A General, Highly Anti-Stereoselective Aldolization Method via Camphor-Derived Boryl Enolates

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Camphor-derived chiral boryl enolates are highly reactive and highly anti-stereoselective enolate synthon systems in aldol addition reactions promoted by a $TiCl_4$ or $SnCl_4$ cocatalyst. More significantly, this high-yield reaction exhibits remarkable generality with respect to the aldehyde nature, as illustrated by the rapid and anti-stereoselective aldolizations with the simple saturated and unsaturated aliphatic aldehydes, and aromatic aldehydes at temperatures as low as −90 °C. The enhanced reaction generality and anti stereoselectivity of camphor-derived boryl enolates suggests the importance of the nature of chiral auxiliary architecture in determining the aldol bond construction process. Final nondestructive camphor-based auxiliary removal via hydroperoxide-mediated hydrolysis affords enantiomerically pure anti-β-hydroxy-α-methyl aldol products.

Introduction

While great strides in asymmetric induction has been made in the development of chiral enolate synthon systems and metal-assisted aldol type reactions,[1,2] control of the facial selectivity in the aldol additions of chiral enolates represents an attractive challenge. The tremendous impact of metal Lewis acid nature[3−5] and stoichiometry[6] in reversing π-facial selection illustrates the importance of the problem. Over the last decade, progress in the development of promising chiral metal enolate systems for achieving the high levels of facial selection in the preparation of anti aldol addition products has been slow, despite the significant utility that metal-assisted aldol bond construction processes would enjoy in the asymmetric synthesis of syn aldols.[2−5] Recently, Heathcock repotrted that *E* enolate **1** derived fromthe chiral silyloxy ketone afforded useful levels of asymmetric induction (typically >95:5) upon reaction with saturated aldehydes[7] however, the general applicability of aldol additions involving enolate **1** is limited, and the source of chirality inherent in the silyloxy ketone is not recoverable and recyclable. Later Heathcock and co-workers made the crucial discovery that dibutylboryl triflate-mediated aldolizations of *Z* enolate derived from the Evans chiral imide gave mainly the anti aldols. However, only the α-substituted aldehydes were highly stereoselective (90:10 to 95:5).[6a] In contrast to the hindered aldehydes, simple aliphatic (saturated or unsaturated) and aromatic aldehydes were somewhat less stereoselective.[6] Helmchen and Oppolzer have also made parallel observations with silyl ketene acetals.[8ab] In the extensive survey of the valine-derived chiral imide enolates, it has been shown by Heathcock et al. that further increase in the steric requirements of the enolate ligand substituent (R′) diminished anti selection (cf. **2** and **3**, Scheme 1).[6a] We contended that this limited anti/syn selectivity was not due to insufficient orientation control of the enolate ligand but to insufficient facial discrimination of the aldehyde carbonyl by the chiral auxiliary architecture. A recent study from this laboratory suggests that the chiral camphor-based oxazolidinones, which are excellent auxiliaries for the metal-assisted aldol reactions of acetate[5b,c] and propionate[5a] imide enolates with aldehydes, might also be effective in anti-stereoselective aldolizations. Quite recently, Oppolzer has reported an efficient asymmetric synthesis of anti aldols from bornanesultam-derived boryl enolates,[9] a

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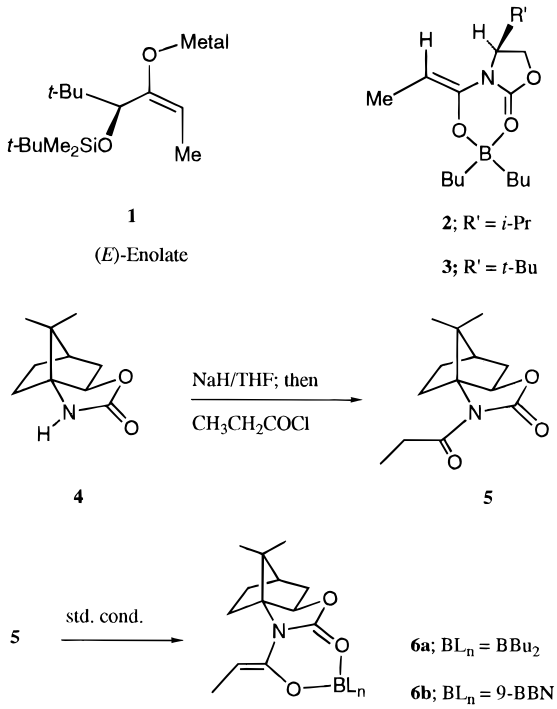
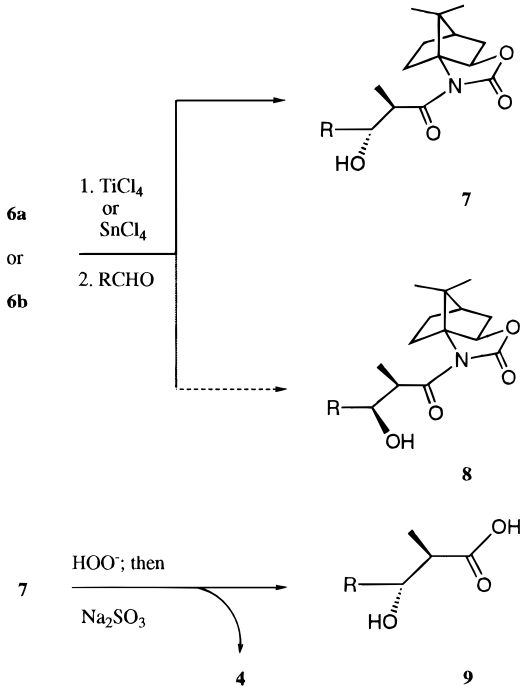
Scheme 1



Scheme 2



RCHO:

a; R = *i*-C_3H_7 b; R = *n*-C_2H_5

c; R = *n*-C_3H_7 d; R = (*E*)-$CH_3CH{=}CH$

e; R = (*E*)-$CH_3(CH_2)_2CH{=}CH$ f; R = C_6H_5

g; R = 2-Furyl

result that also indicates that the camphor-derived boryl imide enolate may exhibit reaction generality and high anti stereoselectivity. We wish to report herein a general and highly anti-stereoselective aldolization method via camphor-derived imide enolates, with the discovery that the nature of the chiral auxiliary architecture may play an influencing role in determining the aldol bond construction process.

