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An efficient asymmetric aldol reaction of Chan's diene promoted by chiral Ti(IV)–BINOL complex

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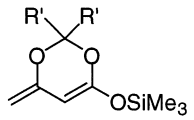
Abstract—1,3-Bis-(trimethylsilyloxy)-1-methoxy-buta-1,3-diene (Chan's diene) can be conveniently used in asymmetric aldol reaction with aromatic, heteroaromatic, α,β-unsaturated and aliphatic aldehydes in the presence of catalytic amounts (2–8% mol) of chiral Ti(IV)/(*R*)-BINOL complex.

1. Introduction

In recent years the development of new procedures for the enantioselective addition of enolsilanes to aldehydes under catalytic conditions has been the main target of several research groups. From a preparative point of view notable results have been obtained by using *O*-silyldienolates of the type **1**, since the formation of polyfunctional C-(5) key intermediates can be achieved in high yield and enantioselectivity.

As regards the mechanistic aspects, the reported procedures may alternatively involve either the activation of the aldehydic functionality by chiral catalysts [Ti(IV)[1–4] and Cu(II)[5,6] complexes] or the formation of a chiral metalloenolate intermediate.[7]



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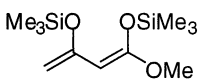

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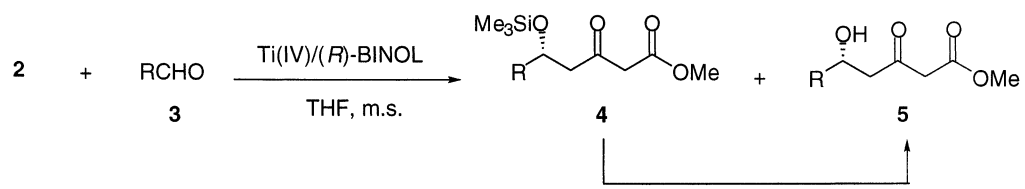
Rather surprisingly, the masked acetoacetic ester **2** (Chan's diene),[8] easily accessible from commercially available methyl 3-trimethylsilyloxy-crotonate,[9] has been used only occasionally in stereoselective aldol condensations, since the presence of a chelating substituent situated α or β to the carbonyl function seemed to be a strict prerequisite for attaining high levels of diastereo- and enantioselectivity.[10]

2. Results and discussion

In the course of an investigation on the reactivity of synthetic equivalents of acetoacetate ester dianion[4,11] we have found that the enantioselective addition of Chan's diene **2** to aldehydes **3** can be performed very conveniently in the presence of catalytic amounts of $Ti(OiPr)_4$/(*R*)-BINOL complex (8 mol%).

As reported in Scheme 1 and Table 1, the reaction proceeded with good efficiency and enantioselectivity leading to silylated aldols **4** as the predominant or exclusive product, while the presence of free aldol **5** could be occasionally detected (entries **b**, **c**, **e**).



Scheme 1.

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Table 1. Chiral Ti(IV)/(*R*)-BINOL-catalyzed asymmetric aldol condensation

Entry	R	Product	Yield (%)[a]	E.e. (%)[b,c]
a	3-Furyl	**5a**	67	99
b	C_6H_5	**5b**	13[d]	99
		5b	65	88
c	*p*-$CH_3OC_6H_4$	**5c**	7[d]	99
		5c	68	91
d[e]	*p*-$NO_2C_6H_4$	**5d**	86	90
e	*n*-C_7H_{15}	**5e**	20[d]	94
		5e	31	92
f	$C_6H_4CH{=}CH$	**5f**	92	99
g[e]		**5g**	66	99

[a] Yields refer to isolated, chromatographically pure compounds **5** (obtained after desilylation of product **4**) and are calculated based on starting materials **3**.
[b] E.e.s were determined by HPLC analysis of the aldol adduct using a Chiralpak AD column.
[c] The absolute configuration of the adducts was established by ^1H NMR analysis (400 MHz) of the corresponding MTPA esters according to Ref. 12.
[d] Yields refer to free aldol directly obtained by purification of crude **4**.
[e] (*S*)-(−)-BINOL was used as chiral auxiliary, consequently **5d** and **5g** were obtained as predominant (*S*)-enantiomers.

