A New Approach for the Chemoselective Debromination of Chiral Bromohydrins. Toward the Development of a Very General Approach to Enantiopure α-Unsubstituted *β*-Hydroxy Acids

Ying-Chuan Wang and Tu-Hsin Yan*

Department of Chemistry, National Chung-Hsing University, Taichung, Taiwan, ROC

thyan@mail.nchu.edu.tw

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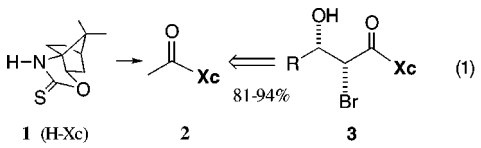
Introduction

The utility of chiral α-unsubstituted *β*-hydroxy carboxylate compounds in synthesis has stimulated the development of new methodology for their construction. The asymmetric aldol reactions appear as a one-step route to the chiral α-unsubstituted *β*-hydroxy carboxylates. However, the levels of diastereofacial selectivity observed in metal-asisted aldolizations of chiral acetate enolates proved unequivalent to those obtained from α-substituted metal enolates.[1] The ease of access to chiral α-sulfenylated and bromohydrin aldol adducts of 85−99% ee makes the conversion of α-substituted aldol adducts into α-unsubstituted *β*-hydroxy carboxylates a useful transformation.[1d,2] Hydrogenolysis (H_2/Raney nickel or H_2/Pd−C) of α-methylthio-*β*-hydroxy and α-bromo-*β*-hydroxy carboxylates at room temperature has been reported to afford *β*-hydroxy carboxylates. However, this protocol is less often synthetically useful because the selective debromination of bromohydrin in the presence of the C=C double bond is not possible. The other main general approach to the debromination of unsaturated bromohydrin aldol adducts involves direct radical cleavage of the carbon−halogen bond with tri-*n*-butyltin hydride.[3] Although the C=C double bond is well tolerated, the requirement for the use of a large excess of *n*-Bu_3Sn−H (2−5 equiv) at high temperatures to effect the debromination and the difficulty to separate the tin byproducts in these reactions greatly limit the general utility of this method.

In searching for a new debromination method based upon simple metal reduction, we turned our attention to the concept of a C−H bond formation based upon a protonolysis of carbon-metal bond. While carbon−metal bond-formimg reactions of halides and metals such as Zn, Mg, and Al−Hg prove to be important approaches for the chemoselective reductive-cleavage of the carbon−halogen bonds of a diverse range of halides, to the best of our knowledge, there have been no reported examples using α-bromo-*β*-hydroxy carboxylate precursors. The extension of the above metal reduction procedures to bromohydrin aldol adducts has remained largely unexplored due mainly to the well-documented proclivity of the intermediate carbanions derived from bromohydrins to undergo dehydroxybromination (*β*-elimination).[4,5] As part of our recent studies directed toward the development of a general chiral α-substituted acetate enolate synthon,[6] we encountered the opportunity to test such a process. Herein, we report the successful utilization of Al−Hg to effect a clean debromination of bromohydrins in the presence of sensitive functionality and demonstrate a facile method for the synthesis of α-unsubstituted *β*-hydroxy acids in essentially >99% ee.

Results and Discussion

We aimed at using the previously reported one-step enolate bromination-aldolization as a route to chiral bromohydrin aldols needed for the generation of α-unsubstituted *β*-hydroxy acids.[6] Equation 1 outlines the route. Enolization of acetate thioimide **2** derived from oxazolidinethione **1** with $TiCl_4$ and diisopropylethylamine and its subsequent reaction with bromine and aldehydes afforded the bromohydrin aldols **3** in 81−94% yield. With



1 (H-Xc) **2** **3** (1)

chiral bromohydrins **3** in hand, the stage was set for establishing the feasibility of Al−Hg as a mild reducing reagent to effect chemoselective cleavage of the C−Br bond in **3**. All attempts to perform the chemoselective debromination of **3** led to disappointing results, which we attributed to the instability of the α-bromo thioimide. We then focused on hydrolysis products derived from thioimide aldols **3** for our studies.[6] We initiated our studies utilizing saturated bromohydroxy acid substrate **4a**. As we had hoped, simply adding Al−Hg (mercury content ∼2.5%) to the bromo acid **4a** led to clean debromination within 10 min to give *β*-hydroxy acid **5a** in 90% yield (Scheme 1). Alternatively, the high degree of purity of acid **4a** allowed for the carrying of material directly to the debromination reaction without further isolation and purification. A standard one-pot operating procedure which involved adding H_2O (5 equiv) to 1 equiv of bromohydrin aldol **3a** in CH_2Cl_2 followed by 1.5 equiv of NEt_3 (or DMAP) for 30 min at 0 °C followed by 3−4 equiv of Al−Hg for 5−10 min at 0 °C was adopted. Having established the feasibility of the one-pot hydrolysis-debromination, its chemoselectivity was explored with a series of bromohydrin aldol adducts. Hindered saturated aldol adduct **3b** gave a similar result. Thus, the same conditions effected deacylation-debromination of **3b**

