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A Simple Procedure for the Synthesis of Enantiopure α-Acetoxy Ketones

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Abstract

Cross-coupling reactions of α-acetoxy carboxylic acid chlorides with organocopper reagents, derived from Grignard reagents, cuprous bromide and lithium bromide, provide a simple and straightforward method for the synthesis of enantiopure α-acetoxy ketones.

Keywords
Organocopper reagents; Ketones; Cross-coupling

Introduction

The α-hydroxy carbonyl structural unit is found in many biologically active natural products and also represents a versatile class of intermediates in organic synthesis [1,2]. Enantiomerically pure α-hydroxy carbonyl compounds are also important chiral building blocks for the asymmetric synthesis of natural products and are useful stereodirecting groups [3-6]. Consequently, numerous studies have been aimed at developing methodologies for the enantioselective synthesis of this structural unit [7-11].

Among the various approaches to the synthesis of α-hydroxy ketones and their derivatives, we believe that in principle the chemoselective cross-coupling reactions of α-hydroxy acid derivatives with organometallic reagents probably should be considered the most direct one. In addition, the great availability of enantiopure α-hydroxy acids make the above mentioned approach to optically active α-hydroxy ketones really competitive. However, the reaction of organometallic reagents with α-hydroxy acid derivatives often failed or result in poor yields [12-15]. Only recently G.. Cahiez and coworkers have reported [16] that chiral α-acyloxy

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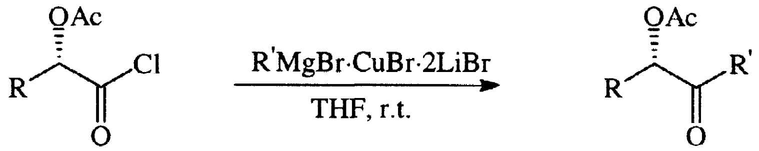
ketones can be conveniently synthesized by reacting α-acyloxy carboxylic acid chlorides with organomanganese reagents in THF or Et_2O at -10 °C.

As a part of our extensive work in the area of the direct acylation of organometallics [17,18], we have recently shown that organocopper reagents derived from Grignard reagents, cuprous bromide and lithium bromide are highly chemoselective reagents [19]. Thus, a chemoselective cross-coupling of these reagents with monoesters of dicarboxylic acid chlorides enabled us to achieve a simple and straightforward method for synthesizing a variety of ketoesters in high yields and under mild reaction conditions.

In an effort to further explore the utility of above mentioned organocopper reagents, we describe herein a simple and effective method for the synthesis of enantiopure α-acetoxy ketones based upon the reactions of organocopper reagents with α-acetoxy carboxylic acid chlorides.

Results and Discussion

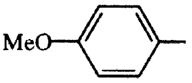
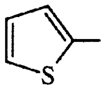
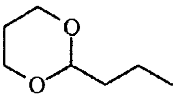
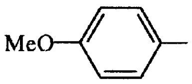
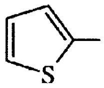
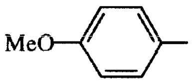
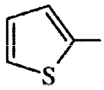
We have carried out the synthesis of a variety of enantiopure α-acetoxy ketones starting from three different acyl chlorides and performing the reactions with several Grignard reagents, in the presence of CuBr and LiBr, in THF at room temperature, according to the equation 1:



1-3 **4-17** (1)

The α-acetoxy carboxylic acid chloride **1** (R = Ph) [16,20-22] and **2** (R = $PhCH_2$) [16,23] were prepared enantioselectively by reaction of the corresponding α-acetoxy acids with oxalyl chloride in the presence of DMF. As starting acids the commercially available (*S*)-(+)-mandelic and (*S*)-(-)-phenyllactic acids were used. Chloride **3** (R = CH_3) [16,24,25] was prepared by acetylation of commercial (*S*)-(+)-lactic acid, followed by the reaction with thionyl chloride in the presence of DMF. The experimental results are listed in Table 1.