In every case compounds **4** have been subjected to deprotection by treatment with CF_3COOH (15 equivalents) in aqueous THF solution at 0°C[2] to give the aldols **5** in satisfactory yields and e.e.s.

However, free aldols **5b** and **5c**, obtained directly in very poor yields by chromatographic purification of crude reaction mixtures, showed significantly higher e.e.s than those observed for the corresponding aldols obtained after cleavage of the trimethylsilyl group of **4**. This suggested the possibility of racemization in the course of the silyl deprotection reaction.

In order to verify this hypothesis, compounds **4b** and **4c** were subjected to treatment with other desilylating agents and the results reported in Table 2 clearly showed that both the resulting chemical yields and the e.e.s could be affected by the type of substrate and the desilylation procedure employed.

Table 2. Deprotection of silylated aldols **4** by procedures A, B and C[a]

Compound	Proc. A[b] Yield (e.e.) %	Proc. B[c] Yield (e.e.) %	Proc. C[d] Yield (e.e.) %	Free aldol E.e. (%)
4b	65 (88)	78 (88.4)	55 (86)	99
4c	69 (91)	75 (99)	78 (99)	99

[a] Yields refer to isolated, chromatographically pure compounds and are calculated based on starting materials **3**. E.e.s were determined by HPLC analysis.
[b] Procedure A: CF_3COOH/H_2O/0°C.[2]
[c] Procedure B: TBAF/THF/0°C.[13]
[d] Procedure C: PPTS/MeOH/rt.[14]

Table 3. Chiral Ti(IV)/(*R*)-BINOL (2 mol%)-catalyzed aldol condensation of Chan's diene

Entry	R	Product	Yield (%)[a]	E.e. (%)[b]
a	3-Furyl	**5a**	82	99
b	C_6H_5	**5b**	94	92
c	$C_6H_4CH{=}CH$	**5f**	84	99
d	*n*-C_9H_{19}	**5h**	70	98

[a] All the yields refer to isolated, chromatographically pure compounds and are calculated based on starting materials **3**.
[b] E.e.s were determined by HPLC analysis.

However, it is noteworthy that greatly improved results were obtained with Carreira's procedure[7] involving in situ desilylation of the crude **4b** and **5b** mixture by acidic treatment at −78°C. Using this deprotection protocol, it was found that aldol **5b** could be obtained in 94% yield and >99% e.e.

Further research, directed at optimizing the level of catalyst loading, showed that in the presence of reduced amounts of catalytic species (2 mol%) the condensation reaction gave **4** as the exclusive product; moreover, deprotection, performed in situ by acidic treatment at −78°C, afforded aldols **5** in very good yields and excellent e.e.s. (Table 3).

The result reported in entry **d** (Table 3) is of particular synthetic value since addition of masked acetoacetic esters to aliphatic aldehydes using the reported procedures is known to proceed with low efficiency and/or enantioselectivity.[7]

Finally, a set of experiments, designed to allow a more careful investigation of the reaction pathway, was completed. Benzaldehyde **3b** was again chosen as the representative substrate. Using the optimized conditions, after desilylation, **5b** was isolated in 94% yield and 92% e.e. (Table 4, entry **a**). However, when the reaction was analyzed after stirring for 2 hours at −78°C no formation of **5b** could be detected (entry **b**). Moreover, **5b** was obtained in poor yield (3%) and an e.e. of 48% (entry **d**) when carrying out the reaction in the presence of 8 mol% Ti(IV)/(*R*)-BINOL complex over 2 hours at −78°C, while very high yield of 94% and an e.e of >99%

Table 4. Influence of temperature on asymmetric aldol condensation

Entry	Catalyst	React. time/temp.	Yield (%)[a]	E.e. (%)[b]
a	**2**	2 h/−78°C+ 16 h/rt	94	92
b	**2**	2 h/−78°C	–	–
c	**8**	2 h/−78°C+ 16 h/rt	94	>99
d	**8**	2 h/−78°C	3	48
e	**8**	6 h/rt	96	98

[a] All the yields refer to isolated, chromatographically pure compounds and are calculated based on starting materials **3**.
[b] Determined by HPLC analysis.

was observed by initially completing the reaction at −78°C for 2 hours then allowing the mixture to warm to room temperature and stirring the mixture for 16 hours (entry **c**).

The results from this study, reported in Table 4, clearly showed that the aldol condensation essentially occurred at room temperature and that the process of amplification[15,16] of the e.e. was involved.

