Novel Camphor-Derived Chiral Auxiliaries: Significant Solvent and Additive Effects on Asymmetric Reduction of Chiral α-Keto Esters

Ying-Yuan Chu,† Chia-Sheng Yu,† Chiou-Juy Chen,† Kung-Shuo Yang, Jung-Chaing Lain, Chun-Hui Lin, and Kwunmin Chen*

Department of Chemistry, National Taiwan Normal University 88 Sec. 4 TingChow Road, Taipei, Taiwan 116, ROC

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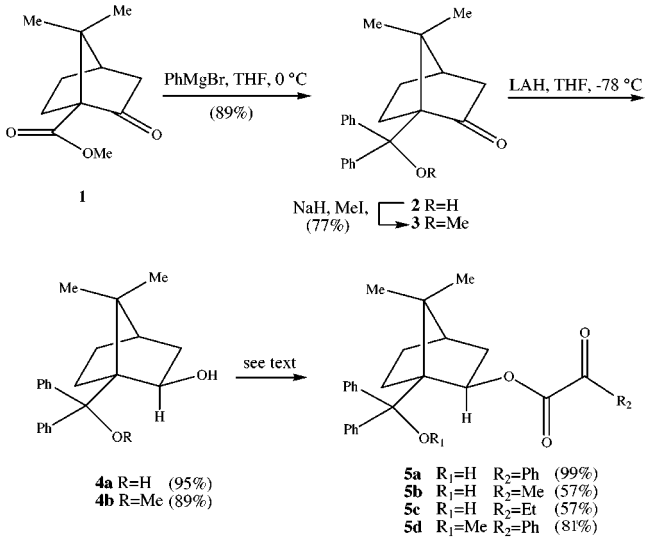
Stereoselective reduction of various α-keto esters **5a**−**d** derived from *exo*-10,10-diphenyl-2,10-camphanediol **4a** and *exo*-10,10-diphenyl-10-methoxy-2-camphanol **4b** is described. High to excellent diastereomeric excess (99% de) with good chemical yields is obtained. The sense of stereoselectivity as a function of C10 modification is remarkable. Further, in the case of **5d**, both diastereomers of α-hydroxyl esters can be obtained with excellent optical purity by the appropriate choice of reaction conditions. The influence of the solvents and additives on the reaction course has been investigated.

Introduction

The synthesis of homochiral α-hydroxyl acid derivatives constitutes one of the most important tasks in organic synthesis because many biologically active substances contain this functionality array.[1] Among the developed methods, the diastereoselective reduction of chiral α-keto esters/α-keto amides that bear an appropriate chiral auxiliary is a conventional strategy.[2] The asymmetric reduction of α-keto amides seems to be a more promising approach owing to the well-known planarity of the amide group and the lower number of possible conformers in the transition state compared to those of α-keto esters.[2i−k] However, asymmetric reduction of α-keto esters with high to excellent diastereoselection is possible if effective chiral auxiliaries can be developed. In a previous publication, we described an efficient method for the preparation of both diastereomers of α-hydroxyl ester derived from a single enantiomer of chiral auxiliary.[3] Stereoselective reduction of α-keto ester **5a** derived from *exo*-10,10-diphenyl-2,10-camphanediol **4a** with various hydrides proceeded with high diastereoselectivities (≥96% de) to afford the corresponding α-hydroxyl ester in excellent yield. In this article, we wish to report more details of the stereoreduction of related α-keto esters **5b**−**d**. The methodology has been successfully utilized for achieving both diastereomers of α-hydroxyl esters without resorting to the enantiomeric auxiliary. This represents a promising tool in asymmetric synthesis.

Results and Discussion

The compounds *exo*-10,10-diphenyl-2,10-camphanediol **4a** and *exo*-10,10-diphenyl-10-methoxy-2-camphanol **4b** can be easily prepared from ketopinic acid methyl ester **1**.[4] Treatment of **1** with 4.0 equiv of phenylmagnesium bromide (THF, 0 °C) afforded hydroxyl ketone **2** in 89% yield. LAH reduction of **2** (THF, −78 °C) provided the desired *exo* alcohol **4a** in 95% yield, together with a minor *endo* product (*exo*:*endo* 95:5). The ^{1}H NMR spectra of the methine proton on C2 of **4a** appeared at δ 4.26 ppm, whereas the corresponding proton of the minor product shifted downfield to δ 4.94 ppm. The tertiary hydroxyl group in **2** may then be protected as its methyl ether (NaH, MeI, THF, 0 °C) in 77% yield. Reduction of compound **3** with LAH (THF, −78 °C) provided the *exo* alcohol **4b** as a sole product in 89% yield. Acylation of **4a** with benzoformic acid chloride,[5] generated in situ by reaction of benzoformic acid with $SOCl_2$ at 65 °C for 1 h, in THF at 0 °C afforded **5a** in almost quantitative yield. Although similar conditions provided α-keto ester **5d**



† Department of Applied Chemistry, Chaoyang University of Technology, 168 Gifeng E. Road, Wufeng, Taichung, Taiwan 413, ROC.