Table 1
Synthesis of enantiopure α-acetoxy ketones **4-17**

Entry	Acyl halides		Ketones		Yield (%)[a]	e.e. (%)[b]
	1-3	R	R'	**4-17**		
1	**1**	Ph	Ph	**4**	89	99.6
2	**1**	Ph		**5**	75	99.5
3	**1**	Ph		**6**	84	99.2
4	**1**	Ph	$CH_3(CH_2)_8CH_2$	**7**	91	99
5	**1**	Ph		**8**	68	99
6	**1**	Ph		**9**	63	95
7	**2**	$PhCH_2$	Ph	**10**	97	99.6
8	**2**	$PhCH_2$		**11**	80	99.6
9	**2**	$PhCH_2$		**12**	92	99.5
10	**2**	$PhCH_2$	$CH_3(CH_2)_8CH_2$	**13**	63	94
11	**3**	CH_3	Ph	**14**	81	98.6
12	**3**	CH_3		**15**	50	98.7
13	**3**	CH_3		**16**	76	98.9
14	**3**	CH_3	$CH_3(CH_2)_8CH_2$	**17**	81	96

[a] Yields refer to isolated purified products; [b] Enantiomeric excesses are determined by HPLC, on a Chiracel OD column for the following compounds: **4** and **14-16** (hexane/2-propanol 95/5), **6** and **10-12** (hexane/2-propanol 90/10), **5** (hexane/2-propanol 85:15) and flow 1 mL/min. For all other compounds e.e. are determined by ^{1}H-NMR spectroscopy with the chiral shift reagent $Eu(hfc)_3$.

All reactions proceeded in high yields and the α-acetoxy ketones were obtained with excellent enantiomeric purity. In particular we have employed aliphatic Grignard reagents (entries 4-6,10 and 14) with e.e. in the range 94-99%, and aromatic organomagnesium derivatives (entries 1-3, 7-9 and 11-13, e.e. 98.6-99.6%). Moreover it should be noted that various functional groups are tolerated on the organocopper reagent, including the aldehyde function in protected form (entry 5).

In conclusion, these results offer a general and simple method leading to a wide spectrum of chiral α-acetoxy ketones. This new approach appears to be competitive with/or superior to other methods previously reported.

Experimental

Macherey-Nagel silica gel (60, particle size 0.040-0.063 mm) for flash column chromatography and Macherey-Nagel aluminum sheets with silica gel 60 F_{254} for TLC were used. GC analysis was performed on a Hewlett-Packard 5890 series II gas chromatograph equipped with a SE-30 (methylsilicone, 30 m x 0.25 mm id) capillary column. GC/mass-spectrometry analysis was performed on a Hewlett-Packard 5970A gas chromatograph equipped with an HP-1 capillary column, 25 m, and HP MSD 5970B mass selective detector. ^{1}H-NMR spectra were recorded in deuterochloroform on a Bruker AM 500 spectrometer at 500 MHz and on a Varian XL 200 spectrometer at 200 MHz. IR spectra were recorded on a Perkin Elmer 1710 FT spectrometer. Elemental analyses were recorded on a Carlo Erba EA 1108 elemental analyzer. Enantiomeric excesses were evaluated by ^{1}H-NMR spectroscopy with the chiral shift reagent Europium tris[3-(heptafluoropropylhydroxy methylene)-(+)-camphorate] Eu(hfc)$_3$ or by HPLC chromatography on a Chiralcel OD (Daicel) column. Melting points (uncorrected) were determined on a Reichert Microscope.

Synthesis of α-acetoxy carboxylic acid chlorides **1-3**

(S)-Acetoxy-phenylacetyl chloride (1) [16,20-22]. An excess of acetyl chloride (3.7 mL, 52.60 mmol) was added to 2 g (13.15 mmol) of (S)-mandelic acid. After stirring for 2 h at room temperature, the excess of acetyl chloride was removed under vacuum, the residue was dissolved in CH_2Cl_2 (35 mL) in the presence of 1% of DMF, and a methylene chloride (15 mL) solution of $(COCl)_2$ (1.15 mL, 13.15 mmol) was added. After reaction completion (2h at room temperature), the solvent was removed under vacuum and compound **1** was purified by distillation (Kugelrohr oven temperature 85 °C, $2x10^{-4}$ mbar) in 75% overall yield (2.1 g). $[\alpha]_D^{20}$ = +185.1 (c 2.05, CCl_4) (lit[16] $[\alpha]_D^{20}$ = +159.2 (c 1.93, CCl_4); lit[22] $[\alpha]_D^{27}$ = +186 (c 3.2, $CHCl_3$)).

