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A pinene-based chiral auxiliary for α-alkylation and aldol reactions: an unexpected effect of the base on the stereoselectivity

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Abstract

While the use of LDA as the base in the kinetic deprotonation step of the pinene-based ester **3** led to moderate diastereoselectivities in α-alkylation and aldol reactions, the use of LICA and LTMP resulted in a reduction in the *anti*/*syn* ratios and π-facial selectivities. © 2000 Elsevier Science Ltd. All rights reserved.

1. Introduction

Stereoselective aldol addition reactions have been the subject of extensive investigations over the last few decades because of their wide applicability to the syntheses of complex molecules. Although the enantioselective approaches have been shown to be attractive,[1] the use of chiral auxiliaries attached to the enolate moiety remains the most common and predictable method for effecting asymmetric aldol reactions. However, while the preparation of *syn*-aldols can be readily achieved,[2] approaches for the direct elaboration of *anti*-aldols from carboxylic esters have met with limited success[3] and efforts are currently in progress to explore the synthetic methods for this counterpart employing covalently bound chiral auxiliaries derived from available chiral pool compounds.

In kinetic aldol reactions from carboxylic esters attached to chiral auxiliaries, the similar bases LDA and LICA have enjoyed widespread acceptance and are equally used in the stereoselective generation of both *E*-lithium enolates[4] and *anti*-aldol adducts.[3a–k] Improvements in the *anti*/*syn* ratios in aldol reactions are achieved by employing either silyl ketene acetals instead of lithium enolates[3e–k] or the more sterically hindered amide LTMP in the deprotonation step.[4]

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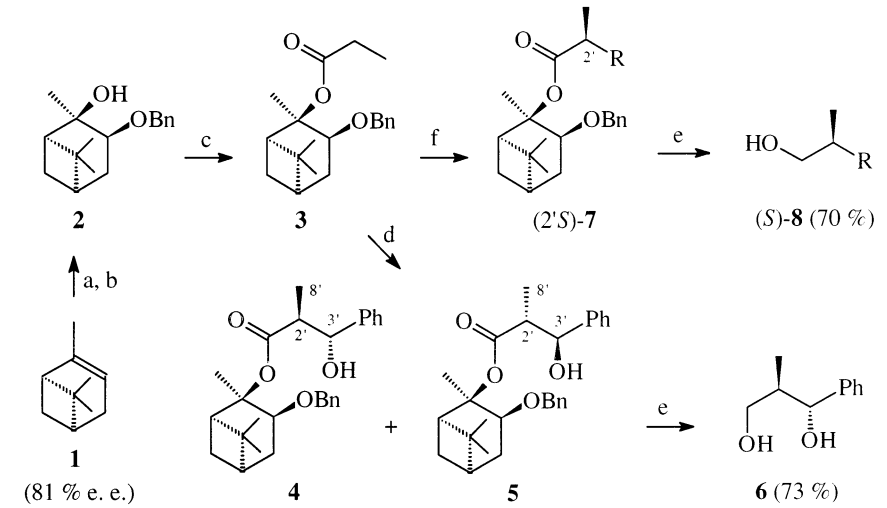
The application of chiral auxiliaries and reagents derived from α-pinene in asymmetric synthesis is well known.[5] However, this natural and readily available starting material has been scarcely employed to build chiral auxiliaries for aldol reactions.[6] Previously, we described (−)-pinanediol as a chiral auxiliary in asymmetric α-alkylations of ester enolates in satisfactory selectivity but in low yields.[7] Herein we report its benzyl derivative at position 3 as a chiral auxiliary in kinetic α-alkylations and aldol reactions, as well as the deleterious effect on the stereoselectivities of these reactions by the use of LICA and LTMP as bases instead of LDA in the kinetic deprotonation step.

2. Results and discussion

The hydroxylation of (−)-α-pinene **1** in the presence of catalytic OsO_4[8] was followed by reaction with benzyl chloride to afford the chiral auxiliary **2** in a multigram scale procedure (Scheme 1). The subsequent esterification using propionyl chloride in the presence of AgCN[9] provided the propionate **3**.



