An Unusual Enantioselective Aldol Type Reaction of Acetate Boryl Enolate Derived from Chiral Thioimide

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The camphor-derived *N*-acetyloxazolidinethione has been used to effect enantioselective aldol type reactions of the derived 9-BBN enolate with a variety of aldehydes. Mechanistically, the observed facial selectivity is best explained by a boatlike transition structure.

Introduction

As a consequence of the importance of enantiomerically pure aldol diastereomers, considerable effort has been directed toward the development of chiral enolate synthon systems and metal-mediated aldolizations.[1] The most efficient of these processes involves the use of α-substituted boryl enolates, which provide a pericyclic chairlike transition state leading to exceptionally high levels of aldol asymmetric induction (>99:1).[2] However, the aldol reactions of acetate boryl enolates derived from chiral carbonyl compounds provide a roughly 70:30 mixture of two diastereomeric aldol adducts.[2a,3a,b] A promising solution to this problem is based on the incorporation of an auxiliary substituent in the α-position as reported by Evans.[2a] Later an alternative approach to the solution of this problem has been offered by the work of Nagao who has demonstrated that stannous triflate ($Sn(OTf)_2$)-mediated aldol reactions of chiral thioimide acetate enolate with unsaturated aldehydes give high levels of facial selectivity for the aldol adducts expected from chelation control.[4] Quite recently, although a series of papers make use of chiral boron Lewis catalysts[5a–f] and chiral borolane triflate[5g] to achieve enantioselective aldol addition of unsubstituted silyl enol ethers or ketene acetals to achiral aldehydes (80–93% ee), the asymmetric aldolization of the acetate enolate of a chiral carbonyl compound with aldehydes by using achiral boron Lewis acid has remained an unrealized goal.[6] In this paper we wish to report that this highly enantioselective aldol process can be achieved by the judicious choice of a chiral carbonyl compound[2f,4] and an achiral boryl triflate.

Results and Discussion

Previous reports from our laboratory have documented the utility of *N*-propionyloxazolidinethione **2** for the construction of "Evans" and "non-Evans" syn aldols.[2f] The excellent diastereoselectivity obtained with thioimide enolates[2d,f,4] prompted us to apply this same concept to the aldol additions of thioimide acetate boryl enolate. Indeed, we have discovered that the 9-BBN enolates, generated directly from *N*-acetyl thioimide **3**, participate in highly selective non-chelation-controlled aldol reactions. Acylation of previously reported chiral oxazolidinethione **1**[2f] with acetyl chloride in the presence of sodium hydride led to a nearly quantitative yield of **3** (Scheme 1). The 9-BBN-OTf-mediated aldolizations of **3** to the unsaturated aldehydes were carried out by a standard procedure (1 equiv of **3**, 1.1 equiv of 9-borabicyclo[3.3.1]-non-9-yl triflate (9-BBN-OTf); 1.2 equiv of *i*-Pr_2NEt; and then RCHO, −78 °C).[2] We were pleased to discover that **5** exhibited high levels of asymmetric induction ranging from 85:15 to 99:1 depending on the aldehyde employed (Table 1).[7] Assignment of the absolute configuration was performed by conversion of the aldol adducts **5** to the corresponding acids **7** of known absolute configuration[6,8] using the standard lithium hydroperoxide hydrolysis conditions.[9] While the high stereoselectivity obtained with the 9-BBN acetate enolate **5** was an outstanding result, an even more surprising observation was made concerning the sense of asymmetric induction. We found that **5** gave principally aldol products expected from the addition of boryl enolate to the *re*-face of the aldehyde

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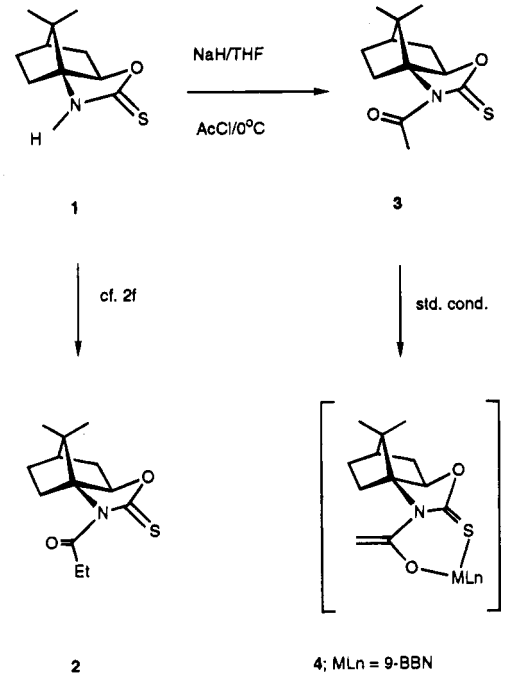
Table 1. Asymmetric Aldol Type Reactions of Thioimide Acetate Boryl Enolate