The procedure we have presented can be considered of enhanced synthetic value as it is highly efficient and occurs with excellent enantioselectivity. Additionally, all reactions, including the preparation of the catalytic species, can be conveniently performed at room temperature with comparable efficiency and virtually no change in the enantioselectivity (Table 4, entry **e**).

3. Experimental

3.1. General procedures

All reactions involving air-sensitive materials were performed using oven dried glassware under an atmosphere of dry nitrogen. THF was distilled from $LiAlH_4$ and then from sodium and benzophenone. Molecular sieves (4 Å) were oven dried at 250°C overnight and stored under an atmosphere of nitrogen. Thin-layer chromatography was performed on Merck Kiesegel 60 F254 plates eluting with the solvents indicated, visualized by a 254 nm UV lamp or aqueous ceric sulfate solution followed by heating. Infrared spectra were recorded on a Bruker 22 series FT-IR spectrometer. NMR spectra were recorded on a Bruker DRX 400 (400.135 MHz for ^1H and 100.03 MHz for ^{13}C) and on a Bruker AM 250 (250.13 MHz for ^1H and 62.89 MHz for ^{13}C) spectrometers. Chemical shifts are given in ppm (δ) scale; for the spectra in $CDCl_3$, the $CHCl_3$ signal was used as internal standard (δ 7.26 ^1H, δ 77.0 ^{13}C). Coupling constants (J) are reported in Hz. MS (EI): VG TRIO 2000. Column chromatographic separations were carried out using silica gel 60 (70–230 mesh and 230–400 mesh, Merck). Optical rotations were measured at the sodium D line (589 nm) at room temperature with a JASCO DIP 1000 polarimeter; concentrations are reported in g/100 mL. HPLC analysis was performed on a Waters 486 equipped with a variable wavelength detector using a Chiralpak AD column.

3.2. Representative procedure for the preparation of aldol adducts 5 using 8 mol% of catalyst

In a typical experiment, a mixture of Ti(O-*i*-Pr)$_4$ (0.08 mmol) and (*R*)-(+)-BINOL (0.08 mmol) in THF (5 mL) and molecular sieves (340 mg) was stirred at rt for 1 h. After cooling the mixture to −78°C the aldehyde (1 mmol) was added dropwise followed, after 30 min, by silyloxydiene **2** (2 mmol). The resulting solution was stirred under an inert gas atmosphere at −78°C for 2 h; after warming at rt the mixture was stirred overnight. The progress of the reaction was monitored by TLC. Upon completion, a saturated aqueous solution of $NaHCO_3$ (2 mL) was added until the evolution of gas ceased (30 min); the reaction mixture was diluted with ether and the organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo affording a yellow oil. The residue was dissolved in THF, cooled to 0°C and treated with TFA (15 equiv.) in water (0.12 mL). After desilylation had proceeded to completion, the solution was warmed to rt and partitioned between Et_2O and water. The organic layer was washed with a saturated aqueous solution of $NaHCO_3$ and then dried over $MgSO_4$ and concentrated in vacuo. Purification by chromatography on silica gel afforded the aldol adducts **5** (eluent 9:1 $CHCl_3$:Et_2O).

3.3. Representative procedure for the preparation of aldol adducts 5 using 2 mol% of catalyst

In a typical experiment, a mixture of Ti(O-*i*-Pr)$_4$ (0.02 mmol) and *R*(+)-BINOL (0.02 mmol) and molecular sieves (77.5 mg) in THF (1 mL) was stirred at rt for 1 h. After cooling the mixture to −78°C the aldehyde (1 mmol) was added dropwise followed, after 30 min, by silyloxydiene **2** (2 mmol). The resulting solution was stirred under an inert gas atmosphere at −78°C for 2 h; after warming at rt the mixture was stirred overnight. The progress of the reaction was monitored by TLC. Upon completion, after cooling the mixture to −78°C, TFA (0.4 mL) was added and the solution was warmed to rt. After stirring at rt for 1 h, desilylation was complete and the reaction mixture was diluted with ether and a saturated aqueous $NaHCO_3$ solution (2 mL) was added dropwise and the mixture stirred until the evolution of gas ceased (30 min); the organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo affording a yellow oil. Purification by chromatography on silica gel using 9:1 $CHCl_3$:Et_2O as eluent afforded the aldol adducts **5**.