Results and Discussion

Boryl triflate (L_nBOTf)[3,5−7] and titanium tetrachloride ($TiCl_4$)[4a,5a,d] have proven to be excellent metal catalysts of choice in the aldolizations of imide enolates with aldehydes. Earlier work in our laboratories also indicates that camphor-based oxazolidinones, which are excellent chiral auxiliaries to effect the syn facial selectivity switch of propionate imide enolates[5a] and the enantioselective aldol type reactions of acetate imide enolate,[5b,c] might also be effective in asymmetric synthesis of anti aldols. In the preliminary study we sought to establish the feasibility of $TiCl_4$ as a cocatalyst to effect high levels of anti selectivity in the aldol addition reactions of camphor-derived dibutylboryl enolate **6a** with isobutyraldehyde. Previously reported camphor-based oxazolidinone **4** was treated successively with NaH and the propionyl chloride to afford imide **5** (Scheme 1).[5] Dibutylboryl enolate **6a** was generated by the standard procedure.[3,5] Treatment of enolate **6a** with $TiCl_4$ (0.6 equiv, −90 °C, 5 min) and isobutyraldehyde led within 20 min to aldol **7a** in good yield. The crude aldol adduct showed a single set of peaks in the high-field NMR spectrum suggestive of complete asymmetric induction. Assignment of the threo configuration is based on the ^1H NMR vicinal coupling using the well-established fact that J_{threo} (7−9 Hz) > $J_{erythro}$ (3−6 Hz),[10] and the absolute stereochemical assignments of the anti aldol **7a** was made via nondestructive removal of the chiral auxiliary and correlation of the resultant β-hydroxy-α-methyl carboxylic acid **9a**.[6a,8a,b] Having established the feasibility of the use of a combination of $TiCl_4$ and camphor-based boryl enolate to effect a high level of anti stereocontrol, we established its generality with respect to the aldehyde nature. Using a standard protocol, a series of representative aldehydes were reacted to give aldol adducts **7a**−**g** (Scheme 2). We were pleased to observe that the absence of the α-methyl substitution does not appear to exert any influence on either the yield or the selectivity of the reaction (Table 1, entries 2, 3; 99:1). In addition, the presence of conjugation in an aldehyde molecule does not alter the reaction anti selectivity. For example, highly anti stereoselective aldolization of simple unsaturated aldehydes (crotonaldehyde and *trans*-2-hexenal) may be realized (entries 4, 5; 99:1). However, aromatic aldehydes do pose a problem. Thus, benzaldehyde and 2-furaldehyde were somewhat less steroselective (entries 6, 8; ∼78:22). Switching the cocatalyst to $SnCl_4$ led to higher reaction anti stereoselectivity (entries 7, 9; ∼88:12). In an effort to further enhance aldol anti selection for aromatic aldehydes, we turned our attention to a redesign of the boryl enolate. In this regard, our previous observations with respect to the effect of the boryl geometry (cyclic vs acyclic) in influencing the reaction stereoselectivity prompted us to examine 9-BBN imide enolate **6b**.[5b,c] It was felt that the enhanced Lewis acid character promoted by the rigid skeletal geometry of 9-BBN[11] should increase the binding forces between the boron and the two

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Table 1. Anti-Stereoselective Aldol Additions of Di-*n*-butylboryl Enolate 6a with Representative Aldehydes

entry	electrophile	cocatalyst	anti:syn[a] **7**:**8**	yield[b] (%)	$[\alpha]^{25}_{D}$[c] deg (*c*, $CHCl_3$)	mp, °C
1	Me_2CHCHO	$TiCl_4$	99:1[d]	90	+68.8 (1.0)	158−159
2	EtCHO	$TiCl_4$	99:1[d]	85	+46.2 (0.9)	78−79
3	*n*-PrCHO	$TiCl_4$	99:1[d]	90	+46.1 (1.1)	93−94
4	MeCH=CHCHO	$TiCl_4$	99:1[d]	91	+35.5 (1.8)	81−82
5	*n*-PrCH=CHCHO	$TiCl_4$	99:1[d]	85	+26.2 (3.6)	−
6	PhCHO	$TiCl_4$	78:22	89	−5.4 (2.1)	159−160
7	PhCHO	$SnCl_4$	88:12	86	−	−
8	(2-furyl)-CHO	$TiCl_4$	78:22	88	+13.5 (2.6)	105−106
9	(2-furyl)-CHO	$SnCl_4$	87:13	85	−	−

[a] Ratios determined by 300-MHz ^{1}H NMR. [b] Combined isolated yield of all diastereomers. [c] Optical rotation of purified anti diastereomers **7**. [d] None of the syn diastereomers could be detected by ^{1}H NMR.

Table 2. Anti-Stereoselective Aldol Additions of 9-BBN Enolate 6b with Representative Aldehydes

					9	
entry	electrophile	cocatalyst	anti:syn[a] **7**:**8**	yield[b] (%)	$[\alpha]^{25}_{D}$, deg (g/100 mL)[c]	$[\alpha]^{25}_{D}$, deg (lit. ref)
1	Me_2CHCHO	$TiCl_4$	99:1[d]	86	−17.6 (0.49)	−15.3 (8a); −14.3 (7)
2	EtCHO	$TiCl_4$	99:1[d]	85	−6.4 (0.68)	−5.9 (8a)
3	*n*-PrCHO	$TiCl_4$	99:1[d]	86	−5.4 (0.44)	−5.0 (8a)
4	MeCH=CHCHO	$TiCl_4$	99:1[d]	84	+11.6 (0.42)[e]	−
					−6.2 (0.91)[f]	−5.0 (8a)
5	*n*-PrCH=CHCHO	$TiCl_4$	99:1[d]	84	+14.8 (2.8)	−
6	PhCHO	$TiCl_4$	88:12	89	−54.3 (0.34)	−49.0 (8a); −17.5 (7)
7	PhCHO	$SnCl_4$	96:4	86	−	−
8	(2-furyl)-CHO	$TiCl_4$	88:12	88	−36.6 (0.10)	−
9	(2-furyl)-CHO	$SnCl_4$	94:6	84	−	−