(1) (a) Braun, M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 24. (b) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1. (c) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099 and references therein. (d) Evans, D. A.; Bartrol, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127−2129. (e) Yan, T.-H.; Hung, A.-W.; Lee, H.-C.; Chang, C.-S. *J. Org, Chem.* **1994**, *59*, 8187−8191.

(2) Fleming, P. R.; Sharpless, K. B. *J. Org. Chem.* **1991**, *56*, 2869−2875.

(3) Corey, E. J.; Choi, S. *Tetrahedron Lett.* **1991**, *32*, 2857−2860.

(4) James, D. R.; Rees, R. W.; Shoppee, C. W. *J. Chem. Soc.* **1955**, 1371−1375.

(5) Jain, S.; Suryawanshi, S. N.; Bhakuni, D. S. *Indian J. Chem., Sect. B* **1987**, *26*, 866.

(6) Wang, Y.-C.; Su, D.-W.; Lin, C.-M.; Tseng, H.-L.; Li, C.-L.; Yan, T.-H. *J. Org. Chem.* **1999**, *64*, 6495−6498.

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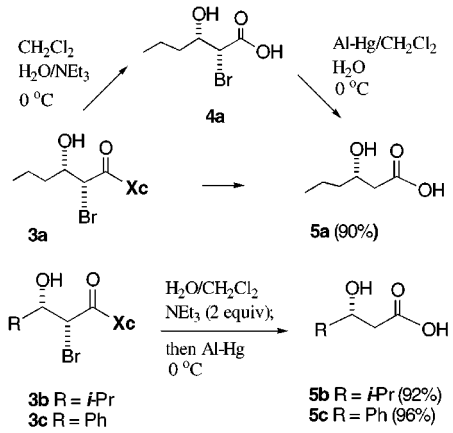
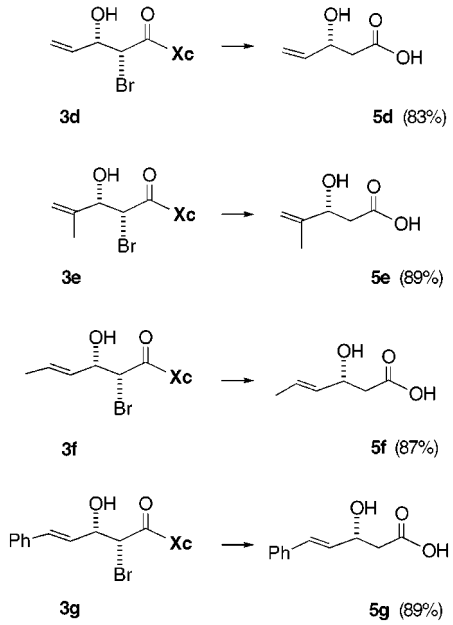
Scheme 1



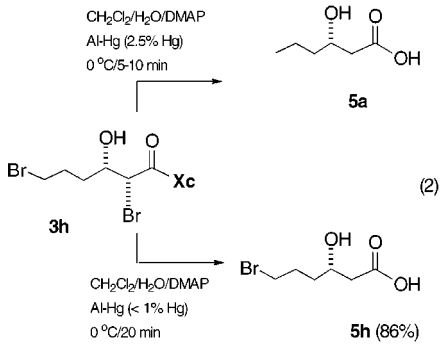
Scheme 2



to afford a 92% yield of *β*-hydroxy acid **5b**. On the other hand, bromohydrin aldol **3c**, which is particularly prone to reductive cleavage of C−OH bond due to the presence of a benzyl-type alcohol, can also be cleanly converted to the corresponding acid **5c** in 96% yield after purification (Scheme 1). Potential *β*-elimination (dehydroxybromination) in the intermediate carbanion does not appear to compete kinetically with carbon−hydrogen bond formation.