Scheme 1. (a) See Ref. 8; (b) NaH, DMSO then benzyl chloride, rt, 90 min, 92%; (c) EtCOCl, AgCN, benzene, reflux, 90 min, 78%; (d) see Table 1; (e) $LiAlH_4$, THF, rt, 2 h; (f) see Table 2

Kinetic aldol reactions of ester **3** with benzaldehyde were carried out following typical procedures already described in the literature (Table 1). The aldolization of **3** using LDA in THF at −78°C[10] produced compound **4** as the main isomer in a characteristic *anti*/*syn* ratio and satisfactory π-facial diastereoselectivity (entry 1). As expected,[11] the enolization performed in the presence of HMPA was less selective (entry 2). Surprisingly the use of LICA[3d] and LTMP[4] as bases instead of LDA (entries 3 and 4) led to somewhat smaller *anti*/*syn* and **4**/**5** ratios. Interestingly the reaction conducted by means of the corresponding silyl ketene acetal (entry 5)[3e–k] did not lead to an increased *anti*/*syn* ratio in comparison with the enolization in LDA. Attempts at increasing the π-facial diastereoselectivities in the presence of LiBr (entry 6)[12] or Et_3N (entry 7)[13] as additives were not successful and this latter protocol showed a deleterious effect on the *anti*/*syn* ratio.

Table 1
Stereoselectivities in aldol reactions of propionate **3** with benzaldehyde

Entry	Aldol	%[a]	*Anti*/*syn*[b]	**4**/**5**[b]
1	LDA, THF, −78°C then PhCHO	80	80/20	87/13
2	LDA, THF, –23% HMPA, −78°C then PhCHO	74	60/40	69/31
3	LICA, THF, −78°C then PhCHO	80	74/26	75/25
4	LTMP, THF, −78°C then PhCHO	78	70/30	80/20
5	LDA, THF, −78°C then TBDMSCl, HMPA and PhCHO, $TiCl_4$	70	80/20	70/30
6	LDA, THF, −78°C then LiBr and PhCHO	90	80/20	29/71
7	LDA, THF, −78°C then Et_3N and PhCHO	81	64/36	77/23

[a] For the mixture of *anti*- and *syn*-aldols.
[b] Ratios by ^1H NMR (300 MHz) from the signals of H8′.

Both the *anti*/*syn* and **4**/**5** ratios were determined from the signals due to the H8′ hydrogens in the ^1H NMR spectra at 300 MHz of this crude mixture. A *syn*-aldol minor isomer, whose stereochemistry was not determined, was separated from the mixture of *anti*-aldols **4** and **5** by flash chromatography on silica gel, allowing the signals of each isomer to be assigned in the NMR spectra. The absolute configurations of the newly created asymmetric centers in the main isomer **4** were determined by reduction of the mixture obtained from entry 1 with $LiAlH_4$ to the known[14] diol **6**, which was also produced in an *anti*/*syn* = 80/20 ratio.[15] The chiral auxiliary **2** was quantitatively recovered unchanged during the purification of **6** by flash chromatography on silica gel (50% EtOAc in hexane as eluant).

Due to the drop in the stereoselectivity using LICA, we decided to investigate the reactions of **3** with allyl and benzyl bromides (Table 2). The α-alkylations of **3** using LDA in THF at −78°C[9] leading to compounds (2′*S*)-**7a**,**b** (entries 1 and 2) occurred with lower π-facial selectivities than in the aldolization of **3** with this base (see entry 1 in Table 1). Similar to the aldol reaction, the use of LICA as base[16] in the deprotonation step led to a significant drop in the d.e. (entries 3 and 4) and the stereoselectivity of the reaction conducted in the presence of HMPA was almost

Table 2
Stereoselectivities in α-alkylation reactions of propionate **3** in THF at −78°C

Entry	Base	R–Br	**7**	%[a]	% d.e.[b]
1	LDA	$H_2C{=}CHCH_2Br$	**a**	52	60
2	LDA	$PhCH_2Br$	**b**	57	41
3	LICA	$H_2C{=}CHCH_2Br$	**a**	50	53
4	LICA	$PhCH_2Br$	**b**	55	21
5	LDA[c]	$H_2C{=}CHCH_2Br$	**a**	54	08
6	LDA[d]	$H_2C{=}CHCH_2Br$	**a**	NR[f]	–
7	LDA[e]	$H_2C{=}CHCH_2Br$	**a**	NR[f]	–