[a] Ratios determined by 300-MHz ^{1}H NMR. [b] Combined isolated yield of all diastereomers. [c] All rotations were measured in $CHCl_3$. [d] None of the syn diastereomers could be detected by ^{1}H NMR. [e] Hydrogenation of the anti aldol **9d** afforded the saturated anti aldol which proved to be identical in all respects with those of **9c**. [f] Hydrogenation of the anti aldol **9d** followed by hydroperoxide-assisted hydrolysis.

carbonyl oxygen atoms, thereby resulting in "transition state compression" which appears to enhance the π-facial stereoselection. As expected, the aldol addition reactions from 9-BBN imide enolate **6b** exhibited high anti stereoselection in the presence of a cocatalyst $TiCl_4$. More significantly, in the aldolizations of aromatic aldehydes, dramatic enhancement in anti selectivity was noted when the tin chloride ($SnCl_4$) was employed as a cocatalyst (Table 2, entries 7, 9; ≥94:6). These comparative experiments highlight the contribution to aldol diastereoselectivity due to the nature of boryl triflates.[5bc,12]

The results in Table 1 and 2 clearly demonstrate that camphor-derived oxazolidinone serves as an excellent chiral auxiliary for asymmetric synthesis of anti aldols. It is noteworthy that the $TiCl_4$-assisted aldol addition reactions of camphor-based boryl imide enolates **6a** and **6b** are highly anti-selective. These results are in marked contrast to those of Heathcock and co-wokers who observed that $TiCl_4$ was syn-selective in the aldolizations of the valine- and *tert*-leucine-derived boryl enolates **2** and **3**.[6a] In view of the observations of Heathcock with respect to the limited steric contribution to aldol anti stereoselection due to the appended side chain in **2** and **3**,[6a] it was felt that some property of the camphor-based auxiliary is important to the observed excellent anti stereoselectivity of the aldolizations of **6a** and **6b**. Given the reasonable postulate that in the presence of a cocatalyst the aldolization proceeds via open transition states,[6,13] syn and anti aldols are derived from the open transition states **E** and **T**, respectively (Scheme 3). A reasonable explanation of the high levels of anti stereoselection achieved with camphor-based boryl enolates derives from consideration of the relative stability of **E** and **T**. In the aldol transition state represented by **E**, the large group R projects toward the ring methylene ($-CH_2CH_2-$), encountering a severe nonbonded interaction. Such a nonbonded interaction is between the small hydrogen atom and ring methylene in transition state **T**. On this basis, the latter would be favored. The presence of steric repulsion between the methyl group and the bulky group $OTiCl_4$ further destabilize transition state **E**, thereby precluding formation of syn aldols **8**. While further mechanistic work is clearly required, the implication from the above data is that the chiral auxiliary architecture plays an important role in influencing the aldol anti stereoselectivity.

Conclusions

The preceding studies highlight the improved face-shielding capability of camphor-based boryl enolates which exhibit remarkable reaction generality and high levels of anti stereoselectivity in the aldol bond construction process. In addition, this work exemplifies once more the general applicability of camphor-derived chiral oxazolidinone as a practical chiral auxiliary for asym-

(11) The rigid 9-BBN moiety had proven to be less sensitive to steric factors than of dialkylboryl in hydroboration reactions, see: Smith, K.; Pelter, A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 8, Chapter 3, p 703.

(12) For examples of the reaction stereoselectivity switch by boryl geometry (*n*-Bu_2B-OTf vs 9-BBN-OTf), see: (a) Inoue, T.; Uchimaru, T.; Mukaiyama, T. *Chem. Lett.* **1977**, 153. (b) Hirama, M.; Garvey, D. S.; Lu, D.-L.; Masamune, S. *Tetrahedron Lett.* **1979**, 3937.

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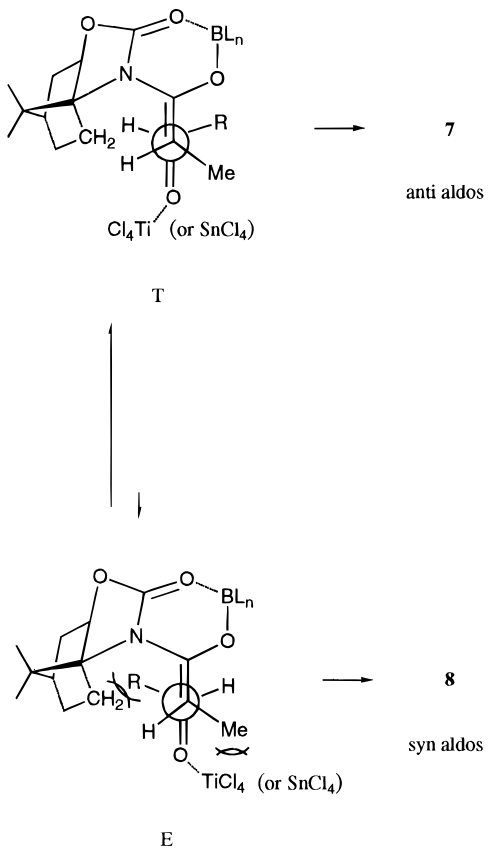
Scheme 3



metric aldol type reactions.[5] Of particular note is the enhanced reactivity[14] and diastereoselectivty promoted by $TiCl_4$ and $SnCl_4$ in camphor-based boryl enolate aldol bond constructions. Significantly, high yields of optically pure anti aldols are easily obtained either by recrystallization or flash chromatography. The high incidence of crystallinity associated with the camphor-derived auxiliary is of great practical advantage (Table 1). Finally, the nondestructive chiral auxiliary removal together with the aforementioned advantages and the remarkable ease of preparation of **4** make camphor-derived boryl imide enolates attractive choices for the asymmetric synthesis of anti aldol products.