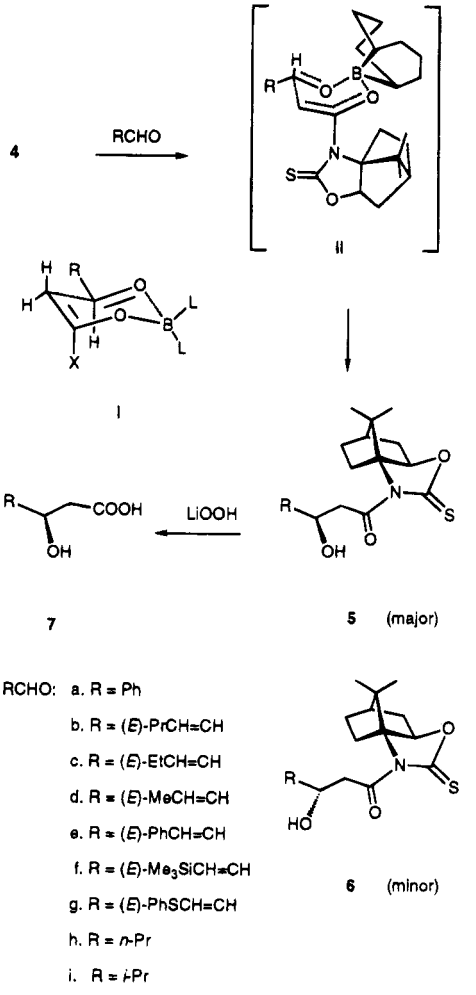
entry	electrophile	enolates	ratio[a] **5:6**	yield[b] (%)	$[\alpha]_D^{25}$ (*c*) **7**	abs config
1	PhCHO	**4**	96:4	86	+20.6° (0.39)[c,d]	*R*
2	(*E*)-PrCH=CHCHO	**4**	>99:1[e]	63	+11.5° (7.8)[c,g]	*R*
3	(*E*)-EtCH=CHCHO	**4**	>99:1[e]	65	−12.5° (1.06)[c]	*R*[h]
4	(*E*)-MeCH=CHCHO	**4**	>99:1[e]	84	+22.5° (0.43)[c]	*R*[h]
5	(*E*)-PhCH=CHCHO	**4**	95:5	61	−19.0° (4.24)[c]	*R*[h]
6	(*E*)-Me_3SiCH=CHCHO	**4**	93:7	59	+8.9° (1.89)[f]	*R*[h]
7	PhSCH=CHCHO	**4**	97:3	78	−20.7° (0.16)[f]	*R*[h]
8	*n*-PrCHO	**4**	87:13	88	+25.7° (0.21)[f,i]	*S*
9	Me_2CHCHO	**4**	86:14	84	+39.9° (2.84)[f,j]	*R*

[a] Ratios determined by 300-MHz ^1H NMR. [b] Combined isolated yield of all diastereomers. [c] In EtOH, if not mentioned otherwise. [d] Literature rotation: $[\alpha]_D$ +14.9° (*c* 1.94, EtOH) (ref. 6g); $[\alpha]_D$ +18.9° (*c* 1.0, EtOH) (ref 8c); $[\alpha]_D$ +17.9° (*c* 2.3, 95%, EtOH) (ref 6h); $[\alpha]_D$ +60.5° (*c* 1.0, $CHCl_3$) (ref 6a). [e] **5** was the only detected aldol by ^1H NMR. [f] $CHCl_3$ was used instead. [g] Literature rotation for antipode of **7b**: $[\alpha]_D$ +16.0° (*c* 0.9, $CHCl_3$) (ref 6a). [h] It seems likely that in view of the uniformly good enantioselection the absolute configuration shown in Table 1 prevails. [i] Literature rotation: $[\alpha]_D$ +25.8° (*c* 0.53, $CHCl_3$) (ref 6a); $[\alpha]_D$ +28.3° (*c* 1.0, $CHCl_3$) (ref 6a). [j] Literature rotation: $[\alpha]_D$ +40.5° (*c* 0.6, $CHCl_3$) (ref 6h); $[\alpha]_D$ +40.2° (*c* 1.2, $CHCl_3$) (ref 8b); $[\alpha]_D$ +41.7° (*c* 1.0, $CHCl_3$) (ref 6a); $[\alpha]_D$ +36.9° (*c* 1.59, $CHCl_3$) (ref 6g).

Scheme 1



Scheme 2



carbonyl. This sense of facial selectivity is opposite to that obtained from the pericyclic chair model **I**, which has been put forth by Evans[2a,3] and Masamune[4] as the preferred transition state for chiral boryl enolate aldol reactions. The absolute configuration corresponds to reaction of the boryl enolate from a nonchelated complex with skewboat arrangement represented by **II** (Scheme 2). The fact that the skew form can be almost the exclusive pathway for the aldol reaction of **5** suggests that boatlike geometry can successfully compete with the chair model in acetate enolate aldolization,[10,11] where the steric contribution of α-substituent is absent.

