *J* = 8.7, 15.0, H-2), 3.5–3.8 (m, 3H, $OC\underline{H}CH_2C\underline{H}_2$), 4.15 (q, 2H, $OC\underline{H}_2CH_3$), 4.9 (dd, 1H, *J* = 5.0, 8.7 H-3)	170.1 (C-1), 140.2, 128.9, 128.2, 126.8 (C_{arom}), 74.2 (C-3), 69.8 ($O\underline{C}HCH_2CH_2$), 60.9, 59.5 (OCH_2), 44.1 (C-2), 39.2 ($OCH\underline{C}H_2CH_2$), 21.2, 14.3 (CH_3)
5b		$C_{16}H_{24}O_4$ (280.4)	235 (M^+-OEt, 3), 217 (5), 194 (15), 183 (83), 177 (15), 152 (15), 135 (65), 107 (100), 105 (70), 69 (33), 45 (50)	3840, 1730, 1450, 1370, 1115	1.04 (d, 3H, *J* = 6.2, $OCHC\underline{H}_3$), 1.17 (d, 3H, *J* = 6.0, $OCHC\underline{H}_3$), 1.23 (t, 3H, $OCH_2C\underline{H}_3$), 1.42 (ddd, 1H, *J* = 3.0, 3.8, 14.4, $CHC\underline{H}_2CH$), 1.62 (ddd, *J* = 8.8, 9.6, 14.4, $CHC\underline{H}_2CH$), 2.59 (dd, 1H, *J* = 4.8, 15.0, H-2), 2.80 (dd, 1H, J = 9.2, 15.0, H-2), 3.4–3.65 (m, 1H, $OC\underline{H}CH_3$), 3.67 (br s, 1H, OH), 3.73–3.90 (m, 1H, $OC\underline{H}CH_3$), 4.13 (q, 2H, $OC\underline{H}_2CH_3$), 4.95 (dd, 1H, *J* = 4.8, 9.2, H-3), 7.37 (m, $5H_{arom}$)	171.3 (C-1), 141.3, 129.2, 128.8, 127.5 (C_{arom}), 75.1, 72.3, 67.3 (OCH), 60.8 ($O\underline{C}H_2CH_3$), 46.3 (C-2), 43.8 (CH_2), 23.4, 19.0, 14.3 (CH_3)

Table 4. (continued)