Extension of these observations to other bromohydroxy acids confirms their generality. Our attention next turned to exploring the chemoselective cleavage of the C−Br bond of bromohydrins **3d**−**g**, which by virtue of the sensitivity of the unsaturation within the molecular framework demands mild reduction conditions (Scheme 2). Fortunately, we found that the Al−Hg promoted debromination not only resulted in the suppression of olefin saturation, which is a major problem with H_2/Pd/C, but also afforded complete control for the desired mode of reductive cleavage with no evidence of dehydroxybromination.

Finally, the scope of the reduction with respect to sensitive substituents that could be utilized in the reaction was of interest. The use of the dibromo thioimide aldol **3h** demonstrates the chemoselectivity possible (eq 2). The identical Al−Hg promoted reduction at 0 °C for 10 min led to extensive reduction of the starting material



to give acid **5a** with a small amount (∼30%) of the desired 6-bromo-3-hydroxy acid **5h**. Reducing the reaction time in an effort to avoid the undesired cleavage of the C(6)−Br bond resulted in a mixture of recovered dibromo acid along with debromination products **5a** and **5h**. This difficulty was overcome by utilizing aluminum amalgam with low mercury content as a reducing agent. Thus, exposing **3h** to a less active aluminum amalgam (mercury content ∼0.8%) led to a smooth monodebromination within 20 min as illustrated in eq 2 wherein the 6-bromo acid **5h** was obtained in 86% yield.[7] The ability to effect such a reductive cleavage of a C−Br bond α to a carbonyl group even in the presence of another reactive C−Br bond highlights the extraordinary chemoselectivity and the mild nature of the Al/Hg-promoted debromination process.

Having established the generality of the debromination, the enantiomeric excesses of these chiral *β*-hydroxy acids were measured by direct comparison to the racemic acids[8] and analyzed by chiral HPLC. The analyses by HPLC on a chiralcel OD column (Daicel Chemical Industries) indicated that saturated acids **5a**, **5b** and **5h** were essentially enantiomerically pure (>99% ee). Since chiral *β*-hydroxy acid **5c** and *β*-alkenyl substituted unsaturated hydroxy acids **5d**−**g** are not stable on silica gel, they were converted to the corresponding benzyl esters and analyzed by HPLC.[9] As expected, analyses by chiral HPLC indicated that they were also enantiomerically pure.

In contrast to the alternative methods employed such as catalytic hydrogenolysis and tri-*n*-butyltin hydride mediated reduction, the Al−Hg promoted chemoselective debromination allows for a clean transformation of bromohydrin aldols into *β*-hydroxy acids in the presence of highly sensitive functionality. Synthetically, the present studies offer a facile and practical asymmetric synthesis of enantiopure α-unsubstituted *β*-hydroxy acids, which is broad in scope and simple in application. The potential of this Al−Hg promoted chemoselective cleavage of other α,*β*-difunctional carboxylates such as α,*β*-epoxy esters, α-halo-*β*-hydroxy amides and esters is being further explored.[10]

(7) The less active Al−Hg was generated by adding aluminum (0.1 g) to a stirred aqueous solution of $HgCl_2$ (0.1%, ∼8 mL). The less active Al−Hg can also be used to debrominate the other bromohydrin aldols such as **3a**−**g**.

(8) Prepared from the aldolizations of acetate lithium enolate derived from acetic acid with aldehydes.

(9) The benzyl esters of **5c**−**g** were prepared by treating **5c**−**g** with $PhCH_2Br$ and NEt_3 in acetone at 0 °C.

Experimental Section

General Methods. Diisopropylethylamine and dichloromethane were dried by distillation under N_2 from calcium hydride. $TiCl_4$ (1 M in CH_2Cl_2) was used as received. 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). Melting points (Pyrex capillary) are uncorrected. Concentrations for rotation data are given as g/100 mL of solvent. Diastereomeric excesses (de) were determined by HPLC on a chiralcel OD column (Daicel Chemical Industries).

General Procedure for the $TiCl_4$-Mediated Bromination−Aldolization of Thioimide 2. Enolization of acetate thioimide **2** derived from oxazolidinethione **1** with $TiCl_4$ and diisopropylethylamine and its subsequent reaction with bromine and aldehydes were performed according to the previously reported procedure.[6] Diastereomer analysis (400 MHz ^{1}H NMR) of the unpurified mixture revealed the presence of essentially a single syn bromohydrin aldol. Purification by flash chromatography (15% ethyl acetate/hexane, silica gel, 0−5 °C) afforded **3a** (91%), **3b** (91%), **3c** (94%), **3d** (81%), **3e** (87%), **3f** (90%), and **3g** (84%), **3h** (87%).