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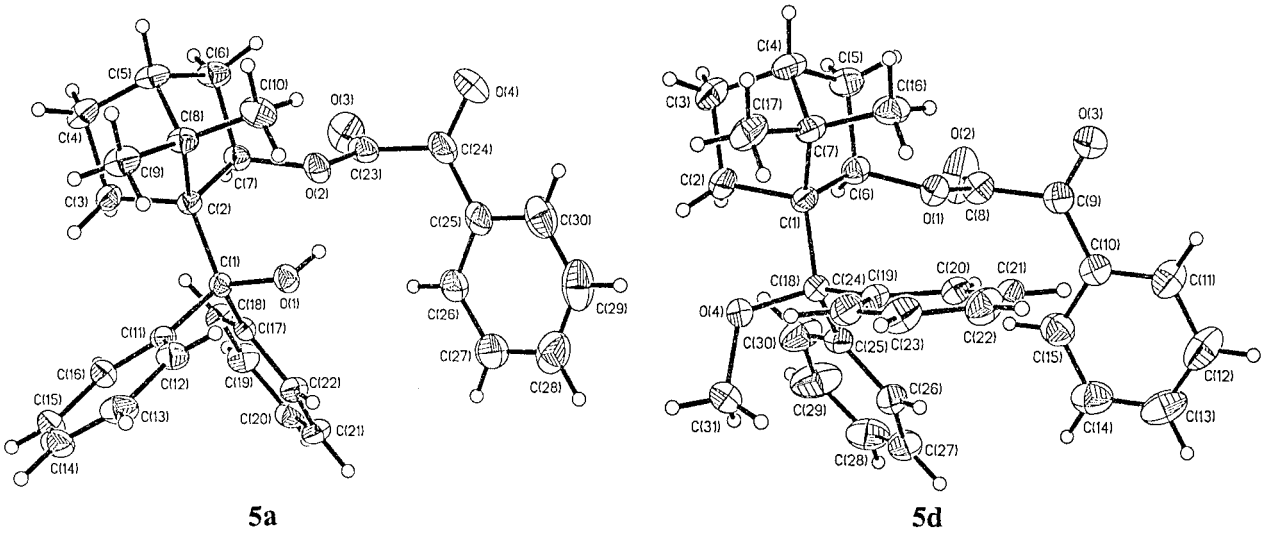

Figure 1. X-ray ORTEP drawings of **5a** and **5d**.

without incident, the preparation of **5b** and **5c** under the same conditions proved troublesome. After extensive experimental investigation, the problem was resolved by treatment of **4a** with freshly prepared pyruvic acid chloride (pyruvic acid, DMF, oxalyl chloride) in CH_2Cl_2 at 0 °C to provide **5b** in 57% yield. Chiral α-keto ester **5c** was obtained under the same conditions when 2-ketobutyric acid was used. The structures of **5a** and **5d** were established via ^1H and ^{13}C NMR spectroscopic analyses and further confirmed by X-ray crystallographic analyses (Figure 1).

With α-keto esters in hand, we turned our attention to the asymmetric reduction. Our preliminary investigations failed to give good diastereoselectivity when **5a** was reduced with $NaBH_4$ or BH_3. For example, reduction of α-keto ester **5a** with $NaBH_4$ gave two inseparable diastereomers in 78% yield with a disappointingly low diastereomeric ratio.[3] However, reduction with a sterically demanding reductant does afford practical levels of diastereoselectivity. Thus, treatment of **5a** with L-Selectride (Aldrich) in THF at −78 °C affords α-hydroxyl ester **6a** with a very high diastereoselectivity (Table 1, entry 1). Because of the inseparable nature of the products on silica gel, the diastereomeric ratios were determined by 200 MHz ^1H NMR analysis of relevant signals. Treatment of **5b** under the same reaction conditions provided **6b** with high stereoselectivity (Table 1, entry 2). This encouraged us to focus on Selectride as reducing agents. A systematic investigation was then carried out, and the chemical yields are generally moderate to excellent. The absolute configurations of the newly generated stereogenic centers were assigned on the basis of the cleaved α-hydroxyl acids **8a**−**c**. Comparison of the sign of specific rotations of the α-hydroxyl acids with literature values[6−8] allows assignment of the absolute configurations (*S*).

In constrast to the **4a**-derived α-keto esters, relatively poor facial selectivity with opposite configuration was obtained when **5d** was reduced (Table 1, entries 6 and 7). We then investigated the solvent effect on this reaction, and the results showed that the reaction is highly dependent on the nature of the solvent. In general, for cases of **5a**−**c**, the use of a noncoordinating solvent such as toluene led to appreciable decreases in diastereoselectivity while the chemical yields remained (Table 1, entries 8−10). Quite surprisingly, in the case of **5d**, the use of CH_2Cl_2 or toluene increases the stereoselectivity significantly (Table 1, entries 11−14). Thus, treatment of α-keto ester **5d** with L-Selectride in either CH_2Cl_2 or toluene resulted in a greater than 99% de for **7d**. The absolute stereochemistry of **7d** was assigned by X-ray crystallographic analysis.

Another interesting and exciting observation is the additive effect. There have been reports of other systems in which the changeover of diastereofacial selectivity is affected by the addition of Lewis acids[9] or crown ethers.[2f,g] The present study indicated that the addition of 18-crown-6 or HMPA enhanced stereoselectivity in the cases of **5a**−**c** (Table 2, entries 1−3). However, the inclusion of additive reversed diastereoselectivity to a significant extent for chiral α-keto ester **5d** (Table 2, entries 4−6). High to excellent diastereoselectivity was attained with *S* configuration dominating in all cases investigated. Thus, treatment of **5c** with K-Selectride in toluene at −78 °C in the presence of 1.0 equiv of 18-crown-6 improved the selectivity to 99% de compared with 6% de in the absence of this additive (Table 2, entry 3 and Table 1, entry 10). Further, 84% de (*S*) was obtained when α-keto ester **5d** was treated with K-Selectride in CH_2Cl_2 in the presence of 18-crown-6 (Table 2, entry 6 and Table 1, entry 13). The reversal of diastereoselectivity is astonishing and suggests that the cation(s) play a major role in determining the transition state conformation.