[a] For the mixture of (2′*S*)-**7** and (2′*R*)-**7**.
[b] Determined by quantitative ^{13}C NMR from the signals of the carbonyl.
[c] THF–23% HMPA was used as the solvent.
[d] In the presence of LiBr as the additive.[12]
[e] Et_3N was used as the additive.[13]
[f] No reaction occurred even with an excess of the additives.

nonexistent (entry 5). Interestingly, in the presence of LiBr[12] and Et_3N[13] (entries 6 and 7) no reaction occurred and ester **3** was unchanged and recovered completely.

Since all the signals in the crude ^{1}H NMR spectra of the mixtures of (2′*S*)-**7a**,**b** and their opposite isomers (2′*R*)-**7a**,**b** are too close together, the diastereoselectivities were determined from the relative intensities of the signals of the carbonyl groups in quantitative ^{13}C NMR spectra of the mixture of these isomers using the 'gated decoupled' procedure. The reductions[9] of the major isomers (2′*S*)-**7a**,**b** obtained from entries 1 and 4 gave the unchanged chiral auxiliary **1** quantitatively along with the known (*S*)-alcohols (*S*)-**8a**,**b**.[17,18]

Although the enolate geometries in the kinetic deprotonation of propionate **3** with LDA, LICA and LTMP were not determined, the formation of the main isomers **4** and (2′*S*)-**7** from enolization of **3** using LDA in THF can be explained by the widely accepted[3a–d] initial formation of the *E*-enolate intermediate, with the aldolization step occurring by a Zimmerman–Traxler transition state.

The unexpected striking drop in the *anti*/*syn* ratios and the π-facial stereoselectivities in the α-alkylation and aldol reactions from ester **3** when using LICA and LTMP instead of LDA is, to the best of our knowledge, without precedent. However, the results obtained in this first report on the use of alcohol **2** as a chiral auxiliary in these reactions show that the chiral moiety of pinenes is promising and can be further exploited in the chemistry of enolates.

3. Experimental

3.1. General

The (−)-α-pinene (81% e.e.) was purchased from Aldrich Chemical Co. Melting points were determined with a Thomas–Hoover apparatus and are uncorrected. Optical rotations were recorded with a Perkin–Elmer 24B polarimeter. Flash chromatography was performed on silica gel 230–400 mesh (Merck). Infrared spectra were recorded with a Perkin–Elmer 1420 spectrophotometer. High-resolution electron-impact mass spectra (HREIMS) and low-resolution electron-impact mass spectra (LREIMS) were measured on a V.G. Auto Spec. Q spectrometer. NMR spectra were recorded with a Varian VXR (300 MHz) for solutions in $CDCl_3$. Elemental analyses were determined with a Carlo Erba 1104 apparatus.

3.2. (*1*R,*2*R,*3*S,*5*R)-*3*-O-*Benzylpinanediol* **2**

DMSO (31.2 mL) was added dropwise to 50% sodium hydride in mineral oil (3.384 g) washed previously with hexane (3×20 mL) and the mixture was stirred under a nitrogen atmosphere for 30 min. A solution of (−)-pinanediol (8.0 g, 47 mmol)[8] in DMSO (20 mL) was added dropwise and the mixture was stirred at room temperature for 10 h. Benzyl chloride (8.88 g, 69.42 mmol) was added to this solution over a period of 30 min and the resulting mixture was stirred for an additional hour, diluted with cold water (20 mL) and partitioned with hexane (3×40 mL). The combined organic layers were washed with brine (3×40 mL) and dried over Na_2SO_4. Solvent removal in vacuo was followed by flash chromatography on silica gel using 5% EtOAc in hexane as eluant to give **2** as a colorless oil (11.24 g, 92% yield). $[\alpha]_D^{25}$ +33.4 (*c* 5.26; CH_2Cl_2). IR (neat, cm^{-1}): 3610–3320; 3074; 2982; 2860; 1705; 1691; 1521; 1484; 1462; 1365; 1289; 1048; 1032; 754; 712. ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): 7.38–7.29 (m, H13–H15); 4.70 (d, 11.7 Hz, H11); 4.61