3.4. General procedure for desilylation using TBAF[12] (procedure B)

The silylated adduct **4** (1 mmol) was dissolved in anhydrous THF (7.5 mL) and the resulting solution was cooled to 0°C. A solution of TBAF in THF (1 M, 2 mmol) was added and the mixture was stirred until the deprotection was complete (15–30 min) by TLC.

The reaction mixture was diluted with ether and a saturated aqueous solution of $NaHCO_3$ (1.5 mL) was added dropwise until the evolution of gas ceased (30 min); the organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo affording, after purification by chromatography, the aldol adduct **5**.

3.5. General procedure for desilylation using PPTS[13] (procedure C)

The silylated adduct **4** (1 mmol) was dissolved in anhydrous MeOH (3 mL) and treated with pyridinium *p*-toluenesulfonate (15 mg).When hydrolysis was complete (1–3 h) by TLC, the volatiles were removed in vacuo and the yellow oil obtained was purified by chromatography affording the aldol adduct **5**.

3.6. 5-(*R*)-(Furan-3-yl)-5-hydroxy-3-oxo-pentanoic acid methyl ester 5a

Pale yellow oil. [Found: C, 56.48; H, 5.61. $C_{10}H_{12}O_5$ requires: C, 56.60; H, 5.70%]; R_f 0.3 (Et_2O:$CHCl_3$ 1:9); ν_{max} (liquid film) 3480, 1740, 1713 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.34 (s, 1H), 7.32 (d, *J* 1.5 Hz, 1H), 6.33 (s, 1H), 5.09 (dd, *J* 8.7, 3.6 Hz, 1H), 3.66 (s, 3H), 3.46 (s, 2H), 2.96 (dd, *J* 17.2, 8.7 Hz, 1H), 2.85 (dd, *J* 17.2, 3.6 Hz, 1H); δ_C (100.03 MHz, $CDCl_3$) 202.5, 167.2, 143.4, 139.0, 127.2, 108.3, 62.8, 52.5, 50.2, 49.5; *m*/*z* (EIMS) 212 (M^+); $[\alpha]_D^{25}=+39.1$ (*c* 1.0, $CHCl_3$), e.e. 99% (*R*); HPLC analysis (hexanes:ethanol:trifluoroacetic acid 95:5:0.01), 1 mL/min; (*R*) enantiomer $t_r=47.05$ min; (*S*) enantiomer $t_r=58.57$ min.

3.7. 5-(*R*)-Phenyl-5-(trimethyl-silyloxy)-3-oxo-pentanoic acid methyl ester 4b

Pale yellow oil. [Found: C, 61.09; H, 7.59. $C_{15}H_{22}O_4Si$ requires: C, 61.19; H, 7.53%]; R_f 0.8 (Et_2O:$CHCl_3$ 1:9); ν_{max} (liquid film) 3508, 2984, 2936, 1740, 1646, 1314, 1106 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.89 (d, *J* 8.4 Hz, 2H), 7.64 (m, 1H), 7.55 (m, 2H),5.16 (dd, *J* 9.0, 3.6 Hz, 1H), 3.72 (s, 3H), 3.48 (s, 2H), 3.01 (dd, *J* 15.1, 9.2 Hz, 1H), 2.67 (dd, *J* 15.2, 3.8 Hz, 1H), 0.02 (s, 9H); *m*/*z* (EIMS) 294 (M^+).

3.8. 5-(*R*)-Phenyl-5-hydroxy-3-oxo-pentanoic acid methyl ester 5b

Pale yellow oil. [Found: C, 64.92; H, 6.28. $C_{12}H_{14}O_4$ requires: C, 64.85; H, 6.35%]; R_f 0.4 (Et_2O:$CHCl_3$ 1:9); ν_{max} (liquid film) 3508, 2984, 2936, 1740, 1646, 1314, 1106 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.36 (m, 5H), 5.20 (dd, *J* 9.1, 3.1 Hz, 1H), 3.51 (s, 3H), 3.46 (s, 2H), 3.01 (dd, *J* 17.4, 9.1 Hz, 1H), 2.91 (dd, *J* 17.4, 3.2 Hz, 1H); δ_C (100.03 MHz, $CDCl_3$) 208.2, 169.0, 139.4, 128.3, 125.7, 68.4, 50.2, 50.1, 44.4; *m*/*z* (EIMS) 222 (M^+); $[\alpha]_D^{25}=+57.1$ (*c* 1.0, $CHCl_3$), e.e. 99% (*R*); HPLC (hexanes:ethanol:trifluoroacetic acid 95:5:0.01), 1 mL/min; (*R*) enantiomer $t_r=25.7$ min; (*S*) enantiomer $t_r=37.7$ min.