(S)-2-Acetoxy-3-phenylpropionyl chloride (2) [16,23]. Acetyl chloride (3.8 mL, 54.18 mmol) was added to 1.5 g (9.03 mmol) of (S)-phenyllactic acid. After 2h the excess of acetyl chloride was removed under vacuum, the residue was dissolved in CH_2Cl_2 (30 mL) in the presence of 1% of DMF, and a methylene chloride (10 mL) solution of $(COCl)_2$ (0.8 mL, 9.03 mmol) was added. After stirring for 2h at room temperature, the solvent was removed under vacuum and the chloride **2** was purified by distillation (Kugelrohr oven temperature 100 °C, $2\mathrm{x}10^{-4}$ mbar) in 83% overall yield (1.7 g). $[\alpha]_D^{20} = +7.8$ (c 2.74, CCl_4) (lit[16] $[\alpha]_D^{20} = +8.1$ (c 2.06, CCl_4)).

(S)-2-Acetoxy-propionyl chloride (3) [16,24,25]. Acetic acid (10 mL) was added to 40 mmol of a 85% aqueous solution of (S)-lactic acid (Aldrich). Water was removed by slow azeotropic distillation and an excess of acetyl chloride (80 mmol) was added dropwise to the solution of lactic acid in AcOH. After reaction completion (2 h at r.t.) the (S)-acetoxy-propionic acid was isolated by distillation (98-100 °C, $1\mathrm{x}10^{-2}$ mbar). An excess of thionyl chloride (2 equiv.) was then added to pure acid in the presence of 1% of DMF. After stirring for 2h at room temperature, the chloride **3** was purified by distillation (Kugelrohr oven temperature 90 °C, 20 mbar) in 70% overall yield (4.21 g) $[\alpha]_D^{20} = -28.6$ (c 2.05, CCl_4) (lit[16] $[\alpha]_D^{20} = -29.9$ (c 1.95, CCl_4)).

General procedure for the synthesis of α-acetoxy ketones 4-17.

A THF solution of anhydrous LiBr (2.4 equiv.) was added at room temperature, under nitrogen, to a stirred suspension of CuBr (1.2 equiv.) in THF and the resulting mixture was stirred at the same temperature until it became homogeneous. A freshly prepared THF solution of Grignard reagent (1.2 equiv.) and soon afterwards α-acetoxy carboxylic acid chloride (1 equiv.) in THF were quickly added to the stirred solution of salts. The mixture was stirred for 30 min, quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate. The organic extracts were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography leading to α-acetoxy ketones **4-17**.

The spectral and physical data are as follows.

(S)-1,2-Diphenyl-2-acetoxyethanone (4). Compound **4** was prepared from **1** (0.30 g, 1.41 mmol) in accordance with general procedure. Purification by flash chromatography (silica gel, petroleum ether/ethyl acetate 8/2) afforded 0.319 g of **4** (89% yield, 99.6% e.e. determined by HPLC, hexane/2-propanol 95/5, 1 mL/min). $[\alpha]_D^{20} = +198.5$ (c 1.5, chloroform) (lit[14] $[\alpha]_D^{18} = -214.3$ (c 1, chloroform) for *R* enantiomer).

(S)-1-(*p*-Methoxyphenyl)-2-acetoxy-2-phenylethanone (5). Compound **5** was prepared from **1** (0.30 g, 1.41 mmol) in accordance with general procedure. Purification by flash chromatography (silica gel, petroleum ether/ethyl acetate 8/2) afforded 0.301 g of **5** (75% yield, 99.5% e.e. determined by HPLC, hexane/2-propanol 85/15, 1 mL/min). The residual solid was crystallized from hexane giving white crystals of **5**, m.p. 83-84 °C.