Conclusions

This study serves to illustrate a striking example of employing the acetate boryl enolate derived from chiral thioimide to obtain high levels of facial selection in aldol reactions. More significantly, in view of the poor stereoselection of the 9-BBN enolate derived from chiral ketone,[1d,5g] the remarkable effect of enolate ligand, thiocarbonyl, on controlling the aldol conformer may provide a powerful new handle for mechanistic analysis of the acetate enolate aldolization. Future work is aimed at disclosing the potential of auxiliary **1** in other types of Lewis acid-catalyzed addition reactions and the control elements governing the aldol bond construction process of boryl acetate enolates. At present, we know that aldol π-facial selection for **4** is a function of the boryl geometry as well as the polar character of imide ring and aldehyde carbonyls.[12]

(10) Hoffmann, R. W.; Ditrich, K.; Froech, S.; Cremer, D. *Tetrahedron* **1985**, *41*, 5517.

(11) Publications discussing and referencing the actual transition geometries of boryl enolate aldol reactions are given in refs 3 and 5g.

(12) T.-H. Yan; A.-W. Hung, manuscript in preparation.

Experimental Section

General. Diisopropylethylamine and dichloromethane were dried by distillation under N_2 from calcium hydride. Sodium hydride (Aldrich Chemical Co.) as a 80% dispersion in mineral oil. All aldehydes were freshly distilled prior to use. Flash chromatography was done as previously described[2f] on E. Merck silica gel 60 (230–400 mesh). Melting points were measured on a Buchi 535 capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Hitachi 270-30 infrared spectrophotometer. Optical rotations were obtained on a Optical Activity AA-100 polarimeter. ^1H and ^{13}C NMR spectra were recorded on either a Varian VXR-300 or Gemini-200 spectrometer at ambient temperature. High-resolution mass spectra were determined on a JEOL JMS-HX 110 spectrometer. Unless otherwise noted, all non-aqueous reactions were carried out under a dry nitrogen atmosphere with oven-dried glassware.

***N*-Acetyl-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-thioxo-2-aza-4-oxatricyclo[5.2.1.0^{1,5}]decane (3).** To a solution of sodium hydride (1.8 g, 75 mmol) in 150 mL of anhydrous THF, stirred at 0 °C under dry N_2, was added via cannula a precooled (0 °C) solution of 9.85 g (50 mmol) of **1**[1f] in 100 mL of dry THF. The mixture was stirred at 0 °C for 25 min and 4.3 mL (4.73 g, 60 mmol, 1.2 equiv) of acetyl chloride was added dropwise over 10 min. The solution is stirred at that temperature for 30 min, and the reaction was quenched with trifluoroacetic acid (80 mmol). THF was removed by rotary evaporation, the resultant slurry was diluted with CH_2Cl_2 (300 mL), and the CH_2Cl_2 solution was washed with two 50 mL portions of saturated aqueous sodium bicarbonate and 50 mL of brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 11.0 g (92%) of the title compound as a white solid. An analytical sample was prepared by recrystallization from dichloromethane/hexane to afford a colorless, crystalline solid: mp 129–130 °C; IR (KBr) 2956, 1710, 1365, 1332, 1275, 1188, 1170 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.45 (dd, J = 8.4, 3.9 Hz, 1H), 2.94–1.19 (m, with s at 2.78, 10H), 1.14 and 1.06 (2s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 188.4, 172.3, 89.4, 76.5, 49.2, 42.5, 34.8, 27.3, 26.0, 25.3, 21.5, 19.2; $[\alpha]_D^{25}$ −64.9° (*c* 7.2, $CHCl_3$); high-resolution MS *m/e* calcd for $C_{12}H_{17}NO_2S$ 239.0980, found 239.0979. Anal. Calcd for $C_{12}H_{17}NO_2S$: C, 60.28; H, 7.17; N, 5.86. Found: C, 60.07; H, 7.26; N, 5.92.

General Procedure for the Aldol Type Reaction of 9-BBN Enolate. To a solution of **3** (1 mmol) in 4 mL of CH_2Cl_2 cooled to 0 °C was added 2.1 mL (0.5 M in hexane, 1.05 mmol, 1.05 equiv) of 9-BBN-OTf. After stirring at 0 °C for 10 min, slow addition of diisopropylethylamine (1 M in CH_2Cl_2, 1.1 mL, 1.1 mmol) and further stirring for 25 min at 0 °C, the reaction mixture was cooled to −78 °C. To the above enolate solution was slowly added a solution of aldehyde (1.2 mmol) in 1 mL of CH_2Cl_2. The reaction mixture was stirred at −78 °C for 2–3 h, allowed to warm to 0 °C, and then quenched with aqueous phosphate buffer (pH = 7), 6 mL of methanol, and 4 mL of 30% H_2O_2. The aqueous layer was extracted with two portions of CH_2Cl_2 (2 × 15 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl (4 mL), and brine (4 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was subjected to ^1H NMR analysis and purified by flash chromatography on silica gel (15% ethyl acetate/hexane).