Product	bp[a] (°C/Torr)	Molecular Formula[b]	MS[c](70 eV) *m/z* (%)	IR (neat) ν (cm^{-1})	^{1}H-NMR[d] ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C-NMR[d] ($CDCl_3$/TMS) δ
5'b		$C_{16}H_{24}O_4$ (280.4)		3840, 1730, 1450, 1370, 1115	0.95 (d, 3H, J = 6.2, $OCHC\underline{H}_3$), 1.25 (t, 3H, $OCH_2C\underline{H}_3$), 1.22 (d, 3H, J = 6.8, $OCHC\underline{H}_3$), 1.42 (ddd, 1H, J = 3.0, 3.8, 14.4, $CHC\underline{H}_2CH$), 4.15 (q, 2H, $OC\underline{H}_2CH_3$), 4.9 (dd, 1H, J = 4.2, 9.2, H-3)	140.9, 128.9, 128.1, 126.7 (C_{arom}), 66.8 (OCH), 60.9 (OCH_2), 45.2 (C-2), 44.2 (CH_2), 24.0 (CH_3)
5c		$C_{16}H_{32}O_4$ (288.4)	243 (M^+-OEt, 7), 215 (27), 199 (29), 189 (9), 153 (30), 119 (20), 117 (100), 101 (19), 69 (40), 55 (75), 43 (54)	3450, 1730, 1365, 1050	0.90 (t, 3H, H-10), 1.15 (d, 3H, J = 5.2, $C\underline{H}_3CHCH_2$), 1.25–1.40 (m, 13H, H-5, H-6, H-7, H-8, H-9, $OCH_2C\underline{H}_3$), 1.45–1.65 (m, 2H, H-4), 1.73 (q, 2H, $CHC\underline{H}_2CH_2$), 2.45 (d, 2H, J = 5.2, H-2), 2.5 (br s, 1H, OH), 3.70–3.95 (m, 3H, $C\underline{H}_2OH$, $OC\underline{H}CH_3$), 4.15 (q, 2H, $OC\underline{H}_2CH_3$), 4.18 (m, 1H, H-3)	172.0 (C-1), 73.5, 72.9 (OCH), 60.7, 60.3 (OCH_2), 40.5 (C-2), 38.9, 33.9, 31.6, 29.5, 29.0, 24.8, 22.4 (CH_2), 19.5, 14.0, 13.8 (CH_3)
5'c		$C_{16}H_{32}O_4$ (288.4)		3450, 1730, 1365, 1050	1.18 (d, 3H, J = 5.0, $C\underline{H}_3CHCH_2$), 2.65 (d, 2H, J = 3.6, H-2)	172.0 (C-1), 73.8, 72.7 (OCH), 60.5, 59.9 (OCH_2), 39.8, 39.3, 35.5, 29.4, 25.2 (CH_2), 20.1 (CH_3)
5d		$C_{17}H_{34}O_4$ (302.45)	257 (M^+-OEt, 5), 243 (12), 215 (41), 199 (44), 153 (31), 127 (26), 117 (90), 69 (100), 45 (64)	3445, 1730, 1365, 1115	0.83 (t, 3H, H-10), 1.15 (d, 3H, J = 1.9, $OCHC\underline{H}_3$), 1.16 (d, 3H, J = 1.9, $OCHC\underline{H}_3$), 1.18–1.31 (m, 13H, H-5, H-6, H-7, H-8, H-9, $OCH_2C\underline{H}_3$), 1.42–1.68 (m, 4H, H-4, $CHC\underline{H}_2CH$), 2.44 (d, 2H, J = 6.4, H-2), 2.9 (br s, 1H, OH), 3.80 (m, 2H, $OC\underline{H}CH_3$), 4.09 (q, 2H, $OC\underline{H}_2CH_3$)	171.9 (C-1), 74.0, 71.4, 64.2 (OCH), 60.2 (OCH_2), 45.0 (C-2), 40.5, 34.0, 31.6, 29.5, 29.0, 24.8 (CH_2), 23.5 (CH_3), 22.4 (CH_2), 19.2, 13.9, 13.8 (CH_3)
5'd		$C_{17}H_{34}O_4$ (302.45)		3445, 1730, 1365, 1115	2.45 (complex $\underline{A}\underline{B}X$ pattern, 2H, H-2), 4.12 (complex $\underline{A}\underline{B}X_3$ pattern, 2H, $OC\underline{H}_2CH_3$)	71.0, 63.6 (OCH), 60.8 (OCH_2), 45.8 (C-2), 39.7, 35.6, 30.0, 29.4, 26.7, 25.2 (CH_2), 23.3 (CH_3)