(d, 11.7 Hz, H11); 3.75 (dd, 9.0 Hz, 5.1 Hz, H3); 2.45–2.34 (m, H4); 2.27–2.14 (m, H7); 1.97 (t, 5.7 Hz, H1); 1.95–1.89 (m, H5); 1.78 (ddd, 13.6 Hz, 5.0 Hz, 2.4 Hz, H4); 1.45 (d, 10.5 Hz, H7); 1.27 (s, CH_3); 1.26 (s, CH_3); 0.89 (s, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): 137.8 (s, C12); 128.3, 127.7 and 127.6 (d, C13–C15); 76.1 (d, C3); 73.2 (s, C2); 72.0 (t, C11); 53.7 (d, C1); 40.2 (d, C5); 38.2 (s, C6); 35.1 (t, C4); 30.6 (q, CH_3); 28.1 (t, C7); 27.7 (q, CH_3); 24.2 (q, CH_3). LREIMS (70 eV, *m/z*): 151 (34); 126 (57); 111 (39); 99 (46); 91 (100); 83 (34); 71 (82). Calcd for $C_{17}H_{24}O_2$: 78.42% C, 9.3% H. Found: 78.38% C, 9.28% H.

3.3. (*1*R,*2*R,*3*S,*5*R)-*3*-O-*Benzylpinanediol propionate* **3**

A solution of the alcohol **2** (2.24 g, 8.62 mmol) in dry benzene (14 mL) was added dropwise to freshly prepared[9] AgCN (2.68 g, 20 mmol) under a nitrogen atmosphere. Propionyl chloride (1.48 mL, 16.92 mmol) was added dropwise and the resulting solution was refluxed for 90 min and allowed to reach room temperature. The mixture was filtered through silica gel and 10% aqueous $NaHCO_3$ (80 mL) was added to the filtrate. This solution was partitioned with ethyl acetate (3×100 mL) and dried over anhydrous Na_2SO_4. Solvent removal in vacuo was followed by flash chromatography on silica gel using 5% EtOAc in hexane as eluant to give **3** as a pale yellow oil (2.12 g, 78% yield). $[\alpha]_D^{25}$ +8.0 (*c* 3.26; CH_2Cl_2). IR (neat, cm^{-1}): 3058; 3023; 2947; 2871; 1746; 1451; 1355; 1193; 1138; 1076; 736; 697. ^1H NMR ($CDCl_3$, 300 MHz, ppm): 7.29–7.19 (m, H13–H15); 4.66 (d, 11.7 Hz, H11); 4.60 (d, 11.7 Hz, H11); 3.87 (dd, 8.7 Hz, 6.2 Hz, H3); 2.74 (t, 6.0 Hz, H1); 2.31–2.22 (m, H4); 2.21 (q, 7.5 Hz, H2′); 2.18–2.12 (m, H7); 1.98–1.93 (m, H5); 1.77 (ddd, 13.7 Hz, 4.9 Hz, 2.4 Hz, H4); 1.61 (s, CH_3); 1.38 (d, 10.2 Hz, H7); 1.20 (s, CH_3); 0.98 (t, 7.5 Hz, H3′); 0.82 (s, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): 173.6 (s, C=O); 138.7 (s, C12); 128.2, 127.6 and 127.4 (d, C13–C15); 85.2 (s, C2); 77.3 (d, C3); 72.2 (t, C11); 52.1 (d, C1); 40.0 (d, C5); 38.4 (s, C6); 35.0 (t, C4); 28.8 (t, C2′); 28.1 (t, C7); 27.6 (q, CH_3); 26.4 (q, CH_3); 23.8 (q, CH_3); 9.1 (q, C3′). LREIMS (70 eV, *m/z*): 105 (100); 91 (84); 77 (24); 57 (65). Calcd for $C_{20}H_{28}O_3$: 75.92% C, 8.92% H. Found: 75.88% C, 8.94% H.