***N*-[(*R*)-Hydroxy-3-phenylpropionyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-thioxo-2-aza-4-oxatricyclo[5.2.1.0^{1,5}]decane (5a).** As described above, acetyloxazolidinethione **3** (478 mg, 2 mmol) and benzaldehyde (0.25 mL, 260 mg, 2.4 mmol) provided a crude reaction mixture. Diastereomer analysis [300 MHz ^1H NMR integration of the C-2 methylene protons (CH_2C=O) and/or C-3 methine proton (CH(OH)C_6H_5)] of the unpurified adduct revealed the presence of two aldols in the ratio of 96:4. The pale yellow oil was purified by flash chromatography on silica gel (20% ethyl acetate/hexane) afforded 593 mg (86%) of **5a**: IR (neat) 3460, 2956, 1714, 1488, 1454, 1365, 1230, 1170 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43–7.26 (m, 5H), 5.29 (dd, J = 9.3, 2.7 Hz, 1H), 4.42 (dd, J = 8.1, 4.2 Hz, 1H), 3.84 (dd, J = 17.1, 3.0 Hz, 1H), 3.62 (dd, J = 17.1, 9.3 Hz, 1H), 3.18 (bs, 1H), 2.87–1.26 (m, 6H), 1.15 and 1.05 (m with 2s at 1.15 and 1.05, 7H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 188.0, 174.5, 142.4, 128.5, 127.7, 125.8, 90.0, 76.5, 70.2, 49.2, 47.0, 42.4, 34.6, 25.9, 24.8, 21.4, 19.2; $[\alpha]_D^{25}$ +79.1° (*c* 12.51, $CHCl_3$); high-resolution MS *m/e* calcd for $C_{19}H_{23}NO_3S$ 345.1406, found 345.1395.

***N*-[(*R*)-(*E*)-3-Hydroxy-4-octenoyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-thioxo-2-aza-4-oxatricyclo[5.2.1.0^{1,5}]decane (5b).** As described above, acetyloxazolidinethione **3** (239 mg, 1 mmol) and (*E*)-2-hexenal (0.14 mL, 120 mg, 1.2 mmol) provided a crude reaction mixture. Diastereomer analysis by 300 MHz ^1H NMR of the unpurified product indicated the presence of essentially a single aldol adduct. The pale yellow oil was purified by flash chromatography on silica gel (20% ethyl acetate/hexane) afforded 213 mg (63%) of **5b**: IR (neat) 3416, 2956, 1698, 1454, 1369, 1332, 1225, 1196, 1177, 1036, 969 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.72 (dt, J = 15.3, 6.6 Hz, 1H), 5.59 (dt, J = 15.3, 1.2 Hz, 1H), 4.61 (m, 1H), 4.43 (dd, J = 8.1, 4.2 Hz, 1H), 3.66 (dd, J = 17.4, 3.3 Hz, 1H), 3.29 (dd, J = 17.4, 8.7 Hz, 1H), 2.91–1.18 (m with bs at 2.71, 12H), 1.12 and 1.03 (2s, 6H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 188.4, 174.6, 132.6, 130.6, 90.0, 76.5, 68.8, 49.2, 45.8, 42.3, 34.6, 34.1, 25.9, 25.0, 22.0, 21.4, 19.1, 13.5; $[\alpha]_D^{25}$ +74.3° (*c* 3.0, $CHCl_3$); high-resolution MS *m/e* calcd for $C_{18}H_{27}NO_3S$ 337.1711, found 337.1709. Anal. Calcd for $C_{18}H_{27}NO_3S$: C, 64.09; H, 8.01; N, 4.15. Found: C, 63.80; H, 8.03; N, 4.45.

***N*-[(*R*)-(*E*)-3-Hydroxy-4-heptenoyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-thioxo-2-aza-4-oxatricyclo[5.2.1.0^{1,5}]decane (5c).** As described above, acetyloxazolidinethione **3** (239 mg, 1 mmol) and (*E*)-2-pentenal (0.12 mL, 103 mg, 1.2 mmol) provided a crude reaction mixture. Diastereomer analysis by 300 MHz ^1H NMR of the unpurified product indicated the presence of essentially a single aldol adduct. The pale yellow oil was purified by flash chromatography on silica gel (15% ethyl acetate/hexane) afforded 210 mg (65%) of **5c**: IR (neat) 3410, 2955, 1695, 1454, 1369, 1332, 1225, 1196, 1177, 1036, 969 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.80 (dt, J = 15.3, 6.6 Hz, 1H), 5.54 (dt, J = 15.3, 1.2 Hz, 1H), 4.64 (m, 1H), 4.46 (dd, J = 8.1, 4.2 Hz, 1H), 3.68 (dd, J = 17.4, 3.3 Hz, 1H), 3.32 (dd, J = 17.4, 8.7 Hz, 1H), 2.93–1.19 (m with d at 2.75, J = 4.2 Hz, 10 H), 1.12 and 1.03 (2s, 6H), 1.01 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 188.0, 174.5, 134.2, 129.4, 90.0, 76.5, 68.8, 49.3, 45.8, 42.4, 34.7, 25.9, 25.1, 25.0, 21.5, 19.2, 13.2; $[\alpha]_D^{25}$ +76.5° (*c* 8.7, $CHCl_3$); high-resolution MS *m/e* calcd for $C_{17}H_{25}NO_3S$ 323.1555, found 323.1561. Anal. Calcd for $C_{17}H_{25}NO_3S$: C, 63.16; H, 7.74; N, 4.33. Found: C, 63.38; H, 7.67; N, 4.55.