***N*-[(2*R*,3*S*)-2-Bromo-3-hydroxyhexanoyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-thioxo-2-aza-4-oxatricyclo[6.2.1.0^{1,5}]decane (3a):** IR (neat) 3508, 1696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61 (d, J = 2.0 Hz, 1 H), 4.54 (dd, J = 8.0, 4.0 Hz, 1 H), 4.01 (m, 1 H), 2.76−1.20 (m, 12 H), 1.08 (s, 3 H), 0.99 (s, 3 H), 0.90 (m, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 187.52, 172.77, 90.64, 69.52, 51.16, 49.19, 42.52, 36.34, 34.63, 31.53, 25.78, 23.90, 21.33, 19.31, 18.56, 18.71, 13.92; $[\alpha]^{25}_D$ +48.0° (*c* 5.1, CH_2Cl_2); high-resolution MS *m/e* calcd for $C_{16}H_{24}NO_3SBr$ 389.0660, found 389.0661. Anal. Calcd for $C_{16}H_{24}NO_3SBr$: C, 49.22; H, 6.20; N, 3.59. Found: C, 49.31; H, 6.16; N, 3.62.

***N*-[(2*R*,3*S*)-2-Bromo-3-hydroxy-4-methylpentanoyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-thioxo-2-aza-4-oxatricyclo[6.2.1.0^{1,5}]decane (3b):** mp 98−99 °C; IR (KBr) 3636, 1694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (d, J = 2.0 Hz, 1 H), 4.54 (dd, J = 8.2, 4.0 Hz, 1 H), 3.68 (dd, J = 8.2, 2.0 Hz, 1 H), 2.68−1.20 (m, 9 H), 1.13 (s, 3 H), 1.09 (d, J = 6.8 Hz, 3 H), 1.05 (s, 3 H), 0.93 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 187.51, 173.15, 90.56, 74.85, 49.25, 42.51, 34.59, 31.77, 31.50, 25.75, 23.83, 21.21, 21.04, 19.28, 18.71, 19.52; $[\alpha]^{25}_D$ +46.5° (*c* 2.4, CH_2Cl_2); high-resolution MS *m/e* calcd for $C_{16}H_{24}NO_3SBr$ 389.0660, found 389.0663. Anal. Calcd for $C_{16}H_{24}NO_3SBr$: C, 49.22; H, 6.20; N, 3.59. Found: C, 49.31; H, 6.16; N, 3.62.

***N*-[(2*R*,3*S*)-2-Bromo-3-hydroxy-3-phenylpropionyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-thioxo-2-aza-4-oxatricyclo[6.2.1.0^{1,5}]decane (3c):** mp 113−114 °C; IR (neat) 3524, 1694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.24 (m, 5 H), 7.00 (d, J = 4.4 Hz, 1 H), 5.28 (d, J = 4.4 Hz, 1 H), 4.52 (dd, J = 8.0, 4.0 Hz, 1 H), 2.73−1.20 (m, 8 H), 1.02 (s, 3 H), 0.90 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 187.19, 171.99, 138.65, 128.30, 126.74, 125.50, 90.40, 72.24, 51.32, 49.08, 42.44, 34.50, 31.53, 25.69, 24.08, 21.03, 18.93; $[\alpha]^{25}_D$ +74.5° (*c* 5.1, CH_2Cl_2); high-resolution MS *m/e* calcd for $C_{19}H_{22}NO_3SBr$ 423.0503, found 423.0501. Anal. Calcd for $C_{19}H_{22}NO_3SBr$: C, 53.76; H, 5.23; N, 3.30. Found: C, 53.79; H, 5.22; N, 3.36.