5e		$C_{11}H_{22}O_4$ (218.3)	173 (M^+-OEt, 12), 155 (5), 145 (21), 128 (44), 117 (82), 101 (85), 89 (36), 83 (36), 71 (41), 55 (100), 45 (54)	3420, 1725, 1370, 1180	0.94 (t, 3H, J = 7.6, H-5), 1.16 (d, 3H, J = 6.2, $OCHC\underline{H}_3$), 1.29 (t, 3H, $OCH_2C\underline{H}_3$), 1.50–1.80 (m, 4H, H-4, $C\underline{H}_2CH_2OH$), 2.45 (d, 2H, J = 5.2, H-2), 2.85 (br s, 1H, OH), 3.60–3.90 (m, 3H, $OC\underline{H}CH_3$, $CH_2C\underline{H}_2OH$), 4.15 (q, 2H, $OC\underline{H}_2CH_3$), 4.20 (m, 1H, H-3)	171.8 (C-1), 74.6, 72.6 (OCH), 60.4 (OCH_2), 40.2, 39.3, 26.7 (CH_2), 19.8, 14.2, 9.2 (CH_3)
5'e		$C_{11}H_{22}O_4$ (218.3)		3420, 1725, 1370, 1180	1.19 (d, 3H, J = 6.0, $OCHC\underline{H}_3$), 1.30 (t, 3H, $OCH_2C\underline{H}_3$), 2.53 (m, 2H, H-2)	75.1 (OCH), 59.8 (OCH_2), 39.6, 39.5, 28.4 (CH_2), 20.5, 9.8 (CH_3)
5f	–	$C_{12}H_{24}O_4$ (232.3)	217 (M^+-Me, 3), 187 (3), 159 (3), 145 (5), 130 (5), 129 (6), 117 (15), 101 (30), 85 (18), 55 (13), 45 (100)	3420, 1720, 1365, 1180, 1110	0.92 (t, 3H, J = 7.4, H-5), 1.17 (d, 3H, J = 2.9, $OCHC\underline{H}_3$), 1.20 (d, 3H, J = 2.9, $OCHC\underline{H}_3$), 1.28 (t, 3H, $OCH_2C\underline{H}_3$), 1.45–1.80 (m, 4H, H-4, $CHC\underline{H}_2CH$), 2.47 (complex $\underline{A}\underline{B}X$ pattern, 2H, H-2), 3.7–4.0 (m, 2H, $OC\underline{H}CH_3$), 4.0–4.3 (m, 3H, H-3, $OC\underline{H}_2CH_3$), 4.7 (br s, 1H, OH)	172.8 (C-1), 75.2, 72.1, 65.1 (OCH), 61.1 (OCH_2), 45.4 (C-2), 40.1, 27.1 (CH_2), 24.0, 19.8, 14.6, 9.9 (CH_3)
5'f	–	$C_{12}H_{24}O_4$ (232.3)		3420, 1720, 1365, 1180, 1110	0.93 (t, 3H, J = 7.4, H-5), 1.17 (d, 3H, J = 2.5, $OCHC\underline{H}_3$), 1.22 (d, 3H, J = 2.7, $OCHC\underline{H}_3$), 1.27 (t, 3H, $OCH_2C\underline{H}_3$), 2.48 (complex $\underline{A}\underline{B}X$ pattern, 2H, H-2)	76.0, 72.4, 64.5 (OCH), 46.3 (C-2), 39.8, 29.0 (CH_2), 23.8, 10.2 (CH_3)
5g	–	$C_{13}H_{26}O_4$ (246.3)	201 (M^+-OEt, 18), 189 (8), 173 (35), 157 (43), 129 (25), 117 (100), 111 (50), 89 (28), 83 (30), 71 (33), 55 (53), 43 (50)	3440, 1730, 1370, 1175, 1110	0.89 (d, 3H, J = 4.2, H-6), 0.93 (d, 3H, J = 4.2, 5-CH_3), 1.14 (d, 3H, J = 6.2, $OCHC\underline{H}_3$), 1.25 (t, 3H, $OCH_2C\underline{H}_3$), 1.30–1.74 (m, 5H, H-4, H-5, $OCHC\underline{H}_2CH_2$) 2.43 (complex $\underline{A}\underline{B}X$ pattern, 2H, H-2), 2.70 (br s, 1H, OH), 3.55–3.95 (m, 4H, H-3, $OC\underline{H}CH_3$, $C\underline{H}_2OH$), 4.13 (complex $\underline{A}\underline{B}X_3$ pattern, 2H, $OC\underline{H}_2CH_3$)	171.7 (C-1), 72.9, 72.4 (OCH), 60.5 (OCH_2), 44.1 (C-2), 41.2, 39.3, 24.7 (CH_2), 23.1, 22.7, 20.0, 14.2 (CH_3)