From a practical synthetic point of view, the preparation of both stereoisomers with excellent optical purity derived from the same chiral source is an attractive tool.[10] Very recently, Duhamel and co-workers reported that chiral auxiliaries containing a "switching center" allow for the synthesis of enantiomerically pure (*R*)- and (*S*)-

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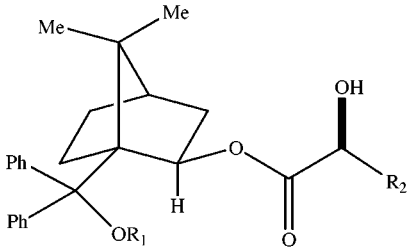
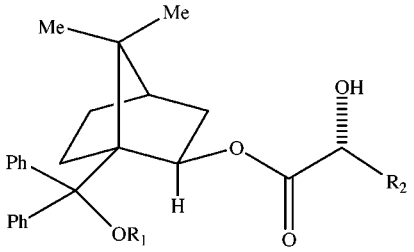
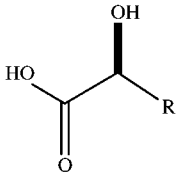
Table 1. Asymmetric Reduction of α-Keto Esters 5[a]



6a R_1=H R_2=Ph
6b R_1=H R_2=Me
6c R_1=H R_2=Et
6d R_1=Me R_2=Ph



7a R_1=H R_2=Ph
7b R_1=H R_2=Me
7c R_1=H R_2=Et
7d R_1=Me R_2=Ph



8a R=Ph
8b R=Me
8c R=Et

entry	ester	hydride	equiv	solvent	yield (%)[b]	**6**/**7**[c]	config[d]
1	**5a**	L-Selectride	1.0	THF	92	**6a**/**7a** (97.5/2.5)	S
2	**5b**	L-Selectride	1.0	THF	92	**6b**/**7b** (95.0/5.0)	S
3	**5b**	K-Selectride	1.0	THF	85	**6b**/**7b** (93.0/7.0)	S
4	**5c**	L-Selectride	1.0	THF	92	**6c**/**7c** (99.0/1.0)	S
5	**5c**	K-Selectride	1.0	THF	94	**6c**/**7c** (94.0/6.0)	S
6	**5d**	L-Selectride	1.0	THF	87	**6d**/**7d** (31.0/69.0)	R
7	**5d**	K-Selectride	1.0	THF	70	**6d**/**7d** (18.0/82.0)	R
8	**5a**	L-Selectride	1.0	toluene	77	**6a**/**7a** (69.0/31.0)	S
9	**5b**	K-Selectride	1.0	toluene	92	**6b**/**7b** (47.0/53.0)	R
10	**5c**	K-Selectride	1.0	toluene	86	**6c**/**7c** (53.0/47.0)	S
11	**5d**	L-Selectride	1.2	CH_2Cl_2	95	**6d**/**7d** (0.5/99.5)	R
12	**5d**	L-Selectride	1.2	toluene	98	**6d**/**7d** (0.5/99.5)	R
13	**5d**	K-Selectride	1.2	CH_2Cl_2	80	**6d**/**7d** (0.5/99.5)	R
14	**5d**	K-Selectride	1.2	toluene	75	**6d**/**7d** (0.5/99.5)	R

[a] All reactions were carried out at −78 °C. [b] Isolated yield. [c] Ratios determined by 200 MHz ^{1}H NMR analysis of relevant signals. [d] The absolute stereochemistry was determined either by comparison of the sign of optical rotation of the cleaved acids, (*S*)-(+)-mandelic acid (**8a**), (*S*)-(+)-lactic acid (**8b**), and (*S*)-(+)-2-hydroxybutyric acid (**8c**), or by X-ray crystallographic analysis (**7d**).

Table 2. Additive Effect of Asymmetric Reduction of α-Keto Esters 5[a]

entry	ester	hydride	additive[b]	solvent	yield (%)[c]	**6**/**7**[d]	config
1	**5a**	L-Selectride	HMPA	toluene	58	**6a**/**7a** (99.5/0.5)	S
2	**5b**	L-Selectride	18-crown-6	CH_2Cl_2	95	**6b**/**7b** (99.0/1.0)	S
3	**5c**	K-Selectride	18-crown-6	toluene	89	**6c**/**7c** (99.5/0.5)	S
4	**5d**	L-Selectride	HMPA	THF	75	**6d**/**7d** (99.0/1.0)	S
5	**5d**	K-Selectride	18-crown-6	THF	60	**6d**/**7d** (99.5/0.5)	S
6	**5d**	K-Selectride	18-crown-6	CH_2Cl_2	60	**6d**/**7d** (92.0/8.0)	S

[a] All reactions were carried out at −78 °C with 1.0 equiv of Selectride. [b] One equivalent of additive was added. [c] Isolated yield. [d] Ratios determined by 200 MHz ^{1}H NMR analysis of relevant signals.