***N*-[(*R*)-(*E*)-3-Hydroxy-4-hexenoyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-thioxo-2-aza-4-oxatricyclo[5.2.1.0^{1,5}]decane (5d).** As described above, acetyloxazolidinethione **3** (239 mg, 1 mmol) and crotonaldehyde (0.10 mL, 86 mg, 1.2 mmol) provided a crude reaction mixture. Diastereomer analysis by 300 MHz ^1H NMR of the unpurified product indicated the presence of essentially a single aldol adduct. The pale yellow oil was purified by flash chromatography on silica gel (20% ethyl acetate/hexane) afforded 260 mg (84%) of **5d**: IR (neat) 3440, 2968, 1708, 1275, 1184 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.77 (ddq, J = 15.3, 6.3, 1.2 Hz, 1H), 5.59 (ddq, J = 15.3, 6.3, 0.9 Hz, 1H), 4.63 (m, 1H), 4.46 (dd, J = 8.4, 4.2 Hz, 1H), 3.67 (dd, J = 17.4, 3.3 Hz, 1H), 3.32 (dd, J = 17.4, 9.0 Hz, 1H), 3.12 (d, J = 4.2 Hz, 1H), 2.93–1.19 (m with dd at 1.72, J = 6.3, 0.9 Hz, 11H), 1.15 and 1.06 (2s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 188.1, 174.5, 131.8, 127.4, 90.0, 76.5, 68.8, 49.3, 45.8, 42.5, 34.7, 26.0, 25.1, 21.5, 19.2, 17.6; $[\alpha]_D^{25}$ +74.3° (*c* 5.1, $CHCl_3$); high-resolution MS *m/e* calcd for $C_{16}H_{23}NO_3S$ 309.1405, found 309.1402.

***N*-[(*R*)-(*E*)-3-Hydroxy-5-phenyl-4-pentenoyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-thioxo-2-aza-4-oxatricyclo[5.2.1.0^{1,5}]decane (5e).** As described above, acetyloxazolidinethione **3** (478 mg, 2 mmol) and *trans*-cinnamaldehyde (0.31 mL, 317 mg, 2.4 mmol) provided a crude reaction mixture. Diastereomer analysis [300 MHz ^1H NMR integration of the C-2 methylene protons (CH_2C=O) and/or C-3 methine proton (CH(OH))] of the unpurified adduct revealed the presence of two aldols in the ratio of 95:5. The pale yellow oil was purified by flash

chromatography on silica gel (20% ethyl acetate/hexane) afforded 452 mg (61%) of **5e**: IR (neat) 3410, 3060, 2960, 1688, 1454, 1370, 1336, 1220, 1196, 1175, 1036, 975 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41–7.21 (m 5H), 6.68 (dd, J = 15.9, 0.9 Hz, 1H), 6.29 (dd, J = 15.9, 5.7 Hz, 1H), 4.88 (m, 1H), 4.45 (dd, J = 8.1, 4.2 Hz, 1H), 3.80 (dd, J = 17.1, 3.3 Hz, 1H), 3.44 (dd, J = 17.1, 9.0 Hz, 1H), 2.95–1.20 (m, 8H), 1.16 and 1.06 (2s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 188.0, 174.3, 136.5, 130.6, 129.9, 128.6, 127.8, 126.5, 90.0, 76.5, 68.8, 49.3, 45.7, 42.4, 34.7, 26.0, 25.0, 21.5, 19.2; $[\alpha]_D^{25}$ +67.6° (*c* 2.9, $CHCl_3$); high-resolution MS *m/e* calcd for $C_{21}H_{25}NO_3S$ 371.1556, found 371.1554.

***N*-[(*R*)-(*E*)-3-Hydroxy-5-(trimethylsilyl)-4-pentenoyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-thioxo-2-aza-4-oxatricyclo-[5.2.1.0^{1,5}]decane (5f).** As described above, acetyloxazolidinethione **3** (478 mg, 2 mmol) and *trans*-3-(trimethylsilyl)-propenal (1 M in CH_2Cl_2, 2.4 mmol) provided a crude reaction mixture. Diastereomer analysis [300 MHz ^1H NMR integration of the C-2 methylene protons (C*H*$_2$C=O) and/or C-3 methine proton (C*H*(OH))] of the unpurified adduct revealed the presence of two aldols in the ratio of 93:7. The pale yellow oil was purified by flash chromatography on silica gel (20% ethyl acetate/hexane) afforded 433 mg (59%) of **5f** as a white solid: mp 84–85 °C; IR (neat) 3406, 2962, 1683, 1638, 1308, 1248, 1227, 1176, 981 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.07 (dd, J = 18.9, 4.5 Hz, 1H), 5.95 (dd, J = 18.9, 1.2 Hz, 1H), 4.64 (m, 1H), 4.44 (dd, J = 8.1, 4.2 Hz, 1H), 3.69 (dd, J = 17.4, 3.3 Hz, 1H), 3.29 (dd, J = 17.4, 8.7, Hz, 1H), 2.89–1.16 (m 8H), 1.13 and 1.04 (2s, 6H), 0.06 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 188.0, 174.4, 145.8, 130.3, 90.0, 76.5, 70.3, 49.3, 45.2, 42.4, 34.7, 25.9, 25.0, 21.5, 19.2, −1.4; $[\alpha]_D^{25}$ +64.1° (*c* 3.0, $CHCl_3$); high-resolution MS *m/e* calcd for $C_{18}H_{29}NO_3SiS$ 367.1638, found 367.1642.