Table 4. (continued)

Product	bp[a] (°C/Torr)	Molecular Formula[b]	MS[c](70 eV) *m/z* (%)	IR (neat) ν (cm^{-1})	^{1}H-NMR[d] ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C-NMR[d] ($CDCl_3$/TMS) δ
5'g	–	$C_{13}H_{26}O_4$ (246.3)		3440, 1730, 1370, 1175, 1110	0.90 (d, 6H, J = 6.6, H-6, 5-CH_3), 1.15 (d, 3H, J = 6.0, $OCHCH_3$) 4.16 (complex ABX$_3$ pattern, OCH_2CH_3)	72.2, 71.9 (OCH), 59.9 (OCH_2), 45.2 (C-2), 40.1, 39.6, 24.5 (CH_2), 23.4, 22.5, 20.2 (CH_3)
5h	–	$C_{14}H_{28}O_4$ (260.4)	215 (M^+-OEt, 5), 189 (18), 187 (13), 171 (10), 143 (13), 119 (23), 117 (100), 101 (20), 89 (18), 71 (30), 55 (35), 43 (28)	3450, 1730, 1445, 1030	0.95 (t, 6H, $CH_3CH_2CHCH_2CH_3$), 1.14 (d, 3H, J = 6.2, $OCHCH_3$), 1.27 (t, 3H, OCH_2CH_3), 1.4–1.8 (m, 7H, $CH_3CH_2CHCH_2CH_3$, $CHCH_2CH_2OH$), 2.35 (d, 2H, J = 6.8, H-2), 2.40 (br s, 1H, OH), 3.60–3.85 (m, 3H, $OCHCH_3$, CH_2OH), 3.85–4.05 (m, 1H, H-3), 4.15 (q, 2H, OCH_2CH_3)	172.4 (C-1), 75.1, 72.4 (OCH), 60.4 (OCH_2), 44.3 (C-4), 32.4, 22.9, 21.9 (CH_2), 19.5, 14.2, 12.6, 12.5 (CH_3)
5'h	–	$C_{14}H_{28}O_4$ (260.4)		3450, 1730, 1445, 1030	0.94 (t, 6H, $CH_3CH_2CHCH_2CH_3$), 1.16 (d, 3H, J = 6.0, $OCHCH_3$), 1.28 (t, 3H, OCH_2CH_3), 2.47 (complex ABX pattern, 2H, H-2)	75.4, 73.1 (OCH), 60.6, 60.2 (OCH_2), 46.0 (C-4), 36.6, 22.4 (CH_2), 20.4, 12.3 (CH_3)
5i	–	$C_{17}H_{22}O_8$ (354,35)	295 (M^+-CO_2Me, 0.5), 207 (4), 194 (12), 193 (100), 177 (22), 161 (10), 147 (17), 135 (73), 131 (20), 107 (19), 105 (62)	3500, 1750, 1730, 1265, 1095, 730	1.30 (t, 6H, OCH_2CH_3), 2.58 (dd, 1H, J = 3.9, 16.4, H-2), 2.95 (dd, 1H, J = 9.5, 16.4, H-2), 3.53 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.90 (br s, 1H, OH), 4.15 (q, 2H, OCH_2CH_3), 4.29 (d, 1H, J = 3.7, OCHCHOH), 4.54 (m, 1H, OCHCHOH), 4.86 (dd, 1H, J = 3.9, 9.5, H-3), 7.2–7.4 (m, 5H, H_{arom})	171.4, 171.1, 169.5 (C=O), 139.1, 128.6, 128.5, 127.3 (C_{arom}), 80.0, 78.4 (OCHCHO), 72.4 (OCH), 60.9 (OCH_2), 52.7, 52.3 (OCH_3), 42.2 (CH_2), 14.1 (CH_3)