α-amino acids.[10c] In our system, the sense of stereoselectivity as a function of C10 modification is remarkable. Further, the dramatic change of diastereoselectivity in **5d** by the appropriate choice of reaction conditions deserves special attention. Although a detailed mechanistic explanation of the present study remained to be answered, the stereochemical outcomes may be rationalized as follows. In the cases of **5a**−**c**, the more extended s-trans conformation is energetically favored over s-cis under either chelation or nonchelation conditions. This may be due primarily to the presence of the C10 hydroxyl functionality toward the direction of the carbonyl groups (Figure 1). Thus, the metal cation chelates more strongly to the C10 hydroxyl group and carbonyl groups than α-dicarbonyl groups. The X-ray data of **5a** indicates that there exists an intramolecular hydrogen-bonding interaction at O(1)H···O(2). The intramolecular distance of O(1)H···O(2) is 2.115 Å. The complex hydride then attacks from the *re*-face, resulting in an (*S*)-configuration of the newly generated stereogenic center. In contrast, the s-cis conformation predominates for **5d**, especially in the presence of strongly coordinating metal cation(s).[2d,2g] However, the s-trans conformation prevails in the presence of additives. This may be due to the avoidance of steric hindrance between the C10 phenyl groups and side chain moiety in a congested area. As a consequence, the reduction proceeded through either cisoid or transoid conformation depending on the reaction conditions and led to the reversal of stereoselection. The different ligating ability of the solvent used affects the transition state conformation to a certain degree. In all the cases, the C10 phenyl and/or C8 methyl group of the chiral auxiliary shields one face of the α-carbonyl sp^2 carbon center, leading to the desired configuration.

The auxiliary can be easily removed by treatment of the reduction product with LiOH in THF/H_2O at room temperature (Table 3). No significative racemization of reduced products was observed.

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Table 3. Hydrolysis of α-Hydroxyl Esters 6

entry	α-hydroxyl ester	acid (%)	$[\alpha]_D$	% ee	**4a** (%)
1	**6a** (95% de)	**8a** (84)	+145.0° (*c* 2.8, H_2O)[a]	95	97[d]
2	**6b** (98% de)	**8b** (80)	−13.1° (*c* 1.5 1.5 N NaOH)[b]	97	90
3	**6c** (99% de)	**8c** (85)	+7.1° (*c* 3.0, $CHCl_3$)[c]	99	91

[a] Lit.[6] $[\alpha]_D$ +153.0° (*c* 0.153, H_2O). [b] Lit.[7] $[\alpha]_D$ −13.5° (*c* 2.5, 1.5 N NaOH). [c] Lit.[8] $[\alpha]_D$ +7.15° (*c* 8.13, $CHCl_3$). [d] Recovered **4a**: $[\alpha]_D$ +164.8° (*c* 1.0, $CHCl_3$); original compound **4a**: $[\alpha]_D$ +166.1° (*c* 1.0, $CHCl_3$).[3]

Conclusions

In summary, *exo*-10,10-diphenyl-2,10-camphanediol **4a** and *exo*-10,10-diphenyl-10-methoxy-2-camphanol **4b** have proved to be effective chiral auxiliaries for the asymmetric reduction of α-keto esters. Our procedure represents a simple and effective alternative for the highly diastereoselective synthesis of α-hydroxyl esters through the reduction of the corresponding α-keto esters. Moreover, both diastereomers of α-hydroxyl esters (**6d** and **7d**) can be prepared with excellent optical purity from a single chiral auxiliary (**5d**) by means of the proper choice of reaction conditions. Further investigations of these novel chiral auxiliaries in asymmetric synthesis are in progress.

Experimental Section

General Methods. All reactions were carried out in flame- or oven-dried glassware under a positive pressure of nitrogen. Air- and moisture-sensitive compounds were introduced by the use of a gastight syringe or cannula through a rubber septum. Most reagents were commercially available and of synthetic grade. Tetrahydrofuran was distilled from sodium/benzophenone ketyl. Dichloromethane and toluene were dried over CaH_2 and distilled before use. Analytical thin-layer chromatography was performed with E. Merck silica gel 60F glass plates, and flash column chromatography performed by the use of E. Merck silica gel 60 (230−400 mesh). HRMS values were measured by a JEOL JMS-SX or JEOL JMS-SX 102A spectrometer. Elemental analyses were performed by a Heraeus CHN-OS rapid instrument. IR spectra were recorded on JASCO FT/IR-300E. ^1H and ^{13}C NMR spectra were recorded routinely in $CDCl_3$ on a Varian Gemini 2000 spectrometer.

***exo*-10,10-Diphenyl-10-hydroxymethyl-7,7-dimethylbicyclo[2.2.1]heptane-2-one (2).** To a solution of ketopinic acid methyl ester **1** (10.0 g, 50.96 mmol) in THF (100 mL) was added PhMgBr (203.84 mmol, 1.0 M solution in THF, 203.84 mL) dropwise at 0 °C under N_2 atmosphere. The resulting mixture was allowed to stir for 30 min and quenched with H_2O/ethyl acetate dropwise at 0 °C. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 200 mL). The combined extracts were washed (brine), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was recrystallized from hexane/ethyl acetate (4:1) to give 14.5 g (89%) of **2** as a colorless crystal: ^1H NMR ($CDCl_3$, 200 MHz) δ 7.45−7.19 (m, 10H), 3.84 (br, 1H), 2.55−2.48 (m, 1H), 2.45 (d, 1H, J = 6.3 Hz), 2.29 (ddd, 1H, J = 13.9, 9.3, 4.8 Hz), 1.96−1.87 (m, 2H), 1.77 (t, 1H, J = 4.8 Hz), 1.41 (ddd, 1H, J = 11.9, 9.3, 4.0 Hz), 1.06 (s, 3H), 0.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 220.19, 147.25, 144.61, 129.23, 128.39, 127.39, 127.28, 126.99, 126.90, 79.98, 68.25, 50.37, 44.69, 43.69, 27.14, 25.76, 22.88, 21.88; IR (film) 3500, 2965, 1715 cm^{-1}; HRMS *m*/*z* 320.1773 (calcd for $C_{22}H_{24}O_2$ 320.1776). Anal. Calcd for $C_{22}H_{24}O_2$: C, 82.46; H, 7.55. Found: C, 82.16; H, 7.58.