$[\alpha]_D^{20}$ = +156.7 (c 1.5, chloroform). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.18 (s, 3H), 3.80 (s, 3H), 6.82 (s, 1H), 6.83-6.87 (m, 2H), 7.30-7.37 (m, 3H), 7.43-7.47 (m, 2H), 7.89-7.93 (m, 2H) ppm. MS *m/e* 284 (M^+, <1), 135 (100), 107 (11), 92 (9), 77 (17), 43 (23). FTIR: ν_{max}(KBr)/cm^{-1} 1740, 1683, 1600, 1234. *Anal.* Calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 71.55, H, 5.79.

(S)-1-(2-Thienyl)-2-acetoxy-2-phenylethanone (6). Compound **6** was prepared from **1** (0.30 g, 1.41 mmol) in accordance with general procedure. Purification by flash chromatography (silica gel, petroleum ether/ethyl acetate 8/2) afforded 0.308 g of **6** (84% yield, 99.2% e.e. determined by HPLC, hexane/2-propanol 90/10, 1 mL/min). The residual solid was crystallized from hexane giving white crystals of **6**, m.p. 88-89 °C.

$[\alpha]_D^{20}$ = +189.2 (c 2.1, chloroform). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.19 (s, 3H), 6.63 (s, 1H), 7.06 (dd, J = 4.9, 3.9 Hz, 1H) 7.32-7.40 (m, 3H), 7.47-7.51 (m, 2H), 7.61 (dd, J = 4.9, 1.1 Hz, 1H), 7.73 (dd, J = 3.9, 1.1 Hz, 1H) ppm. MS *m/e* 200 (9), 149 (41), 111 (100), 107 (53), 79 (13), 77 (12), 43 (75). FTIR: ν_{max}(KBr)/cm^{-1} 1740, 1670, 1413, 1230. *Anal.* Calcd for $C_{14}H_{12}O_3S$: C, 64.60; H, 4.65, S, 12.32. Found: C, 64.48, H, 4.78, S, 12.37.

(S)-1-Acetoxy-1-phenyl-3-dodecanone (7). Compound **7** was prepared from **1** (0.15 g, 0.705 mmol) in accordance with general procedure. Purification by flash chromatography (silica gel, petroleum ether/ethyl acetate 9/1) afforded 0.204 g of **7** as a colorless oil which solidified in the fridge (91% yield, 99% e.e. determined by ^{1}H-NMR shift reagent experiment).

$[\alpha]_D^{20}$ = +169.6 (c 2.5, chloroform). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.85 (t, J = 7.0 Hz, 3H), 1.09-1.29 (m, 14H), 1.40-1.56 (m, 2H), 2.16 (s, 3H), 2.29 (ddd, J = 17.2, 8.3, 6.6 Hz, 1H), 2.43 (ddd, J = 17.2, 8.4, 6.2 Hz, 1H), 5.94 (s, 1H), 7.36-7.39 (m, 5H) ppm. MS *m/e* 318 (M^+, <1), 169 (25), 149 (50), 107 (66), 95 (8), 91 (7), 85 (11), 79 (11), 71 (12), 57 (26), 55 (11), 43 (100), 41 (21). FTIR: ν_{max}(neat)/cm^{-1} 2926, 1747, 1732, 1234. *Anal.* Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.89, H, 9.65.

(S)-1-Acetoxy-1-phenyl-4-(1,3-dioxan-2-yl)-2-butanone (8). Compound **8** was prepared from **1** (0.15 g, 0.705 mmol) in accordance with general procedure. Purification by flash chromatography (silica gel, petroleum ether/ethyl acetate 7/3) gave 0.140 g of a solid (68%

yield, 99% e.e. determined by ^{1}H-NMR shift reagent experiment). The residual was crystallized from hexane giving white crystals of **8**, m.p. 56-57 °C.