5'i	–	$C_{17}H_{22}O_8$ (354.35)		3500, 1750, 1730, 1265, 1035, 730	1.16 (t, 6H, OCH_2CH_3), 2.67 (dd, 1H, J = 6.8, 15.0, H-2), 3.05 (dd, 1H, J = 7.2, 15.0 H-2), 3.48 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.05 (complex ABX$_3$ pattern, 2H, OCH_2CH_3), 4.15 (d, 1H, J = 2.0, OCHCHOH), 4.46 (m, 1H, OCHCHOH), 4.88 (complex ABX pattern, 1H, H-3)	171,3, 170,2, 169.7 (C=O), 139.2, 127.4 (C_{arom}), 78.6, 76.9 (OCH–CHO), 72.2 (OCH), 60.5 (OCH_2), 52.0 (OCH_3), 42.9 (CH_2)
8a	94–96/ 0.2	$C_{11}H_{14}O_3$ (194.2)	194 (M^+, 30), 120 (18), 107 (100), 106 (30), 105 (88), 103 (10), 88 (23), 79 (75), 77 (65), 51 (28), 43 (30)	3470, 1740, 1490, 1190	1.18 (t, 3H, OCH_2CH_3), 2.66 (dd, 2H, J = 5.0, 8.0, H-2), 3.88 (br s, 1H, OH), 4.09 (q, 2H, OCH_2CH_3), 5.08 (dd, 1H, J = 5.0, 8.0, H-3), 7.2–7.4 (m, 5H, H_{arom})	172.0 (C-1), 142.2, 128.4, 127.6, 125.8 (C_{arom}), 70.4 (C-3), 60.6 (OCH_2), 42.8 (C-2), 14.1 (CH_3)
8b	129–131/ 1.0	$C_{12}H_{24}O_3$ (216.3)	171 (M^+-OEt, 2.5), 153 (5), 152 (5), 135 (5), 127 (10), 117 (100), 110 (8), 88 (25), 87 (25), 71 (43), 57 (23), 43 (48)	3500, 1730, 1365, 1165	0.85 (t, 3H, H-10), 1.1–1.6 (m, 15H, H-4, H-5, H-6, H-7, H-8, H-9, OCH_2CH_3), 2.36 (dd, 1H, J = 8.5, 16.4, H-2), 2.48 (dd, 1H, J = 3.7, 16.4, H-2), 3.1 (br s, 1H, OH), 3.95 (m, 1H, H-3), 4.15 (q, 2H, OCH_2CH_3)	173.1 (C-1), 68.1 (C-3), 60.7 (OCH_2), 41.4 (C-2), 36.6, 31.8, 29.5, 29.3, 25.5, 22.7 (CH_2), 14.2, 14.1 (CH_3)
8c	85/10	$C_7H_{14}O_3$ (146.2)	145 (M^+-H, 2.5), 128 (5), 118 (5), 117 (95), 101 (28), 89 (49), 83 (26), 71 (100), 60 (39), 59 (46), 43 (77)	3490, 1720, 1370, 1180, 1095	0.87 (t, 3H, H-5), 1.25 (t, 3H, OCH_2CH_3), 1.44–1.6 (m, 2H, H-4), 1.7 (br s, 1H, OH), 2.38 (dd, 1H, J = 5.4, 15.2, H-2), 2.52 (dd, 1H, J = 7.5, 15.2, H-2), 3.90–3.98 (m, 1H, H-3), 4.18 (q, 2H, OCH_2CH_3)	173 (C-1), 65.1 (C-3), 61 (OCH_2), 40.1 (C-2), 27.4 (C-4), 14.7 (OCH_2CH_3), 9.8 (C-5)