Experimental Section

General. Diisopropylethylamine and dichloromethane were dried by distillation under N_2 from calcium hydride. Sodium hydride (80% dispersion in mineral oil), Bu_2B-OTf (1 M in CH_2Cl_2), 9-BBN-OTf (0.5 M in hexane), $TiCl_4$ (1 M in CH_2Cl_2) and $SnCl_4$ (1 M in CH_2Cl_2) were purchased from Aldrich Chemical Co. All aldehydes were freshly distilled prior to use. Unless otherwise noted, all nonaqueous reactions were carried out under a dry nitrogen atmosphere with oven-dried glassware. Flash chromatography was done on E. Merck silica gel 60 (230−400 mesh).[15] Melting points (Pyrex capillary) are uncorrected. Concentrations for rotation data are given as g/100 mL of solvent. Diastereomeric excesses (de) were determined by 300-MHz ^{1}H NMR. All NMR spectra were measured in $CDCl_3$ solution. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane; coupling constants are expressed in hertz.

***N*-Propionyl-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-oxo-2-aza-4-oxatricyclo[6.2.1.0^{1,5}]decane (5).** To a solution of sodium hydride (1.8 g, 75 mmol) in 200 mL of anhydrous THF at 0 °C was added a solution of (9.05 g, 50 mmol) of oxazolidinone **4** in 100 mL of dry THF. The mixture was stirred at 0 °C for 30 min, allowed to warm to room temperature for an additional 5 h, and then recooled to 0 °C. To the above solution was added via cannula a solution of 5.2 mL (60 mmol) of propionyl chloride in 30 mL of dry THF. The resulting solution was stirred at 0 °C for 1 h and 25 °C for 2 h. The reaction mixture was recooled to 0 °C and quenched with 2 N HCl (15 mL). Following removal of the THF in vacuo on the rotary evaporator, the residue was diluted with 300 mL of dichloromethane and 50 mL of water. The organic extract was washed successively with saturated aqueous sodium bicarbonate and brine, dried ($MgSO_4$), and concentrated in vacuo to yield **5** (11.6 g, 98%) as a viscous oil, which was used without purification. A small portion was purified by flash chromatography on silica gel for analysis: R_f 0.35 (30% hexane/dichloromethane); IR (neat) 2968, 1786, 1710 cm^{-1}; ^{1}H NMR (300-MHz, $CDCl_3$) δ 4.20 (dd, J = 7.8, 4.8 Hz, 1H), 3.20−1.21 (m, 9H), 1.13 (t, J = 10.8 Hz, 3H), 1.11 and 0.99 (2s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 175.1, 154.8, 84.4, 71.9, 47.9, 42.1, 34.4, 29.7, 25.7, 25.5, 21.3, 18.9, 8.1; $[\alpha]^{25}_D$ +58.4° (*c* 13, CH_2Cl_2); high-resolution MS *m*/*e* Calcd for $C_{13}H_{19}NO_3$: 237.1365. Found: 237.1365. Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.85; H, 8.07; N, 5.91. Found: C, 65.63; H, 8.03; N, 5.92.

General Procedure for the Aldol Type Reactions of Boryl Enolates 6a and 6b. Di-*n*-butylboryl triflate (1 M in CH_2Cl_2, 0.55 mL) was added dropwise to a stirred solution of the *N*-propionyloxazolidinone **5** (0.5 mmol) in 2.5 mL of dichloromethane at 0 °C. After stirring at 0 °C for 10 min, 0.6 mmol of diisopropylethylamine (0.5 M in CH_2Cl_2, 1.2 mL) was added dropwise. After allowing 30 min for complete enolization, the resulting enolate solution was cooled to −90 °C, and 0.3 mmol of $TiCl_4$ or $SnCl_4$ (1 M in CH_2Cl_2, 0.3 mL) was added dropwise. To the above solution was added 0.6 mmol of freshly distilled aldehyde (0.3 M in CH_2Cl_2, 2 mL). The reaction mixture was stirred at −90 to −78 °C for 20 min and quenched with aqueous phosphate buffer (pH = 7, 4 mL). In the case of 9-BBN enolate **6b**, the reaction mixture was quenched at 0 °C. The aqueous layer was extracted with two portions of CH_2Cl_2 . The combined organic extracts (16 mL) were cooled to 0 °C and treated with a mixture of 4 mL of methanol and 2 mL of 28% H_2O_2. After stirring at 0 °C for 20 min, the organic layer was separated and washed successively with saturated aqueous NH_4Cl (4 mL), aqueous NaOH (1 N, 3 mL), and brine. The organic extract was dried ($MgSO_4$) and concentrated in vacuo. The residue was subjected to NMR analysis and purification by flash chromatography or recrystallization.

***N*-[(2*R*,3*R*)-3-Hydroxy-2,4-dimethylpentanoyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-thioxo-2-aza-4-oxatricyclo-[6.2.1.0^{1,5}]decane (7a).** As described above, **5** (118 mg, 0.5 mmol) and isobutyraldehyde (44 mg, 0.6 mmol) afforded a crude reaction mixture. Analysis [300-MHz ^{1}H NMR integration of the C-2 and/or C-3 methine protons (C*H*OH and $CH_3CHC{=}O$)] of the unpurified product indicated the presence of a single aldol adduct. Purification by recrystallization (CH_2Cl_2/hexane) gave 139 mg (90%) of **7a** as a white solid: mp 158−159 °C; IR (KBr) 3516, 2980, 1770, 1714, 1456, 1392, 1080 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.24 (dd, J = 8.4, 4.2 Hz, 1H), 3.99 (quintet, J = 7.2 Hz, 1H), 3.42 (m, 1H), 2.99−1.19 (m with d at 2.93, J = 10.5 Hz, 9H), 1.16 (d, J = 7.2 Hz, 3H), 1,14 and 1.04 (2s, 6H), 0.99 and 0.94 (2d, J = 6.9 Hz, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 178.6, 155.8, 84.6, 79.7, 72.7, 48.3, 42.2, 41.1, 34.5, 30.3, 25.9, 25.5, 21.5, 19.8, 18.9, 15.2, 15.1; $[\alpha]^{25}_D$ +68.8° (*c* 1.0, $CHCl_3$); high-resolution MS *m*/*e* calcd for $C_{17}H_{27}NO_4$: 309.1941. Found: 309.1942. Anal. Calcd for $C_{17}H_{27}NO_4$: C, 65.99; H, 8.80; N, 4.53. Found: C, 65.79; H, 8.69; N, 4.51.