$[\alpha]_D^{20}$ = +145.9 (c 0.7, chloroform). ^{1}H-NMR (200 MHz, CDCl$_3$): δ 1.20-1.32 (m, 1H), 1.76-2.09 (m, 3H), 2.18 (s, 3H), 2.35-2.72 (m, 2H), 3.53-3.74 (m, 2H), 3.90-4.09 (m, 2H), 4.44 (t, *J* = 5.0Hz, 1H), 5.99 (s, 1H), 7.36-7.44 (m, 5H) ppm. MS *m/e* 292 (M$^+$, <1), 291 (1), 143 (100), 107 (18), 87 (8), 85 (81), 79 (7), 77 (8), 57 (8). FTIR: ν_{max}(KBr)/cm^{-1} 1748, 1733, 1235. *Anal.* Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.89, H, 6.85.

(S)-1-Acetoxy-1-Phenyl-5-hexen-2-one (9). Compound **9** was prepared from **1** (0.15 g, 0.705 mmol) in accordance with general procedure. Purification by flash chromatography (silica gel, petroleum ether/ethyl acetate 8/2) gave 0.103 g of **9** as a colorless oil (63% yield, 95% e.e. determined by ^{1}H-NMR shift reagent experiment).

$[\alpha]_D^{20}$ = +204.5 (c 0.97, chloroform). ^{1}H-NMR (200 MHz, CDCl$_3$): δ 2.10-2.70 (m, 7H), 4.86-4.99 (m, 2H), 5.58-5.80 (m, 1H), 5.98 (s, 1H), 7.38-7.44 (m, 5H) ppm. MS *m/e* 232 (M$^+$, 1), 149 (67), 107 (100), 83 (20), 79 (18), 77 (16), 55 (40). FTIR: ν_{max}(neat)/cm^{-1} 1746, 1732, 1233. *Anal.* Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.45, H, 6.85.

(S)-1,3-Diphenyl-2-acetoxy-1-propanone (10). Compound **10** [15] was prepared from **2** (0.30 g, 1.32 mmol) in accordance with general procedure. Purification by flash chromatography (silica gel, petroleum ether/ethyl acetate 8/2) afforded 0.344 g of **10** as a pale yellow and thick oil (97% yield, 99.6% e.e. determined by HPLC, hexane/2-propanol 90/10, 1 mL/min).

$[\alpha]_D^{20}$ = +66.4 (c 5.5, chloroform), +59.0 (c 1.02, acetone); (lit[15] $[\alpha]_D$ = -20.0 (c 0.8, acetone, e.e. = 34% for *R* enantiomer). ^{1}H-NMR (500 MHz, CDCl$_3$): δ 2.08 (s, 3H), 3.08 (dd, *J* = 14.4, 9.1 Hz, 1H), 3.18 (dd, *J* = 14.4, 4.2 Hz, 1H), 6.06 (dd, *J* = 9.1, 4.2 Hz, 1H), 7.15-7.30 (m, 5H), 7.40-7.48 (m, 2H), 7.54-7.60 (m, 1H), 7.90-7.95 (m, 2H) ppm. MS *m/e* 208 (27), 207 (15), 105 (100), 103 (8), 91 (23), 77 (60), 65 (10), 51 (26). FTIR: ν_{max}(neat)/cm^{-1} 1742, 1698, 1235.

(S)-1-(*p*-Methoxyphenyl)-2-acetoxy-3-phenyl-1-propanone (11). Compound **11** was prepared from **2** (0.30 g, 1.32 mmol) in accordance with general procedure. Purification by flash chromatography (silica gel, petroleum ether/ethyl acetate 8/2) afforded 0.315 g of **11** as a thick and pale yellow oil (80% yield, 99.6% e.e. determined by HPLC, hexane/2-propanol 90/10, 1 mL/min).