***exo*-10,10-Diphenyl-10-methoxymethyl-7,7-dimethylbicyclo[2.2.1]heptane-2-one (3).** To a suspension of NaH (0.22 g, 9.17 mmol) in THF (10 mL) was added a solution of ketone **2** (1.0 g, 3.10 mmol) in THF (15 mL) dropwise at 0 °C. This was followed by the addition of MeI (0.23 mL, 3.70 mmol) dropwise. The resulting mixture was allowed to warm to room temperature over a period of 30 min and quenched with H_2O. The aqueous layer was extracted with ethyl acetate (2 × 30 mL). The combined extracts were washed (brine), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography, using hexane/ethyl acetate (10:1) as eluent, to give 0.8 g (77%) of **3** as a yellow oil: ^1H NMR ($CDCl_3$, 200 MHz) δ 7.61−7.52 (m, 4H), 7.37−7.25 (m, 6H), 3.14−3.01 (m, 1H), 2.91 (s, 3H), 2.37−2.26 (m, 1H), 2.14−1.97 (m, 2H), 1.69−1.67 (m, 2H), 1.29−1.23 (m, 1H), 0.91 (s, 3H), 0.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 214.56, 140.25, 130.39, 129.89, 127.06, 126.93, 126.89, 126.86, 85.75, 70.32, 52.79, 49.80, 45.37, 44.06, 27.36, 26.08, 21.80, 21.50; IR (film) 3055, 2938, 1738 cm^{-1}; HRMS *m*/*z* 334.1925 (calcd for $C_{23}H_{26}O_2$ 334.1933). Anal. Calcd for $C_{23}H_{26}O_2$: C, 82.60; H, 7.84. Found: C, 82.29; H, 7.60.

***exo*-10,10-Diphenyl-10-hydroxymethyl-7,7-dimethylbicyclo[2.2.1]heptane-2-ol (4a).** To a suspension of LAH (1.77 g, 46.64 mmol) in THF (50 mL) was added a solution of **2** (5.0 g, 15.61 mmol) in THF (100 mL) at −78 °C under N_2 atmosphere. This was allowed to stir at −78 °C for 30 min and quenched with H_2O. The aqueous layer was extracted with ethyl acetate (2 × 50 mL). The combined extracts were washed (brine), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography, using hexane/ethyl acetate (16:1) as eluent, to give 4.8 g (95%) of **4a** as a white solid: ^1H NMR ($CDCl_3$, 200 MHz) δ 7.86 (dd, 2H, J = 7.7, 1.5 Hz), 7.64 (dd, 2H, J = 7.7, 1.5 Hz), 7.33−7.11 (m, 6H), 5.05 (br, 1H), 4.23 (dd, 1H, J = 8.2, 3.7 Hz), 2.31 (ddd, 1H, 12.4, 12.3, 4.2 Hz), 2.10 (br, 1H), 1.91−1.44 (m, 4H), 1.50 (s, 3H), 1.42 (t, 1H, J = 4.4 Hz), 0.99 (ddd, 1H, J = 9.5, 6.2, 3.8 Hz), 0.48 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 150.25, 144.30, 128.47, 128.20, 127.03, 126.59, 126.04, 81.70, 79.95, 59.51, 50.67, 47.53, 40.12, 30.46, 27.38, 24.77, 22.98; IR (film) 3426, 2930, 748 cm^{-1}; HRMS *m*/*z* 322.1935 (calcd for $C_{22}H_{26}O_2$ 322.1933). Anal. Calcd for $C_{22}H_{26}O_2$: C, 81.95; H, 8.13. Found: C, 81.80; H, 8.06.

***exo*-10,10-Diphenyl-10-methoxymethyl-7,7-dimethylbicyclo[2.2.1]heptane-2-ol (4b).** To a suspension of LAH (0.23 g, 6.06 mmol) in THF (10 mL) was added a solution of **3** (1.0 g, 3.0 mmol) in THF (20 mL) at −78 °C under N_2 atmosphere. This was allowed to stir at −78 °C for 30 min and warm to room temperature over a period of 1 h. The mixture was cooled to 0 °C and quenched with H_2O. The aqueous layer was extracted with ethyl acetate (2 × 30 mL). The combined extracts were washed (brine), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The product was recrystallized from hexane/ethyl acetate (4:1) to give 0.9 g (89%) of **4b** as a colorless crystal: ^1H NMR ($CDCl_3$, 200 MHz) δ 7.88 (dd, 2H, J = 8.4, 1.6 Hz), 7.64 (dd, 2H, J = 8.4, 1.6 Hz), 7.46−7.31 (m, 6H), 6.98 (s, 1H), 4.65 (dd, 1H, J = 8.2, 3.4 Hz), 2.86 (s, 3H), 2.02−1.96 (m, 2H), 1.74 (dd, 1H, J = 12.4, 8.0 Hz), 1.50−1.44 (m, 1H), 1.39−1.32 (m, 1H), 1.31 (s, 3H), 0.89−0.79 (m, 2H), −0.22 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 139.06, 137.81, 130.41, 130.28, 128.28, 127.94, 127.74, 127.44, 127.33, 92.65, 80.14, 58.45, 52.49, 48.70, 47.96, 40.70, 29.66, 26.97, 21.65, 21.29; IR (film) 3402, 2937, 1040, 747 cm^{-1}; HRMS *m*/*z* 336.2097 (calcd for $C_{23}H_{28}O_2$ 336.2089). Anal. Calcd for $C_{23}H_{28}O_2$: C, 82.10; H, 8.39. Found: C, 82.14; H, 8.31.