***N*-[(2*R*,3*R*)-3-Hydroxy-2-methylpentanoyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-thioxo-2-aza-4-oxatricyclo[6.2.1.0^{1,5}]-decane (7b).** As described above, **5** (118 mg, 0.5 mmol) and *n*-propionaldehyde (35 mg, 0.6 mmol) afforded a crude reaction mixture. Analysis [300-MHz ^{1}H NMR integration of the C-2

(14) While complete conversion to aldol adducts **7** occurred within 20 min at −90 to −70 °C, the corresponding aldol addition of valine-based enolate **2** with Lewis acid-precomplexed aldehyde required 4 h at −78 °C. This differential reactivity is important to the high-yield anti-stereoselective aldolization of boryl enolate **6**.

(15) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

and/or C-3 methine protons (C*H*OH and $CH_3CHC{=}O$)] of the unpurified product indicated the presence of a single aldol adduct. Purification by flash chromatography (silica gel, 15% ethyl acetate/hexane, R_f 0.35) yielded 126 mg (85%) of **7b** as a white solid: mp 78−79 °C; IR (KBr) 3532, 2944, 1785, 1710, 1464, 1377,1305, 1077 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.25 (dd, J = 8.4, 4.5 Hz, 1H), 3.88 (quintet, J = 7.2 Hz, 1H), 3.55 (m, 1H), 3.01−1.20 (m with d at 2.78, J = 9.6 Hz, 10H), 1.18 (d, J = 7.2 Hz, 3H), 1.16 and 1.05 (2s, 6H), 1.02 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 178.3, 155.7, 84.6, 76.3, 72.7, 48.4, 43.5, 42.3, 34.6, 27.9, 26.0, 25.7, 21.6, 19.0, 15.0, 9.7; $[\alpha]^{25}_D$ +46.2° (*c* 0.9, $CHCl_3$); high-resolution MS *m*/*e* calcd for $C_{17}H_{27}NO_4$: 295.1784. Found: 295.1778. Anal. Calcd for $C_{16}H_{25}NO_4$: C, 65.06; H, 8.53; N, 4.74. Found: C, 64.87; H, 8.45; N, 4.94.

***N*-[(2*R*,3*R*)-3-Hydroxy-2-methylhexanoyl]-(1*S*, 5*R*, 7*R*)-10,10-dimethyl-3-thioxo-2-aza-4-oxatricyclo[6.2.1.0^{1,5}]-decane (7c)**. As described above, **5** (118 mg, 0.5 mmol) and *n*-butylaldehyde (44 mg, 0.6 mmol) afforded a crude reaction mixture. Analysis [300-MHz ^1H NMR integration of the C-2 and/or C-3 methine protons (C*H*OH and $CH_3CHC{=}O$)] of the unpurified product indicated the presence of a single aldol adduct. Purification by recrystallization (CH_2Cl_2/hexane) gave 139 mg (90%) of **7c** as a white solid: mp 93−94 °C; IR (KBr) 3524, 2968, 2884, 1780, 1696, 1416, 1380, 1234, 1180 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.25 (dd, J = 8.1, 4.2 Hz, 1H), 3.87 (quintet, J = 7.2, 1H), 3.63 (m, 1H), 3.01−1.21 (m with d at 2.76, J = 9.6 Hz, 12H), 1.18 (d, J = 7.2 Hz, 3H), 1.15 and 1.04 (2s, 6H), 0.94 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 178.3, 155.7, 84.6, 74.6, 72.7, 48.4, 43.9, 42.3, 37.4, 34.6, 26.0, 25.7, 21.6, 19.0, 18.5, 14.9, 13.9; $[\alpha]^{25}_D$ +46.1° (*c* 1.1, $CHCl_3$); high-resolution MS *m*/*e* calcd for $C_{17}H_{27}NO_4$: 309.1941. Found: 309.1938. Anal. Calcd for $C_{17}H_{27}NO_4$: C, 65.99; H, 8.80; N, 4.53. Found: C, 65.82; H, 8.71; N, 4.63.

***N*-[(2*R*,3*R*)-3-Hydroxy-2-methyl-4-hexenoyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-thioxo-2-aza-4-oxatricyclo[6.2.1.0^{1,5}]-decane (7d).** As described above, **5** (118 mg, 0.5 mmol) and crotonaldehyde (43 mg, 0.6 mmol) gave a crude reaction mixture. Analysis [300-MHz ^1H NMR integration of the C-2 and/or C-3 methine protons (C*H*OH and $CH_3CHC{=}O$)] of the unpurified product indicated the presence of essentially a single aldol adduct. Purification by flash chromatography (silica gel, 15% ethyl acetate/hexane, R_f 0.3) provided 140 mg (91%) of **7d** as a white solid: mp 81−82 °C; IR (KBr) 3496, 2974, 1791, 1710, 1458, 1383, 1077, 1014 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.74 (ddq, J = 15.6, 6.3, 0.6 Hz, 1H), 5.45 (ddq, J = 15.6, 6.9, 1.5 Hz, 1H), 4.25 (dd, J = 8.4, 4.2 Hz, 1H), 4.10 (m, 1H), 3.94 (quintet, J = 7.2 Hz, 1H, 3.02−1.20 (m with d at 1.72, J = 6.0 Hz, 11H), 1.15 (d, J = 7.2 Hz, 1H), 1.14 and 1.04 (2s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 177.7, 155.3, 131.6, 128.2, 84.3, 75.5, 72.5, 48.2, 43.6, 42.1, 34.4, 25.8, 25.6, 21.2, 18.6, 17.4, 14.6; $[\alpha]^{25}_D$ +35.5° (*c* 1.8, $CHCl_3$); high-resolution MS *m*/*e* calcd for $C_{17}H_{25}NO_4$: 307.1784. Found: 307.1781. Anal. Calcd for $C_{17}H_{25}NO_4$: C, 66.43; H, 8.20; N, 4.56. Found: C, 66.36; H, 8.24; N, 4.58.