3.4. *Chiral hydroxyesters* **4** *and* **5**: *aldol in LDA, THF*

A solution of the ester **3** (0.5 g, 1.582 mmol) in dry THF (3 mL) was added dropwise to a cold (−78°C) 1 M solution of LDA in THF (1.9 mL) under a nitrogen atmosphere and the resulting yellowish solution was stirred for 45 min. A solution of benzaldehyde (0.18 mL, 1.741 mmol) in THF (1 mL) was added dropwise and the mixture was stirred at −78°C for 5 min. The reaction was quenched by the addition of sat. NH_4Cl (5 mL) and the mixture was allowed to reach room temperature. The mixture was diluted in ethyl acetate (10 mL) and washed with 10% aqueous $NaHCO_3$ (10 mL). The phases were separated and the aqueous layer was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine (3×20 mL) and dried over anhydrous Na_2SO_4. Solvent removal in vacuo was followed by flash chromatography on silica gel using 5% EtOAc in hexane as eluant to give a mixture of **4** and **5** along with a *syn*-aldol (*anti*/*syn* = 80/20; 74% d.e.) as a white solid (0.530 g, 80% yield). Mp 82–86°C. $[\alpha]_D^{25}$ +13.3 (*c* 1.15; CH_2Cl_2).

Anti-aldols **4** and **5**. IR (KBr, cm^{-1}): 3558; 3042; 2996; 2910; 1741; 1454; 1278; 1143; 766; 712. ^1H NMR ($CDCl_3$, 300 MHz, ppm): 7.42–7.21 (m, H5′–H7′ and H13–H15); 4.74 (d, 11.8 Hz, H11); 4.64 (d, 9.3 Hz, H3′); 4.60 (s, OH); 4.56 (d, 11.8 Hz, H11); 3.84 (dd, 9.0 Hz, 6.6 Hz, H3 of **5**); 3.83 (dd, 9.0 Hz, 6.6 Hz, H3 of **4**); 2.85–2.77 (m, H2′); 2.74 (t, 6.0 Hz, H1 of **4**); 2.69 (t,

6.0 Hz, H1 of **5**); 2.43–2.33 (m, H4); 2.24–2.15 (m, H7); 2.02–1.99 (m, H5); 1.86 (ddd, 13.7 Hz, 5.7 Hz, 2.4 Hz, H4); 1.40 (s, CH_3); 1.38 (d, 11.1 Hz, H7); 1.26 (s, CH_3 of **4**); 1.24 (s, CH_3 of **5**); 1.16 (d, 7.5 Hz, H8′ of **4**); 1.02 (d, 7.2 Hz, H8′ of **5**); 0.88 (s, CH_3 of **5**); 0.86 (s, CH_3 of **4**). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): 173.8 (s, C=O of **5**); 173.0 (s, C=O of **4**); 142.3 and 137.5 (s, C4′ and C12); 128.4, 128.3, 128.0, 127.9, 127.2 and 126.2 (d, C5′–C7′ and C13–C15 of **4**); 128.2, 128.1, 128.0, 127.8, 127.3 and 126.3 (d, C5′–C7′ and C13–C15 of **5**); 86.4 (s, C2 of **5**); 86.0 (s, C2 of **4**); 76.2 (d, C3 of **5**); 75.8 (d, C3 of **4**); 75.6 (d, C3′ of **5**); 75.1 (d, C3′ of **4**); 71.9 (t, C11 of **5**); 71.5 (t, C11 of **4**); 51.7 (d, C1); 48.2 (d, C2′ of **4**); 47.4 (d, C2′ of **5**); 40.1 (d, C5); 38.3 (s, C6); 34.5 (d, C4); 28.1 (q, CH_3); 27.9 (t, C7 of **4**); 27.5 (t, C7 of **5**); 24.8 (q, CH_3); 23.8 (q, CH_3); 15.2 (q, C8′ of **4**); 14.6 (q, C8′ of **5**). LREIMS (70 eV, m/z): 107 (31); 91 (100); 83 (54); 69 (70); 57 (89). Calcd for $C_{27}H_{34}O_4$: 76.75% C, 8.11% H. Found: 76.86% C, 7.88% H.