General Procedure for the Preparation of α-Keto Esters 5a and 5d. To a freshly prepared benzoylformic acid chloride [benzoylformic acid (0.5 g, 3.33 mmol) and thionyl chloride (20 mL) reacted at 65 °C for 1 h; excess thionyl chloride removed *in vacuo* and the residue dried under a high vacuum pump line for 10 min] in THF (15 mL) was added a solution of **4a** (0.3 g, 0.93 mmol) in THF (15 mL) dropwise at 0 °C under N_2 atmosphere. The resulting mixture was stirred for 4 h at 0 °C. This was quenched with saturated $NaHSO_3$

and extracted with ethyl acetate (1 × 30 mL). The organic layer was washed (brine), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography, using hexane/ethyl acetate (10:1) as eluent, to give 0.42 g (99%) of **5a** as a white solid: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.76−7.42 (m, 7H), 7.4 (d, 2H, J = 7.5 Hz), 7.23−7.06 (m, 6H), 5.49 (dd, 1H, J = 7.3, 4.2 Hz), 3.83 (s, 1H), 2.38 (td, 1H, J = 12.1, 4.2 Hz), 2.08−1.90 (m, 3H), 1.66−1.62 (m, 1H), 1.56 (s, 3H), 1.56 (buried, 1H), 1.21(ddd, 1H, J = 11.9, 9.5, 4.2 Hz), 0.65 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 184.72, 160.24, 149.14, 143.57, 134.98, 132.30, 130.49, 128.88, 128.72, 128.28, 126.99, 126.73, 126.44, 126.38, 83.46, 81.33, 59.44, 51.75, 47.95, 38.45, 31.26, 27.26, 24.68, 22.81; IR (film) 3596, 2932, 1734, 1681, 1198 cm^{-1}; HRMS m/z 454.2134 (calcd for $C_{30}H_{30}O_4$ 454.2144). Anal. Calcd for $C_{30}H_{30}O_4$: C, 79.27; H, 6.65. Found: C, 79.59; H, 6.79. Crystal data for **5a** at 22 °C: $C_{30}H_{30}O_4$, M 454.54, monoclinic, $P2_1$, a =6.8806(1) Å, b =14.0735(1) Å, c =12.8483(2) Å, V =1198.83 Å^3, Z = 2, λ = 0.71073 Å, F(000) = 484, D_c = 1.259 Mg/m^3, μ = 0.082 mm^{-1}, 8878 reflections, 308 parameters, R = 0.0376, R_w = 0.0890 for all data.

5d: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.78−7.60 (m, 7H), 7.47 (d, 2H, J = 7.7 Hz), 7.26−7.21 (m, 6H), 5.12 (dd, 1H, J = 8.0, 3.6 Hz), 3.14 (td, 1H, J = 16.7, 4.0 Hz), 2.72 (s, 3H), 2.02 (dd, 1H, J = 13.2, 8.0 Hz), 1.77−1.68 (m, 3H), 1.49 (t, 1H, J = 4.0 Hz), 1.15−1.09 (m, 1H), 0.99 (s, 3H), 0.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 185.99, 162.24, 140.46, 137.78, 134.60, 132.33, 131.79, 130.01, 129.75, 128.68, 127.55, 127.18, 126.73, 126.64, 86.66, 83.27, 61.65, 52.54, 49.26, 49.16, 39.24, 31.11, 25.93, 22.40, 21.54; IR (film) 3056, 2936, 1730, 1687, 1197, 703 cm^{-1}; HRMS m/z 468.2303 (calcd for $C_{31}H_{32}O_4$ 468.2301). Anal. Calcd for $C_{31}H_{32}O_4$: C, 79.46; H, 6.88. Found: C, 79.63; H, 6.83. Crystal data for **5d** at 22 °C: $C_{31}H_{32}O_4$, M 468.57, orthorhombic, $P2_12_12_1$, a = 10.3404(1) Å, b = 14.8728(2) Å, c = 16.7626(1) Å, V = 2577.93 Å^3, Z = 4, λ = 0.71073 Å, F(000) = 1000, D_c = 1.207 Mg/m^3, μ = 0.079 mm^{-1}, 14780 reflections, 317 parameters, R = 0.0613, R_w = 0.1045 for all data.

General Procedure for the Preparation of α-Keto Esters 5b and 5c. To a solution of oxalyl chloride (7.8 g, 61.60 mmol) in CH_2Cl_2 (200 mL) was added a solution of pyruvic acid (5.5 g, 62.12 mmol) in DMF (0.01 mL) dropwise at 0 °C. This was allowed to stir for 5 min at 0 °C, and the solvent was removed *in vacuo* and under high vacuum pump line for 10 min. CH_2Cl_2 (50 mL) was added to the residue, and transferred into a solution of **4a** (2.0 g, 6.21 mmol) and Et_3N (6.27 g, 61.96 mmol) in CH_2Cl_2 (100 mL) dropwise at 0 °C. The resulting mixture was stirred for 30 min and quenched with H_2O. The aqueous layer was extracted with ethyl acetate (2 × 30 mL). The combined extracts were washed (brine), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography, using hexane/ethyl acetate (10:1) as eluent, to give 1.4 g (57%) of **5b** as a colorless oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.74−7.63 (m, 4H), 7.26−7.09 (m, 6H), 5.24 (dd, 1H, J = 7.4, 4.2 Hz), 3.92 (s, 1H), 2.32 (td, 1H, J = 11.5, 5.0 Hz), 2.18 (s, 3H), 2.04−2.02 (m, 1H), 1.92−1.88 (m, 1H), 1.86−1.78 (m, 2H), 1.54 (s, 3H), 1.54 (buried, 1H), 1.54−1.17 (m, 1H), 0.68 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 190.55, 157.05, 148.18, 142.53, 128.50, 127.94, 127.39, 126.30, 126.01, 125.66, 82.66, 80.45, 58.92, 50.93, 47.23, 37.19, 30.50, 26.46, 25.20, 23.96, 21.96; IR (film) 3555, 2941, 1731, 1135, 749 cm^{-1}; HRMS m/z 392.1983 (calcd for $C_{25}H_{28}O_4$ 392.1988; Anal. Calcd for $C_{25}H_{28}O_4$: C, 76.50; H, 7.19. Found: C, 76.70; H, 7.40.