***N*-[(2*R*,3*S*)-2-Bromo-3-hydroxy-4-pentenoyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-thioxo-2-aza-4-oxatricyclo[6.2.1.0^{1,5}]decane (3d).** As described above, 0.24 g (1.0 mmol) of **2** was converted to its chlorotitanium enolate. Condensation with acrolein (1.4 mmol) provided a crude reaction mixture. Diastereomeric analysis (400 MHz ^{1}H NMR) of the unpurified mixture revealed the presence of essentially a single syn bromohydrin aldol. Purification by flash chromatography (15% ethyl acetate/hexane, silica gel, 0−5 °C) afforded 0.31 g (81%) of **3d**: IR (neat) 3483, 1695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 (d, J = 4.4 Hz, 1 H), 5.86 (ddd, J = 17.2, 10.4, 5.6 Hz, 1 H), 5.42 (dt, J = 17.2, 1.2 Hz, 1 H), 5.28 (dt, J = 10.4, 1.2 Hz, 1H), 4.67−4.64 (m, 1 H), 4.52 (dd, J = 8.0, 4.0 Hz, 1 H), 2.98 (bs, 1 H), 2.68−1.18 (m, 7 H), 1.09 (s, 3 H), 1.01 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 187.06, 171.27, 135.25, 118.28, 90.40, 71.23, 50.19, 49.20, 42.52, 34.64, 31.89, 25.84, 24.14, 21.32, 19.33; $[\alpha]^{25}_D$ +12.3° (*c* 0.2, CH_2Cl_2); high-resolution MS *m/e* calcd for $C_{15}H_{20}NO_3SBr$ 373.0347, found 373.0353. Anal. Calcd for $C_{15}H_{20}NO_3SBr$: C, 48.25; H, 5.40; N, 3.75. Found: C, 48.10; H, 5.33; N, 3.66.

***N*-[(2*R*,3*S*)-2-Bromo-3-hydroxy-4-methyl-4-pentenoyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-thioxo-2-aza-4-oxatricyclo[6.2.1.0^{1,5}]decane (3e).** As described above, 0.24 g (1.0 mmol) of **2** was converted to its chlorotitanium enolate. Condensation with 2-methylpropenal (1.4 mmol) provided a crude reaction mixture. Diastereomer analysis (400 MHz ^{1}H NMR) of the unpurified mixture revealed the presence of essentially a single syn bromohydrin aldol. Purification by flash chromatography (15% ethyl acetate/hexane, silica gel, 0−5 °C) afforded 0.34 g (87%) of **3e**: IR (neat) 3485, 1701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61 (d, J = 3.6 Hz, 1 H), 5.20 (bs, 1 H), 5.03 (bs, 1 H), 4.55 (d, J = 3.6 Hz, 1 H), 4.53 (dd, J = 8.4, 4.0 Hz, 1 H), 3.19 (bs, 1 H), 2.69−1.81 (m, 5 H), 1.78 (d, J = 0.4 Hz, 3 H),1.38−1.21 (m, 2 H), 1.10 (s, 3 H), 1.01 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 187.16, 171.84, 141.53, 114.27, 90.40, 72.48, 49.22, 48.93, 42.59, 34.68, 31.91, 25.89, 24.16, 21.31, 19.35, 19.23; $[\alpha]^{25}_D$ +6.4° (*c* 0.5, CH_2Cl_2); high-resolution MS *m/e* calcd for $C_{16}H_{22}NO_3SBr$ 387.0504, found 387.0501. Anal. Calcd for $C_{16}H_{22}NO_3SBr$: C, 49.48; H, 5.71; N, 3.61. Found: C, 49.53; H, 5.70; N, 3.55.

***N*-[(2*R*,3*S*)-2-Bromo-3-hydroxy-(*E*)-4-hexenoyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-thioxo-2-aza-4-oxatricyclo[6.2.1.0^{1,5}]decane (3f):** IR (neat) 3488, 1698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (d, J = 4.4 Hz, 1 H), 5.87 (dq, J = 15.6, 6.8 Hz, 1 H), 5.56 (dd, J = 15.6, 6.8 Hz, 1 H), 4.60 (dd, J = 6.8, 4.4 Hz, 1 H), 4.54 (dd, J = 8.0, 4.0 Hz, 1 H), 2.73−1.18 (m, 11 H), 1.07 (s, 3 H), 0.98 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 187.40, 171.77, 130.81, 128.37, 90.43, 71.50, 50.63, 49.14, 42.41, 34.51, 31.43, 25.85, 24.17, 21.31, 19.24, 17.87; $[\alpha]^{25}_D$ +60.4° (*c* 4.8, CH_2Cl_2); high-resolution MS *m/e* calcd for $C_{16}H_{22}NO_3SBr$ 387.0503, found 387.0506. Anal. Calcd for $C_{16}H_{22}NO_3SBr$: C, 49.48; H, 5.71; N, 3.61. Found: C, 49.50; H, 5.73; N, 3.56.