3.9. 5-(*R*)-*p*-Methoxyphenyl-3-oxo-5-(trimethyl-silyl-oxy)-pentanoic acid methyl ester 4c

Pale yellow oil. [Found: C, 59.15; H, 7.54. $C_{16}H_{24}O_5Si$ requires: C, 59.23; H, 7.46%]; R_f 0.8 (Et_2O:$CHCl_3$ 1:9); ν_{max} (liquid film) 3500, 2988, 2940, 1740, 1616, 1514, 1378, 1106 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.25 (d, $J=8.5$ Hz, 2H), 6.84 (d, *J* 8.5 Hz, 2H), 5.10 (dd, *J* 8.9, 3.9 Hz, 1H), 3.79 (s, 3H), 3.72 (s, 3H), 3.50 (s, 2H), 3.00 (dd, *J* 15.0, 8.9 Hz, 1H), 2.65 (dd, *J* 15.0, 3.9 Hz, 1H), 0.03 (s, 9H); *m*/*z* (EIMS) 324 (M^+).

3.10. 5-(*R*)-*p*-Methoxyphenyl-5-hydroxy-3-oxo-pentanoic acid methyl ester 5c

Pale yellow oil. [Found: C, 61.96; H, 6.32. $C_{13}H_{16}O_5$ requires: C, 61.90; H, 6.39%]; R_f 0.3 (Et_2O:$CHCl_3$ 1:9); ν_{max} (liquid film) 3500, 2988, 2940, 1740, 1616, 1514, 1378, 1106 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.26 (m, *J* 8.3 Hz, 2H), 6.86 (d, *J* 8.3 Hz, 2H), 5.12 (dd, *J* 9.1, 3.2 Hz, 1H), 3.79 (s, 3H), 3.72 (s, 3H), 3.50 (s, 2H), 2.98 (dd, *J* 17.0, 9.2 Hz, 1H), 2.86 (dd, *J* 17.0, 3.2 Hz, 1H); δ_C (62.89 MHz, $CDCl_3$) 208.2, 169.0, 159.2, 131.7, 129.3, 113.9, 68.4, 50.2, 50.1, 44.4; *m*/*z* (EIMS) 252 (M^+); $[\alpha]_D^{25}=+48.0$ (*c* 1.0, $CHCl_3$), e.e. 91% (*R*); HPLC analysis (hexanes:ethanol:trifluoroacetic acid 95:5:0.01), 1 mL/min; (*R*) enantiomer $t_r=42.5$ min; (*S*) enantiomer $t_r=57.7$ min.

3.11. 5-(*S*)-*p*-Nitrophenyl-5-hydroxy-3-oxo-pentanoic acid methyl ester 5d

Pale yellow oil. [Found: C, 53.83; H, 4.96; N, 5.30. $C_{12}H_{13}NO_6$ requires: C, 53.93; H, 4.90; N, 5.24%]; R_f 0.2 (Et_2O:$CHCl_3$ 1:9); ν_{max} (liquid film) 3510, 2987, 2950, 1740, 1646, 1314, 1106 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.12 (d, *J* 8.6 Hz, 2H), 7.50 (d, *J* 8.6 Hz, 2H), 5.26 (dd, *J* 7.3, 4.3 Hz, 1H), 3.69 (s, 3H), 3.50 (s, 2H), 2.93 (m, 2H); δ_C (62.89 MHz, $CDCl_3$) 208.2, 169.0, 145.5, 145.6, 129.2, 123.4, 68.4, 50.1, 44.4; *m*/*z* (EIMS) 267 (M^+); $[\alpha]_D^{25}=-39.1$ (*c* 1.0, $CHCl_3$), e.e. 90% (*S*); HPLC analysis (hexanes:isopropanol:trifluoroacetic acid 60:40:0.01), 0.3 mL/min; (*R*) enantiomer $t_r=23.7$ min; (*S*) enantiomer $t_r=24.6$ min.