***N*-[(2*R*, 3*R*)-3-Hydroxy-2-methyl-4-octenoyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-thioxo-2-aza-4-oxatricyclo[6.2.1.0^{1,5}]-decane (7e).** As described above, **5** (118 mg, 0.5 mmol) and (*E*)-2-hexenal (59 mg, 0.6 mmol) gave a crude reaction mixture. Analysis [300-MHz ^1H NMR integration of the C-2 and/or C-3 methine protons (C*H*OH and $CH_3CHC{=}O$)] of the unpurified product indicated the presence of essentially a single aldol adduct. Purification by flash chromatography (silica gel, 15% ethyl acetate/hexane, R_f 0.3) provided 142 mg (85%) of **7e** as a colorless oil: IR (neat) 3502, 2968, 1785, 1713, 1464, 1383, 1179, 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.65 (ddt, J = 15.0, 6.6, 0.6 Hz, 1H), 5.45 (ddt, J = 15.6, 6.9, 1.2 Hz, 1H), 4.25 (dd, J = 8.4, 4.2 Hz, 1H), 4.03 (m, 1H), 3.86 (quintet, J = 7.2 Hz, 1H), 2.94−1.13 (m, 12H), 1.07 (d, J = 7.2 Hz, 3H), 1.07 and 0.97 (2s, 6H), 0.83 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 177.9, 155.6, 133.8, 130.5, 84.6, 75.9, 72.7, 48.4, 43.9, 42.3, 34.6, 34.2, 25.9, 25.8, 22.1, 21.5, 18.9, 14.8, 13.6; $[\alpha]^{25}_D$ +26.2° (*c* 3.6, $CHCl_3$); high-resolution MS *m*/*e* calcd for $C_{19}H_{29}NO_4$: 335.2097. Found: 335.2094. Anal. Calcd for $C_{19}H_{29}NO_4$: C, 68.03; H, 8.71; N, 4.18. Found: C, 67.85; H, 8.64; N, 4.17.

***N*-[(2*R*,3*S*)-3-Hydroxy-2-methyl-3-phenylpropionyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-oxo-2-aza-4-oxatricyclo-[6.2.1.0^{1,5}]decane (7f).** As described above, **5** (118 mg, 0.5 mmol) and benzaldehyde (62 mg, 0.6 mmol) afforded a crude reaction mixture. Diastereomer analysis [300-MHz ^1H NMR integration of the C-2 and/or C-3 methine protons (C*H*(OH)-C_6H_5 and $CH_3CHC{=}O$)] of the unpurified adduct revealed the presence of two aldols **7f** and **8f**. The ratio of **7f** vs **8f** was a function of the boryl enolate and cocatalyst, varying from 78: 22 to 88:12 to 88:12 to 96:4 on switching from **6a**/$TiCl_4$ to **6a**/$SnCl_4$ to **6b**/$TiCl_4$ to **6b**/$SnCl_4$ in CH_2Cl_2. Purification by recrystallization (CH_2Cl_2/hexane) provided 153 mg (89%) of **7f** as a colorless, crystalline solid: mp 159−160 °C; IR (KBr) 3504, 2976, 1778, 1682, 1456, 1384 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45−7.21 (m, 5H), 4.70 (t, J = 8.1 Hz, 1H), 4.37 (quintet, J = 7.2 Hz, 1H), 4.24 (dd, J = 8.4, 4.2 Hz, 1H), 3.49 (d, J = 8.4 Hz, 1H), 3.02−1.21 (m, 7H), 1.09 (d, J = 7.2 Hz, 3H), 1.05 and 0.90 (2s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 178.1, 155.6, 142.4, 128.5, 127.8, 126.6, 84.6, 77.5, 72.7, 48.4, 44.8, 42.3, 34.6, 26.0. 25.8, 21.4, 18.7, 15.2; $[\alpha]^{25}_D$ −5.4° (*c* 2.1, $CHCl_3$); high-resolution MS *m*/*e* calcd for $C_{20}H_{25}NO_4$: 343.1784. Found: 343.1789. Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.33; N, 4.08. Found: C, 69.76; H, 7.28; N, 4.06. **8f**:[5a] mp 43−44 °C; IR (KBr) 3468, 2972, 1784, 1694, 1488 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46−7.20 (m, 5H), 5.15 (t, J = 3.6 Hz, 1H), 4.23 (dq, J = 7.2, 4.2 Hz, 1H), 4.22 (dd, J = 7.8, 4.5 Hz, 1H), 3.04 (d, J = 3 Hz, 1H), 2.98−1.18 (m, 7H), 1.13, (d, J = 6.9 Hz, 3H), 1.026 and 0.878 (2s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 177.9, 154.7, 141.5, 128.1, 127.5, 127.4, 84.4, 73.6, 72.4, 48.1, 44.9, 42.3, 34.6, 25.8, 25.7, 21.3, 18.8, 11.4; $[\alpha]^{25}_D$ +44.2° (*c* 2.4, $CHCl_3$); high-resolution MS *m*/*e* calcd for $C_{20}H_{25}NO_4$: 343.1784. Found: 343.1789. Anal. calcd for $C_{20}H_{25}NO_4$: C, 70.00; H, 7.34; N, 4.08. Found: C, 69.97; H, 7.28; N, 4.05.