Syn-aldol. ^1H NMR ($CDCl_3$, 300 MHz, ppm): 7.40–7.23 (m, H5′–H7′ and H13–H15); 5.13 (s, OH); 4.74 (d, 12.3 Hz, H11); 4.58 (d, 12.3 Hz, H11); 4.45 (d, 2.4 Hz, H3′); 3.85 (dd, 8.9 Hz, 6.6 Hz, H3); 2.80 (t, 6.0 Hz, H1); 2.63 (dq, 7.2 Hz, 2.4 Hz, H2′); 2.44–2.34 (m, H4); 2.23–2.12 (m, H7); 2.04–1.96 (m, H5); 1.87 (ddd, 13.5 Hz, 6.3 Hz, 2.1 Hz, H4); 1.59 (s, CH_3); 1.37 (d, 10.5 Hz, H7); 1.27 (s, CH_3); 1.05 (d, 7.2 Hz, H8′); 0.89 (s, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): 173.3 (s, C=O); 141.3 and 137.7 (s, C4′ and C12); 128.4, 128.3, 128.1, 127.8, 126.3 and 126.0 (d, C5′–C7′ and C13–C15); 86.1 (s, C2); 76.0 (d, C3); 75.1 (d, C3′); 71.6 (t, C11); 51.8 (d, C1); 47.5 (d, C2′); 39.9 (d, C5); 38.2 (s, C6); 34.7 (d, C4); 28.0 (q, CH_3); 27.8 (t, C7); 25.6 (q, CH_3); 25.2 (q, CH_3); 10.5 (q, C8′).

*3.5. Chiral esters **7a**,**b**: alkylation in LDA, THF*

A solution of the ester **3** (0.4 g, 1.264 mmol) in dry THF (2.4 mL) was added dropwise to a cold (−78°C) 1 M solution of LDA in dry THF (0.7 mL) under a nitrogen atmosphere and the resulting yellowish solution was stirred for 45 min. A 1 M solution of the appropriate alkyl bromide (3.0 equiv.) in dry THF was added dropwise and the mixture was stirred for 6 h. Saturated aqueous NH_4Cl (4 mL) was added and the mixture was allowed to reach room temperature. The mixture was diluted in ethyl acetate (10 mL) and washed with 10% aqueous $NaHCO_3$ (10 mL). The phases were separated and the aqueous layer was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine (3×20 mL) and dried over anhydrous Na_2SO_4. Solvent removal in vacuo was followed by flash chromatography on silica gel using 5% EtOAc in hexane as eluant to give **7a**,**b** as colorless oils in the yields shown in Table 2.

Ester **7a** (60% d.e.). $[\alpha]_D^{25}$ +10.5 (*c* 3.15; CH_2Cl_2). IR (neat, cm^{-1}): 3058; 3020; 2962; 2921; 2863; 1741; 1638; 1492; 1448; 1371; 1355; 1183; 1142; 1115; 910; 732; 693. ^1H NMR ($CDCl_3$, 300 MHz, ppm): 7.41–7.25 (m, H13–H15); 5.82–5.67 (m, H4′); 5.07–4.95 (m, H5′); 4.68 (d, 11.7 Hz, H11 of (2′*R*)-**7a**); 4.67 (d, 11.7 Hz, H11 of (2′*S*)-**7a**); 4.60 (d, 11.7 Hz, H11 of (2′*S*)-**7a** and (2′*R*)-**7a**); 3.88 (dd, 8.9 Hz, 5.7 Hz, H3); 2.79 (t, 5.7 Hz, H1 of (2′*R*)-**7a**); 2.76 (t, 5.7 Hz, H1 of (2′*S*)-**7a**); 2.54–2.35 (m, H2′ and H3′); 2.20–2.06 (m, H4 and H7); 1.99–1.93 (m, H5); 1.86 (ddd, 13.7 Hz, 5.7 Hz, 2.4 Hz, H4); 1.69 (s, CH_3); 1.43 (d, 10.2 Hz, H7 of (2′*S*)-**7a**); 1.42 (d, 10.2 Hz, H7 of (2′*R*)-**7a**); 1.27 (s, CH_3); 1.10 (d, 6.9 Hz, H6′ of (2′*S*)-**7a**); 1.09 (d, 6.9 Hz, H6′ of (2′*R*)-**7a**); 0.93 (s, CH_3 of (2′*S*)-**7a**); 0.88 (s, CH_3 of (2′*R*)-**7a**). ^{13}C NMR ($CDCl_3$, 50 MHz, ppm): 175.1 (s, C=O of (2′*R*)-**7a**); 175.0 (s, C=O of (2′*S*)-**7a**); 138.7 (s, C12 of (2′*R*)-**7a**); 135.9 (s, C12 of (2′*S*)-**7a**); 128.1, 127.5 and 127.4 (d, C13–C15 of (2′*S*)-**7a**); 128.0, 127.3 and 127.2 (d, C13–C15 of (2′*R*)-**7a**); 116.4 (t, C5′ of (2′*R*)-**7a**); 116.3 (t, C5′ of (2′*S*)-**7a**); 85.3 (s, C2 of (2′*R*)-**7a**); 85.2