[a] Boiling points are not reported for inseparable mixtures, of diastereoisomer.

[b] Satisfactory microanalyses: C ±0.33, H ±0.28.

[c] In all GC-MS analyses, both diastereoisomers gave rise to identical MS spectra; only the spectra of the major components are reported.

[d] In the case of inseparable mixtures of diastereoisomers (e.g. **5** and **5'**), the major component is fully characterized; only the peaks which can be unambiguously attributed to the minor isomer are reported.

Method B: The standard solution of $BrZnCH_2CO_2Et$ (**2a**) in $CHCl_3$ (0.97 M, 10 mL) is added to CH_2Cl_2 (10 mL). This solution is cooled to −78 °C and the acetal **1** or **4** and $TiCl_4$ are added as in Method A. The mixture is stirred at −78 °C for 2 h and then worked up as in Method A.

Method C: A mixture of the $BrZnCH_2CO_2Et$ (**2a**) solution (10 mmol; prepared according to Method A) and the acetal **1** or **4** (2.5 mmol) is cooled to −60 °C and $Et_2O \cdot BF_3$ (0.92 mL, 7.5 mmol) in CH_2Cl_2 (5 mL) is added dropwise, with stirring. After 2 h at −60 °C, the mixture is worked up as in Method A.

Ethyl *erythro*- and *threo*-3-Methoxy-2-methyl-3-phenylpropanoates (*erythro*-3c and *threo*-3c):

A solution of ethyl 2-bromopropanoate (1.81 g, 10 mmol) in CH_2Cl_2 (5 mL) is added to a stirred suspension of Zn-Cu couple (20 mmol) in CH_2Cl_2 (5 mL) and the mixture is warmed at 38 °C for 3 h (disappearance of the GC peak of the bromoester), then filtered into the reaction flask. The clear solution is cooled to −78 °C, benzaldehyde dimethyl acetal (**1a**; 0.38 g, 2.5 mmol) and $TiCl_4$ (0.8 mL, 7.5 mmol) are successively added, and the procedure of Method A is followed. After 2 h, workup as in Method A and column chromatography (cyclohexane/EtOAc, 8:2) affords products *erythro*-**3c** (yield: 0.30 g, 54%) and *threo*-**3c** (yield: 0.15 g, 26%).

When the above reaction is performed according to Method C, products *erythro*-**3c** (0.29 g, 53%) and *threo*-**3c** (0.09 g, 17%) are obtained.

Ethyl (*E*)-5-Methoxy-5-phenyl-2-pentenoate (3d):

To a stirred and cooled (0 °C) suspension of Zn-Cu couple (20 mmol) in CH_2Cl_2 (5 mL), a solution of ethyl (*E*)-4-bromo-2-butenoate (1.4 mL, 10 mmol) in CH_2Cl_2 (5 mL) is added dropwise and stirring is continued for 2 h at 0 °C. The mixture containing the zinc derivative **2c** is then filtered and submitted to the reaction with acetal **1a** according to Method C. Workup according to Method A and column chromatography affords ester **3d** (yield: 0.30 g, 50%) and an inseparable mixture of the diastereoisomers of ethyl α-ethenyl-β-methoxybenzenepropanoate (yield: 0.06 g, 10%).

Ethyl 3-Hydroxyalkanoates 8b,f,d; General Procedure:

A solution of DMSO (0.17 mL, 2.2 mmol) in CH_2Cl_2 (1 mL) is added to a stirred solution of oxalyl chloride (0.1 mL, 1.1 mmol) in CH_2Cl_2 (2.5 mL) at −60 °C. The mixture is stirred for 2 min and a solution of the respective mixture **5/5'** (1 mmol; obtained by Method A) in CH_2Cl_2 (1 mL) is added within 5 min. Stirring is continued for 15 min. Then, Et_3N (0.7 mL, 5 mmol) is added, the mixture is stirred for 5 min at −60 °C, and allowed to warm at r.t. Water (5 mL) is added and the aqueous layer is extracted with CH_2Cl_2 (3 × 5 mL). The organic layers are combined, dried (Na_2SO_4), and concentrated under reduced pressure. The mixture of diastereoisomeric ketones **7** thus obtained is added to a solution of piperidinium acetate (0.23 mL, 0.12 mmol) in benzene (10 mL) and the mixture is refluxed for 2 h. The solvent is removed under reduced pressure and the residue is column chromatographed on silica gel (cyclohexane/EtOAc, 8:2) to afford the pure compound **8b,d,f**.

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