***N*-[(2*R*,3*S*)-2-Bromo-3-hydroxy-4-methyl-(*E*)-4-pentenoyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-thioxo-2-aza-4-oxatricyclo[6.2.1.0^{1,5}]decane (3g).** As described above, 0.24 g (1.0 mmol) of **2** was converted to its chlorotitanium enolate. Condensation with cinnamaldehyde (1.4 mmol) provided a crude reaction mixture.

Diastereomer analysis (400 MHz ^{1}H NMR) of the unpurified mixture revealed the presence of essentially a single syn bromohydrin aldol. Purification by flash chromatography (15% ethyl acetate/hexane, silica gel, 0−5 °C) afforded 0.38 g (84%) of **3g**: IR (neat) 3480, 1681 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.15 (m, 5 H), 6.71 (d, J = 4.8 Hz, 1 H), 6.68 (d, J = 16.0 Hz, 1 H), 6.20 (dd, J = 16.0, 3.6 Hz, 1 H), 4.81 (ddd, J = 4.8, 3.6 1.2 Hz, 1 H), 4.47 (dd, J = 8.4, 4.0 Hz, 1 H), 3.40 (bs, 1 H), 2.68−1.15 (m, 7 H), 1.03 (s, 3 H), 0.88 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 186.66, 170.65, 135.54, 133.03, 127.99, 127.49, 126.19, 126.06, 89.96, 76.95, 71.51, 49.97, 48.82, 42.11, 34.23, 25.48, 23.84, 21.01, 18.80; $[\alpha]^{25}_D$ +3.5° (*c* 0.2, CH_2Cl_2); high-resolution MS *m/e* calcd for $C_{21}H_{24}NO_3SBr$ 449.0659, found 449.0654. Anal. Calcd for $C_{21}H_{24}NO_3SBr$: C, 56.12; H, 5.38; N, 3.12. Found: C, 56.03; H, 5.30; N, 3.15.

***N*-[(2*R*,3*S*)-2,6-Dibromo-3-hydroxyhexanoyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-thioxo-2-aza-4-oxatricyclo[6.2.1.0^{1,5}]decane (3h).** As described above, 0.24 g (1.0 mmol) of **2** was converted to its chlorotitanium enolate. Condensation with 4-bromobutyraldehyde (1.4 mmol) provided a crude reaction mixture. Diastereomeric analysis (400 MHz ^{1}H NMR) of the unpurified mixture revealed the presence of essentially a single syn bromohydrin aldol. Purification by flash chromatography (15% ethyl acetate/hexane, silica gel, 0−5 °C) afforded 0.41 g (87%) of **3h**: IR (neat) 3498, 1702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61 (d, J = 2.8 Hz, 1 H), 4.56 (dd, J = 8.0, 4.0 Hz, 1 H), 4.07−4.03 (m, 1 H), 3.65 (bs, 1 H), 3.50−3.40 (m, 2 H), 2.69−1.22 (m, 11 H), 1.13 (s, 3 H), 1.05 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 186.67, 171.50, 90.13, 68.78, 50.62, 48.81, 42.12, 34.24, 33.17, 32.46, 28.39, 28.01, 25.44, 23.57, 20.94, 18.99; $[\alpha]^{25}_D$ +30.9° (*c* 3.2, CH_2Cl_2); high-resolution MS *m/e* calcd for $C_{16}H_{23}$-

(10) At present, we know reduction of α,β-epoxy esters under the same conditions affords only recovered starting materials. A search for reaction conditions that would effect transformation of epoxy carboxylates into β-hydroxy carboxylates is currently underway.

NO_3SBr_2 466.9765, found 466.9767. Anal. Calcd for $C_{16}H_{23}NO_3SBr_2$: C, 41.11; H, 4.96; N, 3.00. Found: C, 41.28; H, 4.99; N, 3.05.

Typical Procedure for the Hydrolysis−Debromination Reaction of 3. Aluminum amalgam was prepared from aluminum granular (∼40 mesh, 0.1 g), which was immersed, all at once, into an aqueous solution of $HgCl_2$ (1%, 2.5 mL). After shaking for 10 s, the gray amalgamated metal was washed with distilled water and used at once. The less active Al−Hg was generated by adding aluminum (0.1 g) to a stirred aqueous solution of $HgCl_2$ (0.1%, ∼8 mL). To a solution of bromohydrin **3** (1 mmol) and H_2O (3 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added NEt_3 or DMAP (1.5 mmol). The mixture was stirred at 0 °C for 30 min, and aluminum amalgam was added. After stirring for 10 min at 0 °C, the mixture was filtered, the residue was washed with two portions of CH_2Cl_2. The combined organic extracts were washed with 5% HCl and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to give hydroxy acids **5**. Enantiomeric excesses were determined by chiral HPLC using a Chiralcel OD column (Daicel Chemical Industries).