***N*-[(*R*)-(*E*)-3-Hydroxy-5-(phenylthio)-4-pentenoyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-thioxo-2aza-4-oxatricyclo-[5.2.1.^{1,5}]decane (5g).** As described above, acetyloxazolidinethione **3** (478 mg, 2 mmol) and *trans*-3-(phenylthio)propenal (1 M in CH_2Cl_2, 2.4 mmol) provided a crude reaction mixture. Diastereomer analysis [300 MHz ^1H NMR integration of the C-2 methylene protons (C*H*$_2$C=O) and/or C-3 methine proton (C*H*(OH))] of the unpurified adduct revealed the presence of two aldols in the ratio of 97:3. The pale yellow oil was purified by flash chromatography on silica gel (15% ethyl acetate/hexane) afforded 628 mg (78%) of **5g**: IR (neat) 3450, 2954, 1686, 1580, 1333, 1035, 729 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.22 (m, 5H), 6.52 (dd, J = 15.3, 1.5 Hz, 1H), 5.86 (dd, J = 15.3, 5.7 Hz, 1H), 4.74 (m, 1H), 4.44 (dd, J = 8.1, 4.2 Hz, 1H), 3.72 (dd, J = 17.4, 3.3 Hz, 1H), 3.32 (dd, J = 17.4, 8.7 Hz, 1H), 2.93 (d, J = 4.5 Hz, 1H), 2.89–1.16 (m, 7H), 1.12 and 1.03 (2s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 188.0, 174.1, 134.6, 132.0, 130.1, 129.1, 127.0, 125.5, 90.0, 76.5, 68.6, 49.2, 45.3, 42.4, 34.7, 25.9, 25.0, 21.4, 19.2; $[\alpha]_D^{25}$ +47.5° (*c* 3.6, $CHCl_3$); high-resolution MS *m/e* calcd for $C_{21}H_{25}NO_3S_2$ 403.1282, found 403.1276.

***N*-[(*S*)-3-Hydroxyhexanoyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-thioxo-2-aza-4-oxatricyclo[5.2.1.0^{1,5}]decane (5h).** As described above, acetyloxazolidinethione **3** (478 mg, 2 mmol) and *n*-butyraldehyde (1 M in CH_2Cl_2, 2.4 mmol) provided a crude reaction mixture. Diastereomer analysis [300 MHz ^1H NMR integration of the C-2 methylene protons (C*H*$_2$C=O) and/or C-3 methine proton (C*H*(OH))] of the unpurified adduct revealed the presence of two aldols in the ratio of 87:13. The pale yellow oil was purified by flash chromatography on silica gel (15% ethyl acetate/hexane) afforded 547 mg (88%) of **5h**: IR (neat) 3440, 2956, 1706, 1460, 1184 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.47 (dd, J = 8.1, 4.2 Hz, 1H), 4.18 (m, 1H), 3.74 (dd, J = 17.7, 2.4 Hz, 1H), 3.10 (dd, J = 17.7, 9.3 Hz, 1H), 2.93–1.20 (m, 12H), 1.15 and 1.06 (2S, 6H), 0.95 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 188.1, 175.1, 89.9, 76.5, 67.4, 49.2, 45.8, 42.7, 38.4, 34.7, 25.9, 25.0, 21.4, 19.2, 18.6, 13.9; $[\alpha]_D^{25}$ +79.6° (*c* 4.2, $CHCl_3$); high-resolution MS *m/e* calcd for $C_{16}H_{25}NO_3S$ 311.1555, found 311.1553. Anal. Calcd for $C_{16}H_{25}NO_3S$: C, 61.74; H, 8.04; N, 4.50. Found: C, 61.50; H, 8.17; N, 4.76.

***N*-[(*R*)-3-Hydroxy-4-methylpentanoyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-thioxo-2-aza-4-oxatricyclo[5.2.1.0^{1,5}]decane (5i).** As described above, acetyloxazolidinethione **3** (478 mg, 2 mmol) and isobutyraldehyde (1 M in CH_2Cl_2, 2.4 mmol) provided a crude reaction mixture. Diastereomer analysis [300 MHz ^1H NMR integration of the C-2 methylene protons (C*H*$_2$C=O) and/or C-3 methine proton (C*H*(OH))] of the unpurified adduct revealed the presence of two aldols in the ratio of 86:14. The pale yellow oil was purified by flash chromatography on silica gel (15% ethyl acetate/hexane) afforded 522 mg (84%) of **5i** as a white solid: mp 58–59 °C; IR (neat) 3472, 2964, 1704, 1311, 1230, 1170, 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.47 (dd, J = 8.1, 4.2 Hz, 1H), 3.94 (m, 1H), 3.72 (dd, J = 17.4, 2.4 Hz, 1H), 3.13 (dd, J = 17.4, 9.9 Hz, 1H), 2.93–1.20 (m, 9H), 1.15 and 1.06 (2s, 6H), 0.98 and 1.01 (2d, J = 6.9 Hz, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 188.2, 175.5, 89.9, 76.5, 72.7, 49.3, 43.1, 42.5, 34.7, 33.2, 26.0, 25.1, 21.5, 19.3, 18.4, 17.8; $[\alpha]_D^{25}$ +75.2° (*c* 12.3, $CHCl_3$); high-resolution MS *m/e* calcd for $C_{16}H_{25}NO_3S$ 311.1555, found 311.1553.