***N*-[(2*R*,3*S*)-3-(2-Furyl)-3-hydroxy-2-methylpropionyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-oxo-2-aza-4-oxatricyclo-[6.2.1.0^{1,5}]decane (7g).** As described above, **5** (118 mg, 0.5 mmol) and 2-furaldehyde (58 mg, 0.6 mmol) afforded a crude reaction mixture. Diastereomer analysis [300-MHz ^1H NMR integration of the C-2 and/or C-3 methine protons (C*H*(OH)-furyl and $CH_3CHC{=}O$)] of the unpurified adduct revealed the presence of two aldols **7g** and **8g**. The ratio of **7g** vs **8g** was a function boryl enolate and cocatalyst, varying from 78:22 to 88:12 to 88:12 to 94:6 on switching from **6a**/$TiCl_4$ to **6a**/$SnCl_4$ to **6b**/$TiCl_4$ to **6b**/$SnCl_4$ in CH_2Cl_2. Purification by recrystallization (CH_2Cl_2/hexane) afforded 147 mg (88%) of **7g** as a colorless, crystalline solid: mp 105−106 °C; IR (KBr) 3502, 3010, 2968, 1752, 1713, 1506, 1455, 1378. 1306 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (m, 1H), 6.34−6.32 (m, 2H), 4.73 (t, J = 8.4 Hz, 1H), 4.40 (quintet, J = 7.2 Hz, 1H), 4.26 (dd, J = 8.1, 4.2 Hz, 1H), 3.58 (d, J = 8.4 Hz, 1H), 3.01−1.20 (m, 7H), 1.14 (d, J = 7.2 Hz, 3H), 1.10 and 1.01 (2s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 177.6, 155.5, 154.9, 142.2, 110.2, 107.3, 84.6, 72.6, 71,0, 48.4, 42.7, 42.3, 34.6, 26.0. 25.8, 21.4, 18.8, 14.8; $[\alpha]^{25}_D$ +13.5° (*c* 2.6, $CHCl_3$); high-resolution MS *m*/*e* calcd for $C_{18}H_{23}NO_5$: 333.1576. Found: 333.1574. Anal. calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.89; H, 7.11; N, 4.23. **8g**: IR (neat) 3512, 3008, 2964, 1750, 1710, 1503, 1451, 1379 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (t, J = 1.4 Hz, 1H), 6.32−6.22 (m, 2H), 5.06 (d, J = 5.4 Hz, 1H), 4.28 (dq, J = 6.6, 5.4 Hz, 1H), 4.18 (dd, J = 8.1, 4.2 Hz, 1H), 3.01−1.16 (m with d at 1.21, J = 6.9 Hz, 11H), 0.97 and 0.91 (2s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 177.4, 154.8, 154.7, 142.2, 110.2, 106.7, 84.4, 72.3, 68.5, 48.1, 43.0, 42.2, 34.5, 25.7, 25.6, 21.1, 18.7, 12.5; $[\alpha]^{25}_D$ +44.9° (*c* 4.4, $CHCl_3$); high-resolution MS *m*/*e* calcd for $C_{18}H_{23}NO_5$: 333.1576. Found: 333.1574. Anal. Calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.89; H, 7.11; N, 4.23.

General Procedure for the Hydroperoxide-Assisted Saponification α-Methyl-β-hydroxy Carboxylic acid 9. To a solution of aldol adduct **7** (1 equiv) in THF/H_2O (3:1, 0.16 M) at 0 °C was added a solution of LiOH (6 equiv) in 10 equiv of 28% H_2O_2. The resulting mixture was stirred at 0 °C for 0.5−3 h and treated with a solution of 12 equiv of Na_2SO_3 in H_2O. Following removal of the THF in vacuo on the rotary evaporator, the aqueous residue was diluted with H_2O and extracted with three portions of CH_2Cl_2. The combined CH_2Cl_2

extracts were dried ($MgSO_4$) and evaporated in vacuo to give recovered auxiliary **5** (>95%). The aqueous phase was acidified with 3 N HCl and extracted with three portions of ether. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to afford pure α-methyl-β-hydroxy carboxylic acid **9**. In the case of **9b**, the acid was treated with a solution of CH_2N_2 (excess) in ether at 0 °C. After the reaction mixture was stirred at 0 °C for 1 h, it was concentrated in vacuo to yield the esterification product of **9b**.

(2*R*,3*R*)-2,4-Dimethyl-3-hydroxypentanoic acid (9a): IR (neat) 3472, 3364, 2964, 1700, 1458, 1374 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.10 (bs, 2H), 3.44 (dd, J = 7.2, 6.6 Hz, 1H), 2.69 (quintet, J = 7.2 Hz, 1H), 1.80 (octet, J = 6.6 Hz, 1H), 1.25 (d, J = 7.2 Hz, 3H), 0.99 and 0.94 (2d, J = 6.6 Hz, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 181.3, 78.0, 42.7, 30.5, 19.7, 15.9, 14.7; $[\alpha]^{25}_D$ −17.6° (*c* 0.49, $CHCl_3$); lit.[8a] $[\alpha]^{25}_D$ −15.3° (*c* 1.2, $CHCl_3$); lit.[7] $[\alpha]^{25}_D$ −14.3° (*c* 1.0, $CHCl_3$); high-resolution MS *m*/*e* calcd for $C_7H_{14}O_3$: 146.0943. Found: 146.0947.

(2*R*,3*R*)-2-Methyl-3-hydroxypentanoic acid (9b): IR (neat) 3456, 2940, 1712, 1464, 1264, 1090 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) d 6.58 (bs, 2H), 3.65 (m, 1H), 2.58 (quintet, J = 7.2 Hz, 1H), 1.72−1.41 (m, 2H), 1.23 (d, J = 7.2 Hz, 3H), 0.99 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 180.7, 74.6, 44.8, 27.2, 14.1, 9.6; $[\alpha]^{25}_D$ −6.4° (*c* 0.68, $CHCl_3$); lit.[8a] $[\alpha]^{25}_D$ −5.0° (*c* 0.2, $CHCl_3$); observed $[\alpha]^{25}_D$ values for the methyl ester derived from **9b**: $[\alpha]^{25}_D$ −7.3° (*c* 0.43, $CHCl_3$); lit.[6b] $[\alpha]^{25}_D$ −7.9° (*c* 0.52, $CHCl_3$); lit.[8c] $[\alpha]^{25}_D$ −9.9° (*c* 0.28, $CHCl_3$); high-resolution MS *m*/*e* calcd for $C_6H_{12}O_3$: 132.0787. Found: 132.0789.