3.12. 5-(*S*)-5-Hydroxy-3-oxo-dodecanoic acid methyl ester 5e

Pale yellow oil. [Found: C, 63.84; H, 9.84. $C_{13}H_{24}O_4$ requires: C, 63.91; H, 9.90%]; R_f 0.5 (Et_2O:$CHCl_3$ 1:9); ν_{max} (liquid film) 1740, 1616, 1514, 1378, 1106 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.05 (s, 1H), 3.73 (s, 3H), 3.48 (s, 2H), 2.75–2.60 (m, 2H), 1.53–1.26 (m, 12H), 0.88 (t, 2H, *J* 6.1 Hz). δ_C (100.03 MHz, $CDCl_3$) 208.2, 169.0, 65.2, 50.1, 44.4, 37.4,32.5, 30.6, 30.3, 30.0, 23.8, 23.1, 14.0; *m*/*z* (EIMS) 244 (M^+); $[\alpha]_D^{25}=+25.2$ (*c* 1.0, $CHCl_3$), e.e. 94% (*S*); HPLC analysis (hexanes:ethanol:trifluoroacetic acid 95:5:0.01), 1 mL/min; (*S*) enantiomer t_r 10.3 min; (*R*) enantiomer $t_r=11.9$ min.

3.13. 5-(*R*)-5-Hydroxy-3-oxo-7-phenyl-hept-6-enoic acid methyl ester 5f

Pale yellow oil. [Found: C, 67.72; H, 6.56. $C_{14}H_{16}O_4$ requires: C, 67.63; H, 6.50%]; R_f 0.4 (Et_2O:$CHCl_3$ 1:9); ν_{max} (liquid film) 3478, 3026, 2953, 1712, 1651, 1494 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.18 (m, 5H), 6.6–6.61 (dd, *J* 15.9, 1.1 Hz, 1H), 6.24–6.15 (dd, *J* 15.9, 6.1 Hz, 1H), 4.80 (m, 1H), 3.74 (s, 3H), 3.52 (s, 2H), 2.86 (d, *J* 6.1 Hz, 2H); δ_C (100.03 MHz, $CDCl_3$) 202.7, 169.0, 136.5, 130.7, 130.2, 128.8, 128.0, 126.7, 68.5, 52.6, 49.8, 43.2; *m*/*z* (EIMS) 248 (M^+); $[\alpha]_D^{25}=+20.2$ (*c* 1.0, $CHCl_3$), e.e. 99% (*R*); HPLC analysis (hexanes:ethanol:trifluoroacetic acid 95:5:0.01), 1 mL/min; (*R*) enantiomer $t_r=28.2$ min; (*S*) enantiomer $t_r=36.1$ min.

3.14. 5-(*S*)-5-Hydroxy-3-oxo-7-phenyl-hept-6-enoic acid methyl ester 5g

See above; $[\alpha]_D^{25}=-18.5$ (*c* 1.0, $CHCl_3$), e.e. 99% (*S*).

3.15. 5-(*S*)-5-Hydroxy-3-oxo-tetradecanoic acid methyl ester 5h

Pale yellow oil. [Found: C, 66.25; H, 10.44. $C_{15}H_{28}O_4$ requires: C, 66.14; H, 10.36%]; R_f 0.5 (Et_2O:$CHCl_3$ 1:9); ν_{max} (liquid film) 1740, 1616, 1514, 1378, 1106 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.06 (s, 1H), 3.77 (s, 3H), 3.46 (s, 2H), 2.75–2.64 (m, 2H), 1.51–1.25 (m, 16H), 0.87 (t, 2H, $J=6.2$ Hz). δ_C (100.03 MHz, $CDCl_3$) 208.2, 169.0, 65.2, 50.1, 44.4, 37.4, 32.5, 30.6, 30.3, 30.0, 23.8, 23.1, 14.0; m/z (EIMS) 272 (M^+); $[\alpha]_D^{25}=+26.2$ (c 1.0, $CHCl_3$), e.e. 98% (*S*); HPLC analysis (hexanes:ethanol:trifluoroacetic acid 95:5:0.01), 1 mL/min; (*S*) enantiomer $t_r=9.7$ min; (*R*) enantiomer $t_r=11.1$ min.

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