5c: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.73−7.68 (m, 4H), 7.27−7.10 (m, 10 H), 5.25 (dd, 1H, J = 7.6, 4.2 Hz), 3.94 (s, 1H), 2.57−2.45 (m, 2H), 2.31 (td, 1H, J = 12.3, 4.2 Hz), 2.04−1.82 (m, 3H), 1.72−1.62 (m, 2H), 1.54 (s, 3H), 1.21−1.15 (m, 1H), 0.99 (t, 3H, J = 7.2 Hz), 0.67 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 194.03, 157.69, 148.78, 143.12, 129.59, 128.47, 128.04, 127.84, 126.81, 126.49, 126.19, 83.02, 80.95, 59.42, 51.48, 47.76, 37.78, 31.83, 31.03, 26.66, 24.49, 23.00, 6.63; IR (film) 3558, 2940, 1731, 749 cm^{-1}; HRMS m/z 406.2140 (calcd for $C_{26}H_{30}O_4$ 406.2144). Anal. Calcd for $C_{26}H_{30}O_4$: C, 76.82; H, 7.44. Found: C, 76.69; H, 7.57.

General Procedure for the Asymmetric Reduction of α-Keto Esters 5. To a solution of **5a** (0.12 g, 0.26 mmol) in THF (2.0 mL) was added a solution of L-Selectride (0.26 mmol, 1.0 M in THF, 0.26 mL) dropwise at −78 °C under N_2 atmosphere. The resulting mixture was stirred for 30 min and quenched with H_2O. The aqueous layer was extracted with ethyl acetate (2 × 20 mL). The combined extracts were washed (brine), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography, using hexane/ethyl acetate (16:1) as eluent, to give 0.11 g (92%) of **6a** as a white solid: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.81 (d, 2H, J = 8.6 Hz), 7.55 (d, 2H, J = 8.6 Hz), 7.42−7.07 (m, 11H), 5.15 (dd, 1H, J = 8.1, 3.3 Hz), 4.57 (d, 1H, J = 3.3 Hz), 3.26 (s, 1H), 3.13 (d, 1H, J = 3.5 Hz), 2.23 (td, 1H, J = 12.3, 4.2 Hz), 2.04−1.80 (m, 2H), 1.60−1.40 (m, 2H), 1.36 (t, 1H, J = 4.4 Hz), 1.13 (ddd, 1H, J = 9.3, 8.1, 4.4 Hz), 0.90 (s, 3H), 0.56 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 171.72, 149.41, 143.24, 137.96, 129.24, 129.02, 128.61, 128.36, 127.04, 126.99, 126.94, 126.44, 126.05, 83.85, 81.44, 73.11, 59.24, 51.55, 47.79, 38.37, 31.39, 27.08, 23.73, 22.65; IR (film) 3580, 2952, 1737, 1183, 749 cm^{-1}; HRMS m/z 456.2296 (calcd for $C_{30}H_{32}O_4$ 406.2144). Anal. Calcd for $C_{30}H_{32}O_4$: C 79.09; H 6.86. Found: C 78.97; H 6.99.

6b: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.73 (d, 2H, J = 7.9 Hz), 7.59 (d, 2H, J = 7.9 Hz), 7.31−7.09 (m, 6H), 5.26 (dd, 1H, J = 8.0, 3.6 Hz), 3.85 (q, 1H, J = 7.0 Hz), 3.65 (br, 1H), 2.58 (br, 1H), 2.29 (td, 1H, J = 12.3, 4.3 Hz), 2.03−1.95 (m, 2H), 1.82−1.67 (m, 2H), 1.54−1.40 (m, 1H), 1.50 (s, 3H), 1.23 (d, 3H, J = 7.0 Hz), 1.23−1.20 (m, 1H), 0.65 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 173.02, 149.15, 143.13, 128.39, 128.29, 128.04, 126.83, 126.63, 126.24, 125.91, 82.80, 81.32, 66.30, 59.20, 51.46, 47.70, 38.40, 31.13, 26.93, 24.51, 22.50, 19.81; IR (film) 3520, 2989, 2939, 1738 cm^{-1}; HRMS m/z 394.2148 (calcd for $C_{25}H_{30}O_4$ 394.2144). Anal. Calcd for $C_{25}H_{30}O_4$: C, 76.11; H, 7.66. Found: C, 76.01; H, 7.58.