(*S*)-3-Hydroxyhexanoic acid (5a): IR (neat) 3487, 1703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.88 (bs, 1 H), 4.08−3.98 (m, 1 H), 2.50 (dd, J = 16, 3.2 Hz, 1 H), 2.40 (dd, J = 16, 8.8 Hz, 1 H), 1.27−1.56 (m, 4 H), 0.89 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.85, 67.98, 41.33, 38.52, 18.61, 13.85; $[\alpha]^{25}_D$ +26.8° (*c* 1.1, CH_2Cl_2) [lit.[11a] $[\alpha]^{25}_D$ +25.8° (*c* 0.53, $CHCl_3$); lit.[11b] $[\alpha]^{25}_D$ +28.3° (*c* 1.0, $CHCl_3$)]; high-resolution MS *m*/*e* calcd for $C_6H_{12}O_3$ 132.0787, found 132.0788; HPLC (Chiralcel OD; 95:5:0.1 hexane/isopropyl alcohol/CF_3COOH; flow rate 1 mL/min; UV 254 nm); t_R = 6.2 min (*S*), 10.1 min (*R*).

(*R*)-3-Hydroxy-4-methylpentanoic acid (5b): IR (neat) 3495, 1700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.49 (bs, 1 H), 3.82−3.77 (m, 1 H), 2.53 (dd, J = 16.4, 2.8 Hz, 1 H), 2.44 (dd, J = 16.4, 9.6 Hz, 1 H), 1.71 (octet, J = 6.4 Hz, 1 H), 0.91 and 0.93 (2d, J = 6.4 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.89, 73.01, 38.49, 33.25, 18.36, 17.79; $[\alpha]^{25}_D$ +40.8° (*c* 0.7, CH_2Cl_2) [lit.[11c] $[\alpha]^{25}_D$ +40.5° (*c* 0.6, $CHCl_3$); lit.[11d] $[\alpha]^{25}_D$ +40.2° (*c* 1.2, $CHCl_3$); lit.[11b] $[\alpha]^{25}_D$ +41.7° (*c* 1.0, $CHCl_3$)]; high-resolution MS *m*/*e* calcd for $C_6H_{12}O_3$ 132.0787, found 132.0789; HPLC (Chiralcel OD; 95:5:0.1 hexane/isopropyl alcohol/CF_3COOH; flow rate 1 mL/min; UV 254 nm); t_R = 11.5 min (*S*), 15.3 min (*R*).

(*R*)-3-Hydroxy-3-phenylpropanoic acid (5c): IR (neat) 3498, 1703, 1618, 1550 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33−7.21 (m, 5 H), 5.09 (dd, J = 9.2, 3.6 Hz, 1 H), 2.74 (dd, J = 16.4, 9.2 Hz, 1 H), 2.70 (dd, J = 16.4, 3.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.13, 141.96, 128.56, 127.95, 125.55, 70.26, 43.02; $[\alpha]^{25}_D$ +19.5° (*c* 0.4, CH_2Cl_2) [lit.[11a] $[\alpha]^{25}_D$ +14.9° (*c* 1.9, EtOH); lit.[11c] $[\alpha]^{25}_D$ +17.9° (*c* 2.3, 95% EtOH); lit.[11e] $[\alpha]^{25}_D$ +18.9° (*c* 1.0, EtOH)]; high-resolution MS *m*/*e* calcd for $C_9H_{10}O_3$ 166.0630, found 166.0625; benzyl ester derived from **5c**: HPLC (Chiralcel OD; 95:5 hexane/isopropyl alcohol; flow rate 1 mL/min; UV 254 nm); t_R = 21.2 min (*S*), 29.7 min (*R*).

(*R*)-3-Hydroxy-4-pentenoic acid (5d): IR (neat) 3502, 1704, 1639 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.84 (ddd, J = 17.2, 10.4, 1.6 Hz, 2 H), 5.27 (dd, J = 17.2, 2.4 Hz, 1 H), 5.12 (dd, J = 10.4, 2.4 Hz, 1 H), 4.55−4.50 (m, 1 H), 2.60−2.48 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.83, 138.22, 115.65, 68.96, 41.15; $[\alpha]^{25}_D$ +6.8° (*c* 2.2, CH_2Cl_2); high-resolution MS *m*/*e* calcd for $C_5H_8O_3$ 116.0473, found 116.0467. benzyl ester derived from **5d**: HPLC (Chiralcel OD; 95:5 hexane/isopropyl alcohol; flow rate 1 mL/min; UV 254 nm); t_R = 17.6 min (*S*), 32.2 min (*R*).