$[\alpha]_D^{20}$ = +86.1 (c 4.7, chloroform). ^{1}H-NMR (500 MHz, CDCl$_3$): δ 2.06 (s, 3H), 3.08 (dd, *J* = 14.4, 9.1 Hz, 1H), 3.16 (dd, *J* = 14.4, 4.3 Hz, 1H), 3.84 (s, 3H), 6.03 (dd, *J* = 9.1, 4.3 Hz, 1H), 6.89-6.94 (m, 2H), 7.17-7.30 (m, 5H), 7.89-7.95 (m, 2H) ppm. MS *m/e* 238 (13), 135 (100), 107 (8), 92 (14), 91 (13), 77 (22), 65 (6), 64 (8), 63 (6). **FTIR: ν_{max}(neat)/cm^{-1} 1742, 1687,** 1600, 1239. *Anal.* Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: **C, 72.45, H, 6.15.**

(S)-1-(2-Thienyl)-2-acetoxy-3-phenyl-1-propanone (12). Compound **12** was prepared from **2** (0.30 g, 1.32 mmol) in accordance with general procedure. Purification by flash chromatography (silica gel, petroleum ether/ethyl acetate 7/3) afforded 0.333 g of **12** as a thick and pale yellow oil (92% yield, 99.5% e.e. determined by HPLC, hexane/2-propanol 90/10, 1 mL/min).

$[\alpha]_D^{20}$ = +70.3 (c 5.3, chloroform). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.07 (s, 3H), 3.14 (dd, *J* = 14.3, 8.8 Hz, 1H), 3.21 (dd, *J* = 14.3, 4.7 Hz, 1H), 5.82 (dd, *J* = 8.8, 4.7 Hz, 1H), 7.10 (dd, *J* = 4.9, 3.9 Hz, 1H) 7.19-7.30 (m, 5H), 7.66 (dd, *J* = 4.9, 1.1 Hz, 1H), 7.75 (dd, *J* = 3.9, 1.1 Hz, 1H) ppm. MS *m/e* 214 (30), 213 (21), 185 (3), 111(100), 103 (7), 91 (25), 83 (10), 77 (8), 65 (13). FTIR: ν_{max}(neat)/cm^{-1} 1745, 1672, 1415, 1230. *Anal.* Calcd for $C_{15}H_{14}O_3S$: C, 65.67; H, 5.14; S, 11.69. Found: C, 65.80; H, 5.15; S, 11.80.

(S)-1-Phenyl-2-acetoxy-3-tridecanone (13). Compound **13** was prepared from **2** (0.30 g, 1.32 mmol) in accordance with general procedure. Purification by flash chromatography (silica gel, petroleum ether/ethyl acetate 7/3) gave 0.276 g of **13** as a colorless oil (63% yield, 94% e.e. determined by ^{1}H-NMR shift reagent experiment).

$[\alpha]_D^{20}$ = +4.0 (c 4.0, chloroform). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.86 (t, *J* = 7.0 Hz, 3H), 1.15-1.32 (m, 14H), 1.45-1.57 (m, 2H), 2.05 (s, 3H), 2.24 (ddd, *J* = 17.7, 8.0, 6.7 Hz, 1H), 2.39 (ddd, *J* = 17.7, 8.1, 6.6 Hz, 1H), 2.96 (dd, *J* = 14.2, 8.5 Hz, 1H), 3.07 (dd, *J* = 14.2, 4.9 Hz, 1H), 5.19 (dd, *J* = 8.5, 4.9 Hz, 1H), 7.16-7.30 (m, 5H) ppm. MS *m/e* 272 (6), 188 (6), 169 (26), 163 (7), 146 (100), 131 (25), 103 (15), 95 (15), 91 (40), 85 (18), 71 (20), 57 (52), 55 (35). FTIR: ν_{max}(neat)/cm^{-1} 2926, 1747, 1731, 1236. *Anal.* Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.80; H, 9.76.

(S)-1-Phenyl-2-acetoxy-1-propanone (14) [26,27]. Compound **14** was prepared from **3** (0.30 g, 1.99 mmol) in accordance with general procedure. Purification by flash chromatography (silica gel, petroleum ether/ethyl acetate 8.5/1.5) afforded 0.309 g of **14** (81% yield, 98.6% e.e. determined by HPLC, hexane/2-propanol 95/5, 1 mL/min).
$[\alpha]_D^{20}$ = -46.0 (c 2.5, chloroform) (lit[27] $[\alpha]_D^{20}$ = -41.5 (c 1.04, chloroform, e.e. = 88%)).