6c: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.76 (d, 2H, J = 7.5 Hz), 7.59 (d, 2H, J = 7.5 Hz), 7.36−7.11 (m, 6H), 5.26 (dd, 1H, J = 7.9, 3.5 Hz), 3.71 (td, 1H, J = 6.6, 4.5 Hz), 3.60 (s, 1H), 2.24 (td, 2H, J = 12.0, 4.2 Hz), 1.97 (q, 2H, J = 7.2 Hz), 1.82−1.52 (m, 4H), 1.49 (s, 3H), 1.52−1.43 (m, 1H), 1.25−1.16 (m, 1H), 0.86 (t, 3H, J = 7.2 Hz), 0.65 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 172.67, 149.04, 143.08, 128.37, 128.08, 126.84, 126.65, 126.25, 125.85, 82.89, 81.32, 70.77, 59.18, 51.43, 47.70, 38.42, 31.12, 26.92, 26.84, 24.46, 22.51, 8.59; IR (film) 3541, 2968, 2880, 1730, 750 cm^{-1}. Anal. Calcd for $C_{26}H_{32}O_4$: C, 76.44; H, 7.90. Found: C, 76.44; H, 7.87.

7d: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.53−7.51 (m, 2H), 7.48−7.36 (m, 2H), 7.35−7.12 (m, 11H), 4.87 (s, 1H), 4.78 (dd, 1H, J = 7.8, 2.8 Hz), 2.73−2.63 (m, 1H), 2.61 (s, 3H), 1.78 (dd, 1H, J = 13.2, 7.8 Hz), 1.62−1.47 (m, 2H), 1.38−1.33 (m, 1H), 1.05−0.94 (m, 1H), 0.90 (s, 3H), 0.85−0.78 (m, 1H), 0.66 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 171.50, 139.40, 139.11, 131.15, 129.80, 128.71, 128.55, 127.36, 127.04, 126.96, 126.81, 87.93, 83.30, 74.15, 60.99, 52.57, 49.72, 49.09, 39.42, 31.24, 25.70, 22.89, 22.83; IR (film) 3502, 2937, 1727, 1054, 744 cm^{-1}; HRMS m/z 470.2455 (calcd for $C_{31}H_{34}O_4$ 470.2457). Crystal data for **7d** at 23 °C: $C_{31}H_{34}O_4$, M 470.58, orthorhombic, $P2_12_12_1$, a = 11.3199(2) Å, b = 13.16400(10) Å, c = 17.2638(3) Å, V = 2572.57 Å^3, Z = 4, λ = 0.71073 Å, F(000) = 1008, D_c = 1.215 Mg/m^3, μ = 0.079 mm^{-1}, 10668 reflections, 316 parameters, R = 0.1121, R_w = 0.1998 for all data.

General Procedure for the Asymmetric Reduction of α-Keto Esters 5 in the Presence of Additive. To a solution of **5d** (0.20 g, 0.43 mmol) and HMPA (0.09 mL, 0.51 mmol) in THF (5 mL) was added a solution of L-Selectride (0.43 mmol, 1.0 M in THF, 0.43 mL) dropwise at −78 °C under N_2 atmosphere. This was allowed to stir for 3 h and quenched with H_2O. The aqueous layer was extracted with ethyl acetate (2 × 20 mL). The combined extracts were washed (brine), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography, using hexane/ethyl acetate (10:1) as eluent, to give 0.15 g (75%) of **6d** as a white solid: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.77−7.74 (m, 2H), 7.52 (d, 2H, J = 7.0 Hz), 7.42−7.37 (m, 6H), 7.28−7.26 (m, 3H), 7.04−6.99 (m, 2H), 4.81 (dd, 1H, J = 7.9, 3.3

Hz), 4.68 (s, 1H), 3.43 (br, 1H), 2.80 (s, 3H), 2.67 (t, 1H, J = 10.9 Hz), 1.65−1.47 (m, 2H), 1.28−1.12 (m, 2H), 1.09 (s, 3H), 0.88−0.81 (m, 2H), 0.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 172.49, 139.88, 138.94, 137.79, 131.48, 129.42, 128.37, 128.30, 127.49, 127.11, 127.04, 126.86, 126.73, 87.70, 82.59, 72.61, 60.83, 52.67, 50.09, 48.73, 38.49, 31.40, 25.12, 22.94, 22.87; IR (film) 3508, 2934, 1727, 1184, 742 cm^{-1}; HRMS m/z 470.2456 (calcd for $C_{31}H_{34}O_4$ 470.2457). Anal. Calcd for $C_{31}H_{34}O_4$: C, 79.12; H, 7.28. Found: C, 79.04; H, 7.39.

General Procedure for the Hydrolysis of α-Hydroxyl Esters 6a−c. To a solution of **6a** (0.14 g, 0.31 mmol) in THF/H_2O (10 mL, 1:1) was added LiOH (50.3 mg, 1.20 mmol) portionwise at room temperature. The resulting mixture was stirred for 2 h. The organic solvent was removed *in vacuo*, and the residue was extracted with ethyl acetate (2 × 20 mL). The combined extracts were washed (brine), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography, using hexane/ethyl acetate (10:1) as eluent, to give 98 mg (97%) of **4a** as a white foam (recovered **4a**: $[\alpha]_D$ +164.8° (*c* 1.0, $CHCl_3$); original compound **4a**: $[\alpha]_D$ +166.1° (*c* 1.0, $CHCl_3$)).[3] The aqueous layer was acidified (pH = 1) with 2 N HCl and extracted with ethyl acetate (3 × 20 mL). The combined extracts were washed (brine), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was purifed by flash column chromatography, using hexane/ethyl acetate (4:1) as eluent, to give 39.3 mg (84%) of **8a**: $[\alpha]_D$ +145.0° (*c* 2.8, H_2O).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **2**, **3**, **4a**, **4b**, **5a**−**d**, **6a**−**d**, and **7d** and X-ray crystallographic data (table of atomic coordinates, hydrogen coordinates, bond lengths and angles and ORTEP diagrams) for structures **5a**, **5d**, and **7d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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