(*R*)-3-Hydroxy-4-methyl-(*E*)-4-pentenoic acid (5e): IR (neat) 3509, 1699, 1621 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.03 (d, J = 0.8 Hz, 2 H), 4.89 (d, J = 0.8 Hz, 1 H), 4.49 (dd, J = 7.6, 4.4 Hz, 1 H), 2.64 (dd, J = 16.4, 4.8 Hz, 1 H), 2.58 (dd, J = 16.4, 8.4 Hz, 1 H), 1.68 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.58, 144.72, 111.67, 71.45, 39.86, 18.05; $[\alpha]^{25}_D$ +24.9° (*c* 3.8, CH_2Cl_2); high-resolution MS *m*/*e* calcd for $C_6H_{10}O_3$ 130.0629, found 130.0625; benzyl ester derived from **5e**: HPLC (Chiralcel OD; 95:5 hexane/isopropyl alcohol; flow rate 1 mL/min; UV 254 nm); t_R = 14.1 min (*S*), 19.2 min (*R*).

(*R*)-3-Hydroxy-(*E*)-4-hexenoic acid (5f): IR (neat) 3477, 1706, 1636 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.75 (ddq, J = 15.6, 6.4, 0.8 Hz, 1 H), 5.48 (ddq, J = 15.6, 6.4, 1.6 Hz, 1 H), 4.48 (dt, J = 6.8, 6.4 Hz, 1 H), 2.57 (d, J = 6.8 Hz, 2 H), 1.68 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.44, 131.29, 127.90, 68.88, 41.40, 17.75; $[\alpha]^{25}_D$ +22.1° (*c* 0.5, CH_2Cl_2); high-resolution MS *m*/*e* calcd for $C_6H_{10}O_3$ 130.0631, found 130.0634; benzyl ester derived from **5f**): HPLC (Chiralcel OD; 95:5 hexane/isopropyl alcohol; flow rate 1 mL/min; UV 254 nm); t_R = 13.1 min (*S*), 18.2 min (*R*).

(*R*)-3-Hydroxy-5-phenyl-(*E*)-4-pentenoic acid (5g): IR (neat) 3509, 1711, 1607 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39−7.24 (m, 5 H), 6.66 (d, J = 16.0 Hz, 1 H), 6.22 (dd, J = 16.0, 6.4 Hz, 1 H), 4.77−4.71 (m, 1 H), 2.73 (dd, J = 16.4, 4.4 Hz, 1 H), 2.67 (dd, J = 16.4, 8.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.86, 136.08, 131.14, 129.30, 128.47, 127.83, 126.46, 68.82, 41.42; $[\alpha]^{25}_D$ +10.3° (*c* 0.4, CH_2Cl_2); high-resolution MS *m*/*e* calcd for $C_{11}H_{12}O_3$ 192.0786, found 192.0787. benzyl ester derived from **5g**: HPLC (Chiralcel OD; 95:5 hexane/isopropyl alcohol; flow rate 1 mL/min; UV 254 nm); t_R = 33.6 min (*S*), 46.1 min (*R*).

(*S*)-3-Hydroxy-6-bromohexanoic acid (5h): IR (neat) 3501, 1701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.82 (bs, 1 H), 3.99−4.11 (m, 1 H), 3.44 (t, J = 6.8 Hz, 1 H), 2.58 (dd, J = 17, 2.4 Hz, 1 H), 2.48 (dd, J = 17, 6.4 Hz, 1 H), 1.82−2.14 (m, 2 H), 1.55−1.69 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.48, 67.08, 41.06, 34.71, 33.56, 28.70; $[\alpha]^{25}_D$ +9.2° (*c* 0.9, CH_2Cl_2); high-resolution MS *m*/*e* calcd for $C_6H_{11}O_3Br$ 209.9891, found 209.9893; HPLC (Chiralcel OD; 100:1:0.1 hexane/isopropyl alcohol/CF_3COOH; flow rate 1 mL/min; UV 254 nm); t_R = 17.3 min (*S*), 10.5 min (*R*).

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