(S)-1-(*p*-Methoxyphenyl)-2-acetoxy-1-propanone (15). Compound **15** was prepared from **3** (0.30 g, 1.99 mmol) in accordance with general procedure. Purification by flash chromatography (silica gel, petroleum ether/ethyl acetate 8/2) afforded 0.221 g of **15** as a colorless oil (50% yield, 98.7% e.e. determined by HPLC, hexane/2-propanol 95/5, 1 mL/min).

$[\alpha]_D^{20}$ = -24.3 (c 2.2, chloroform). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.48 (d, *J* = 7.0 Hz, 3H), 2.11 (s, 3H), 3.83 (s, 3H), 5.90 (q, *J* = 7.0 Hz, 1H), 6.89-6.93 (m, 2H), 7.87-7.92 (m, 2H) ppm. MS *m/e* 222 (M^+ , 3), 136 (9), 135 (100), 107 (8), 92 (12), 77 (15), 64 (8), 63 (6), 43 (32). FTIR: ν_{max}(neat)/cm^{-1} 1732, 1677, 1601, 1250. *Anal.* Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 65.00; H, 6.48.

(S)-1-(2-Thienyl)-2-acetoxy-1-propanone (16). Compound **16** was prepared from **3** (0.15 g, 0.995 mmol) in accordance with general procedure. Purification by flash chromatography (silica gel, petroleum ether/ethyl acetate 8/2) afforded 0.150 g of **16** as a pale yellow oil (76% yield, 98.9% e.e. determined by HPLC, hexane/2-propanol 95/5, 1 mL/min).

$[\alpha]_D^{20}$ = -44.4 (c 2.6, chloroform). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.53 (d, *J* = 7.0 Hz, 3H), 2.11 (s, 3H), 5.70 (q, *J* = 7.0 Hz, 1H), 7.12 (dd, *J* = 4.9, 3.8 Hz, 1H), 7.66 (dd, *J* = 4.9, 1.1 Hz, 1H), 7.77 (dd, *J* = 3.8, 1.1 Hz, 1H) ppm. MS *m/e* 198 (M^+ , 3), 155 (4), 154 (5), 138 (12), 111 (100), 83 (9), 57 (7), 43 (97), 39 (33). FTIR: ν_{max}(neat)/cm^{-1} 1743, 1671, 1416, 1240. *Anal.* Calcd for $C_9H_{10}O_3S$: C, 54.53; H, 5.08; S, 16.18. Found: C, 54.78; H, 5.15; S, 16.43.

(S)-2-Acetoxy-3-tridecanone (17). Compound **17** was prepared from **3** (0.30 g, 1.99 mmol) in accordance with general procedure. Purification by flash chromatography (silica gel, petroleum ether/ethyl acetate 9/1) afforded 0.413 g of **17** as a colorless oil (81% yield, 96% e.e. determined by ^{1}H-NMR shift reagent experiment).

$[\alpha]_D^{20}$ = -22.9 (c 2.7, chloroform). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.83 (t, *J* = 6.9 Hz, 3H), 1.18-1.30 (m, 14H), 1.35 (d, *J* = 7.1 Hz, 3H), 1.50-1.58 (m, 2H), 2.09 (s, 3H), 2.37 (dt, *J* = 17.3, 7.4 Hz, 1H), 2.47 (dt, *J* = 17.3, 7.4 Hz, 1H), 5.04 (q, *J* = 7.1 Hz, 1H) ppm. MS *m/e* 256 (M^+ , <1), 214 (5), 169 (72), 130 (9), 109 (5), 95 (15), 87 (14), 85 (17), 71 (18), 57 (33), 43 (100). FTIR: ν_{max}(neat)/cm^{-1} 2926, 1747, 1735, 1236. *Anal.* Calcd for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01. Found: C, 70.32; H, 11.11.

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