(s, C2 of (2′*S*)-**7a**); 77.5 (d, C3); 72.2 (t, C11 of (2′*S*)-**7a**); 67.8 (t, C11 of (2′*R*)-**7a**); 51.9 (d, C1 of (2′*S*)-**7a**); 49.1 (d, C1 of (2′*R*)-**7a**); 40.2 (d, C2′ of (2′*S*)-**7a**); 40.0 (d, C2′ of (2′*R*)-**7a**); 39.9 (d, C5); 38.4 (s, C6); 37.8 (t, C3′ of (2′*R*)-**7a**); 37.5 (t, C3′ of (2′*S*)-**7a**); 35.2 (t, C4); 28.0 (q, CH_3); 27.6 (t, C7); 26.4 (q, CH_3); 25.5 (q, CH_3 of (2′*R*)-**7a**); 23.8 (q, CH_3); 16.6 (q, C6′ of (2′*S*)-**7a**); 16.4 (q, C6′ of (2′*R*)-**7a**). LREIMS (70 eV, *m*/*z*): 356 (M^+, 3); 160 (22); 151 (26); 108 (27); 105 (25); 91 (100); 69 (71). HREIMS calcd for $C_{23}H_{32}O_3$ (M^+): 356.456. Found: 356.4594.

Ester **7b** (41% d.e.). $[\alpha]_D^{25}$ +7.3 (*c* 3.36; CH_2Cl_2). IR (neat, cm^{-1}): 3080; 3057; 3021; 2962; 2918; 2863; 1743; 1493; 1449; 1372; 1357; 1271; 1149; 1116; 731; 696. ^1H NMR ($CDCl_3$, 300 MHz, ppm): 7.41–7.10 (m, H5′–H7′ and H13–H15); 4.65 (d, 11.7 Hz, H11 of (2′*S*)-**7b**); 4.59 (d, 11.7 Hz, H11 of (2′*S*)-**7b**); 4.51 (d, 11.7 Hz, H11 of (2′*R*)-**7b**); 4.43 (d, 11.7 Hz, H11 of (2′*R*)-**7b**); 3.87 (dd, 9.0 Hz, 6.0 Hz, H3 of (2′*S*)-**7b**); 3.82 (dd, 9.0 Hz, 6.0 Hz, H3 of (2′*R*)-**7b**); 3.05 (dd, 13.2 Hz, 7.2 Hz, H3′ of (2′*S*)-**7b**); 2.99 (dd, 13.2 Hz, 7.2 Hz, H3′ of (2′*R*)-**7b**); 2.79 (t, 5.7 Hz, H1 of (2′*R*)-**7b**); 2.75–2.63 (m, H2′); 2.70 (t, 5.7 Hz, H1 of (2′*S*)-**7b**); 2.56 (dd, 13.2 Hz, 7.2 Hz, H3′ of (2′*S*)-**7b**); 2.55 (dd, 13.2 Hz, 7.2 Hz, H3′ of (2′*R*)-**7b**); 2.46–2.33 (m, H4); 2.18–2.08 (m, H7 of (2′*R*)-**7b**); 2.08–2.01 (m, H7 of (2′*S*)-**7b**); 1.96–1.89 (m, H5); 1.88–1.79 (m, H4); 1.66 (s, CH_3 of (2′*S*)-**7b**); 1.58 (s, CH_3 of (2′*R*)-**7b**); 1.37 (d, 10.2 Hz, H7 of (2′*R*)-**7b**); 1.30 (d, 10.2 Hz, H7 of (2′*S*)-**7b**); 1.29 (s, CH_3 of (2′*R*)-**7b**); 1.25 (s, CH_3 of (2′*S*)-**7b**); 1.09 (d, 6.6 Hz, H8′ of (2′*R*)-**7b**); 1.08 (d, 6.6 Hz, H8′ of (2′*S*)-**7b**); 0.91 (s, CH_3 of (2′*S*)-**7b**); 0.90 (s, CH_3 of (2′*R*)-**7b**). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): 175.1 (s, C=O of (2′*R*)-**7b**); 174.9 (s, C=O of (2′*S*)-**7b**); 139.7 and 138.7 (s, C4′ and C12); 128.9, 128.2, 127.9, 127.4, 127.3 and 125.9 (d, C5′–C7′ and C13–C15 of (2′*S*)-**7b**); 129.0, 128.1, 128.0, 127.4, 127.2 and 126.0 (d, C5′–C7′ and C13–C15 of (2′*R*)-**7b**); 85.3 (s, C2 of (2′*S*)-**7b**); 85.2 (s, C2 of (2′*R*)-**7b**); 77.5 (d, C3 of (2′*S*)-**7b**); 77.1 (d, C3 of (2′*R*)-**7b**); 72.2 (t, C11 of (2′*S*)-**7b**); 72.1(t, C11 of (2′*R*)-**7b**); 51.9 (d, C1 of (2′*S*)-**7b**); 51.8 (d, C1 of (2′*R*)-**7b**); 42.5 (d, C2′ of (2′*R*)-**7b**); 42.3 (d, C2′ of (2′*S*)-**7b**); 39.9 (d, C5); 39.8 (t, C3′ of (2′*R*)-**7b**); 39.3 (t, C3′ of (2′*S*)-**7b**); 38.3 (s, C6); 35.3 (t, C4 of (2′*R*)-**7b**); 35.2 (t, C4 of (2′*S*)-**7b**); 28.0 (q, CH_3 of (2′*S*)-**7b**); 27.9 (q, CH_3 of (2′*R*)-**7b**); 27.4 (t, C7 of (2′*S*)-**7b**); 27.3 (t, C7 of (2′*R*)-**7b**); 26.5 (q, CH_3 of (2′*R*)-**7b**); 26.3 (q, CH_3 of (2′*S*)-**7b**); 23.8 (q, CH_3); 16.9 (d, C8′ of (2′*R*)-**7b**); 16.8 (d, C8′ of (2′*S*)-**7b**). LREIMS (70 eV, *m*/*z*); 406 (M^+, 2); 243 (22); 199 (24); 160 (32); 151 (41); 109 (36); 97 (70); 91 (67); 69 (100). HREIMS calcd for $C_{27}H_{34}O_3$ (M^+): 406.512. Found: 406.5480.

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15. All spectral data are in agreement with the literature.[13] For (*R,R*)-**6** (*anti*/*syn* = 80/20; 74% e.e.): $[\alpha]_D^{25}$ +25 (*c* 0.68; $CHCl_3$). Lit.[13] for (*S,S*)-**6** (100% *anti*; 66% e.e.): $[\alpha]_D^{25}$ −32.8 (*c* 0.68; $CHCl_3$).
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18. All spectral data are in agreement with the literature. For (*S*)-**7a** (60% e.e.): $[\alpha]_D^{25}$ −1.2 (*c* 1.5; C_6H_6). Lit.[17a] for (*S*)-**7a** (99% e.e.): $[\alpha]_D^{25}$ −2.1 (*c* 1.5; C_6H_6). For (*S*)-**7b** (21% e.e.): $[\alpha]_D^{25}$ −2.4 (*c* 1.3; C_6H_6). Lit.[17b] for (*R*)-**7b** (98% e.e.): $[\alpha]_D^{25}$ +11 (*c* 1.15; C_6H_6).