General Procedure for the Hydroperoxide-Assisted Saponification. To a solution of aldol adduct **5** (1 equiv) in THF/H_2O (3:1, 0.16 M) at 0 °C was added a solution of LiOH (2 equiv) in 6 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 8 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 wer dried ($MgSO_4$) and evaporated in vacuo to give recovered auxiliary **1**. The aqueous phase was acidified with **3** N HCl, saturated with NaCl, and extracted with three portions of ether. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give an colorless oil **7**.

(*R*)-3-Hydroxy-3-phenylpropanoic acid (7a): IR (neat) 3510, 3060, 2960, 1711, 1608, 1551, 1497, 1455 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31–7.12 (m, 5H), 5.16 (dt, J = 8.7, 3.9 Hz, 1H), 2.85 (dd, J = 16.5, 8.7 Hz, 1H), 2.77 (dd, J = 16.8, 3.9 Hz, 1H); ^{13}C (75.5 MHz, $CDCl_3$) δ 177.2, 142.2, 128.7, 128.1, 125.7, 70.2, 42.7; $[\alpha]_D^{25}$ +20.6° (*c* 0.39 EtOH); lit.[6g] $[\alpha]_D^{25}$ +14.9° (*c* 1.94, EtOH); lit.[8c] $[\alpha]_D^{25}$ +18.9° (*c* 1.0, EtOH); lit.[6h] $[\alpha]_D^{25}$ +17.9° (*c* 2.3, 95%, EtOH); lit.[6a] $[\alpha]_D^{25}$ +60.5° (*c* 1.0, $CHCl_3$); high-resolution MS *m/e* calcd for $C_9H_{10}O_3$ 166.0645, found 166.0627.

(*R*)-(*E*)-3-Hydroxy-4-octenoic acid (7b): IR (neat) 3505, 3010, 2961, 1705, 1638, 1310, 1230 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.74 (dt, J = 15.6, 6.6 Hz, 1H), 5.51 (dd, J = 15.6, 6.6 Hz, 1H), 4.52 (dt, J = 6.6, 6.6 Hz, 1H), 2.60 (d, J = 6.6 Hz, 2H), 2.01 (dt, J = 6.9, 6.9 Hz, 2H), 1.40 (sextet, J = 6.9, 2H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C (75.5 MHz, $CDCl_3$) δ 177.0, 133.2, 130.3, 68.9, 41.3, 34.1, 22.1, 13.5; $[\alpha]_D^{25}$ +11.5° (*c* 7.8 EtOH); high-resolution MS *m/e* calcd for $C_8H_{14}O_3$ 158.0943, found 158.0945.

(*R*)-(*E*)-3-Hydroxy-4-heptenoic acid (7c): IR (neat) 3496, 3009, 2959, 1710, 1633, 1308, 1228 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.80 (dt, J = 15.3, 6.3 Hz, 1H), 5.50 (ddt, J = 15.3, 6.6, 1.5 Hz, 1H), 4.53 (dt, J = 6.0, 6.0 Hz, 1H), 2.60 (d, J = 6.0 Hz, 2H), 2.06 (dt, J = 6.3, 6.3 Hz, 2H), 0.99 (t, J = 7.2 Hz, 3H); ^{13}C (75.5 MHz, $CDCl_3$) δ 177.2, 134.9, 129.1, 68.9, 41.3, 25.1, 13.1; $[\alpha]_D^{25}$ −12.5° (*c* 1.0 EtOH); high-resolution MS *m/e* calcd for $C_7H_{12}O_3$ 144.0787, found 144.0788.

(*R*)-(*E*)-3-Hydroxy-4-hexenoic acid (7d): IR (neat) 3476, 3010, 2955, 1707, 1638, 1308, 1227 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.74 (ddq, J = 15.8, 6.4, 0.8 Hz, 1H), 5.49 (ddq, J = 15.8, 6.6, 1.6 Hz, 1H), 4.49 (dt, J = 6.6, 6.6 Hz, 1H), 2.58 (d, J = 6.6 Hz, 2H), 1.69 (d, J = 6.4 Hz, 3H); ^{13}C (75.5 MHz, $CDCl_3$) δ 177.0, 131.5, 128.3, 68.8, 41.2, 17.5; $[\alpha]_D^{25}$ +22.5° (*c* 0.43 EtOH); high-resolution MS *m/e* calcd for $C_6H_{10}O_3$ 130.0631, found 130.0633.