(2*R*,3*R*)-2-Methyl-3-hydroxyhexanoic acid (9c): IR (neat) 3488, 3308, 2968, 2736, 2696, 2572, 1716, 1456 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.67 (bs, 2H), 3.71 (m, 1H), 2.56 (quintet, J = 7.2 Hz, 1H), 1.61−1.36 (m, 4H), 1.24 (d, J = 7.2 Hz, 3H), 0.95 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 180.9, 73.0, 45.2, 36.6, 18.6, 14.1, 13.9; $[\alpha]^{25}_D$ −5.4° (*c* 0.44, $CHCl_3$); lit.[8a] $[\alpha]^{25}_D$ −5.0° (*c* 0.2, $CHCl_3$); high-resolution MS *m*/*e* calcd for $C_7H_{14}O_3$: 146.0943. Found: 146.0951.

(2*R*,3*R*)-2-Methyl-3-hydroxy-(*E*)-4-hexenoic acid (9d): IR (neat) 3544, 2986, 1722, 1464, 1263, 969 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.76 (ddq, J = 14.7, 6.6, 0.3 Hz, 1H), 5.43 (ddq, J = 14.7, 7.5, 1.2 Hz, 1H), 4.91 (bs, 2H), 4.16 (dd, J = 7.8, 7.5 Hz, 1H), 2.55 (quintet, J = 7.5 Hz, 1H), 1.73 (dd, J = 6.6, 1.2 Hz, 3H), 1.16 (d, J = 7.5 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 180.3. 130.7, 129.9, 74.8, 45.5, 17.6, 13.9; $[\alpha]^{25}_D$ +11.6° (*c* 0.42, $CHCl_3$); observed $[\alpha]^{25}_D$ values for the hydrogenation (Raney-nickel) product of **9d**: $[\alpha]^{25}_D$ −6.1° (*c* 0.91, $CHCl_3$); lit.[8a] $[\alpha]^{25}_D$ −5.0° (*c* 0.2, $CHCl_3$); high-resolution MS *m*/*e* calcd for $C_7H_{12}O_3$: 144.0786. Found: 144.0781.

(2*R*,3*R*)-2-Methyl-3-hydroxy-(*E*)-4-octenoic acid (9e): IR (neat) 3494, 2972, 1716, 1464, 972 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.76 (ddt, J = 15.3, 6.9, 0.3 Hz, 1H), 5.43 (ddt, J = 15.3, 7.2, 0.3 Hz, 1H), 4.91 (bs, 2H), 4.18 (dd, J = 7.5, 7.2 Hz, 1H), 2.55 (quintet, J = 7.2 Hz, 1H), 2.03 (dt, J = 6.9, 6.6 Hz, 2H), 1.41 (sextet, J = 7.2, 2H), 1.17 (d, J = 7.2 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 180.8. 135.0, 129.5, 74.8, 45.5, 34.2, 22.1, 13.9, 13.5; $[\alpha]^{25}_D$ +14.8° (*c* 2.8, $CHCl_3$); high-resolution MS *m*/*e* calcd for $C_9H_{16}O_3$: 172.1100. Found: 172.1101. Anal. Calcd for $C_9H_{16}O_3$: C, 62.81; H, 9.37. Found: C, 62.79; H, 9.31.

(2*R*,3*S*)-2-Methyl-3-hydroxy-3-phenylpropanoic acid (9f): mp 101−102 °C; IR (neat) 3488, 3028, 2980, 2620, 1686, 1554, 1454 cm^{-1}; ^1H NMR δ (300 MHz, $CDCl_3$) δ 7.41−7.31 (m, 5H), 4.71 (d, J = 8.7 Hz, 1H), 2.86 (dq, J = 8.7, 7.2 Hz, 1H), 1.03 (d, J = 7.2 Hz, 3H); ^{13}C (75.5 MHz, $CDCl_3$) δ 180.3, 141.1, 128.7, 128.4, 126.8, 76.3, 46.9, 14.3; $[\alpha]^{25}_D$ −53.4° (*c* 0.34 $CHCl_3$); lit.[8a] $[\alpha]^{25}_D$ −49.0° (*c* 0.44, $CHCl_3$); lit.[7] $[\alpha]^{25}_D$ −17.5° (*c* 2.3, $CHCl_3$); lit.[8d] $[\alpha]^{25}_D$ −19.7° (*c* 0.094, EtOH); high-resolution MS *m*/*e* calcd for $C_{10}H_{12}O_3$: 180.0787. Found: 180.0790.

(2*R*,3*S*)-2-Methyl-3-hydroxy-3-(2-furyl)propanoic acid (9g): IR (neat) 3452, 3020, 2936, 1726, 1466, 1012, 908 cm^{-1}; ^1H NMR δ (300 MHz, $CDCl_3$) δ 7.41 (bs, 1H), 6.33 (m, 2H), 4.80 (d, J = 8.7 Hz, 1H), 3.06 (quintet, J = 7.2 Hz, 1H), 1.11 (d, J = 7.2 Hz, 3H); ^{13}C (75.5 MHz, $CDCl_3$) δ 180.1, 153.5, 142.6, 110.2, 108.0, 69.5, 44.7, 14.0; $[\alpha]^{25}_D$ −36.6° (*c* 0.1 $CHCl_3$); high-resolution MS *m*/*e* calcd for $C_8H_{10}O_4$: 170.0580. Found: 170.0585. Anal. Calcd for $C_8H_{10}O_4$: C, 56.50; H, 5.93. Found: C, 56.72; H, 5.91.

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