(*R*)-(*E*)-3-Hydroxy-5-phenyl-4-pentenoic acid (7e): IR (neat) 3476, 3040, 2962, 1709, 1618, 1550, 1491, 1450, 1308, 1227 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.24 (m, 5H), 6.67 (d, J = 15.9 Hz, 1H), 6.23 (dd, J = 15.8, 6.0 Hz, 1H), 4.75 (dt, J = 6.0, 5.1 Hz, 1H), 2.75–2.69 (m, 2H); ^{13}C (75.5 MHz, $CDCl_3$) δ 175.9, 136.2, 131.3, 129.4, 128.6, 128.0, 126.6, 68.8, 41.0; $[\alpha]_D^{25}$ −19.0° (*c* 4.24 EtOH); high-resolution MS *m/e* calcd for $C_{11}H_{12}O_3$ 192.0786, found 192.0791.

(*R*)-(*E*)-3-Hydroxy-5-(trimethylsilyl)-4-pentenoic acid (7f): IR (neat) 3505, 3049, 2961, 1710, 1638, 1308, 1227, 1176 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.12–5.90 (m, 2H), 4.54 (m, 1H), 2.66 (dd, J = 16.4, 4.2 Hz, 1H), 2.54 (dd, J = 16.4, 8.2 Hz, 1H), 0.05 (s, 9H); ^{13}C (75.5 MHz, $CDCl_3$) δ 177.4, 145.2, 131.2, 70.1, 29.6, −1.6; $[\alpha]_D^{25}$ +8.9° (*c* 1.89 $CHCl_3$); high-resolution MS *m/e* calcd for $C_8H_{16}O_3Si$ 188.1963, found 188.1955.

(*R*)-(*E*)-3-Hydroxy-5-(phenylthio)-4-pentenoic acid (7g): IR (neat) 3450, 3059, 2950, 1710, 1638, 1580, 1328, 1035 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.96–7.50 (m, 5H), 6.95 (dd, J = 16.4, 2.4 Hz, 1H), 6.71 (dd, J = 16.4, 0.8 Hz, 1H), 4.77 (m, 1H), 2.74 (dd, J = 16.6, 2.8 Hz, 1H), 2.58 (dd, J = 16.6, 8.0 Hz, 1H); ^{13}C (75.5 MHz, $CDCl_3$) δ 177.8, 132.2, 130.0, 129.3, 128.3, 127.0, 125.6, 70.3, 31.7; $[\alpha]_D^{25}$ −20.7° (*c* 0.16 $CHCl_3$); high-resolution MS *m/e* calcd for $C_{11}H_{12}O_3S$ 224.1426, found 224.1421.

(*S*)-3-Hydroxyhexanoic acid (7h): IR (neat) 3430, 2962, 1707, 1401, 1260, 1017, 792 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.03 (m, 1H), 2.55 (dd, J = 16.5, 3.3 Hz, 1H), 2.45 (dd, J = 16.5, 9.0 Hz, 1H), 1.59–1.32 (m, 4H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C (75.5 MHz, $CDCl_3$) δ 177.6, 67.7, 41.0, 38.5, 18.5, 13.8; $[\alpha]_D^{25}$ +25.7° (*c* 0.21 $CHCl_3$); lit.[6g] $[\alpha]_D^{25}$ +25.8° (*c* 0.53, $CHCl_3$); lit.[6a] $[\alpha]_D^{25}$ +28.3° (*c* 1.0, $CHCl_3$); high-resolution MS (CI+) *m/e* calcd for $C_6H_{13}O_3$ 133.0864, found 133.0861.

(*R*)-3-Hydroxy-4-methylpentanoic acid (7i): IR (neat) 3448, 2960, 1712, 1455 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.83 (dt, J = 12.3, 6.6 Hz, 1H), 2.55 (dd, J = 16.2, 3.3 Hz, 1H), 2.45 (dd, J = 16.2, 9.9 Hz, 1H), 1.74 (octet, J = 6.6 Hz, 1H), 0.95 and 0.93 (2d, J = 6.6 Hz, 6H); ^{13}C (75.5 MHz, $CDCl_3$) δ 177.7, 68.7, 38.3, 33.1, 18.2, 17.6; $[\alpha]_D^{25}$ +39.9° (*c* 2.84 $CHCl_3$); lit.[6h] $[\alpha]_D^{25}$ +40.5° (*c* 0.6, $CHCl_3$); lit.[8b] $[\alpha]_D^{25}$ +40.2° (*c* 1.2, $CHCl_3$); lit.[6a] $[\alpha]_D^{25}$ +41.7° (*c* 1.0, $CHCl_3$); lit.[6g] $[\alpha]_D^{25}$ +36.9° (*c* 1.6, $CHCl_3$); high-resolution MS (CI+) *m/e* calcd for $C_6H_{13}O_3$ 133.0864, found 133.0858.

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Supplementary Material Available: ^1H NMR spectra of compounds **5a–i** and **7a–i** (18 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.