Toward the Development of a General Chiral α-Substituted Acetate Enolate Synthon for Aldolization. DMAP- and NEt_3-Promoted Oxazolidinethione "Deacylation"

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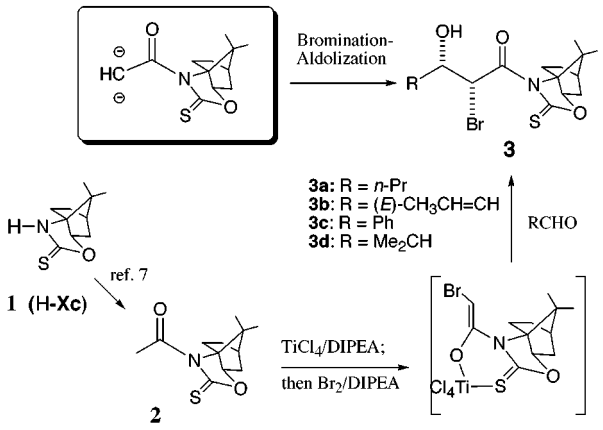
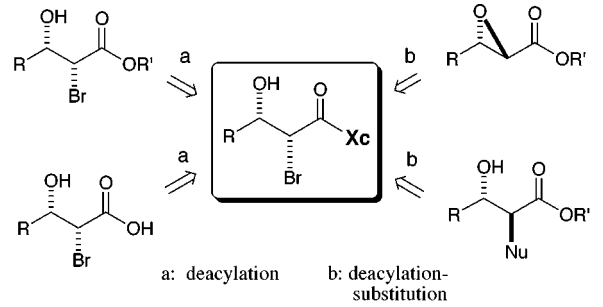
Introduction

α,β-Difunctional carboxylates such as α,β-epoxy esters, α-azido-β-hydroxy esters, and α-amino-β-hydroxy acids are versatile synthons for the synthesis of biologically active peptides,[1] aziridines,[2] and β- and γ-lactam antibiotics.[3] The vast importance of chiral difunctional carboxylates has stimulated the development of new methodology for their construction. Several examples of highly diastereoselective and enantioselective aldolizations employing chiral boron bromoacetate enolates[4,5] and stannous isothiocyanoacetate enolates[6] have been reported. Despite the significant utility that these metal-mediated aldolizations would enjoy in the construction of *syn*-[4] and *anti*-bromohydrin aldols,[5] issues associated with the conversion efficiency, synthetic flexibility of the initial aldol transformation, stereoisomers separation, reaction generality, and chemistry efficiency continue to pose an important challenge in the area of reaction design. In light of recent reports, wherein the boron-mediated bromoacetate enolate aldolizations consistently proceeded to no more than 80% conversion[4a] and 52% yield,[4b] we report that acetate titanium enolate derived from thioimide efficiently effects one-step bromination−aldolization with excellent yields and exceptionally high levels of asymmetric induction in aldol additions (Scheme 1). Synthetic efficiency will be enhanced if the initial thioimide aldols can be transformed into a different product. However, control of the transformation profile (Scheme 2, deacylation vs substitution) is difficult for basic reagents, e.g. LiOBn- and LiOH-mediated deacylation of the oxazolidinone bromohydrin.[4] We envisioned the feasibility of complete control of the reaction profile, which requires a very mild condition for removing the chiral auxiliary from bromohydrin aldols.

Scheme 1



Scheme 2



Results and Discussion

Since earlier work in our laboratories established the fesasibility of $TiCl_4$ as a Lewis acid to effect rapid and highly stereoselective aldolization of camphor-based *N*-acyloxazolidinethione with aldehydes,[7] we aimed at using previously reported camphor-based chiral *N*-acetyloxazolidinethione **2** as starting material and explored one-step enolate bromination−aldolization reactions (Scheme 1). The titanium enolate,[8,9] generated by the sequential addition of $TiCl_4$ (1.6 equiv) and diisopropylethylamine (1.2 equiv) to a cold (0 °C) solution of the thioimide **2** (0.25 M in CH_2Cl_2), was treated with bromine (1 equiv) at −78 °C to give an intermediate adduct, which was isolated and characterized by ^{1}H NMR spectroscopy [(400 MHz, $CDCl_3$) δ 5.03 (d, J = 12 Hz, 1 H), 4.83 (d, J = 12 Hz, 1

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Table 1. Titanium-Mediated Bromination−Aldolization Reactions of Acetate Thioimide 2 (Scheme 1)

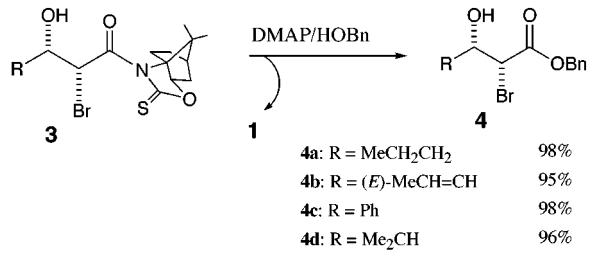
entry	electrophile	ratio[a]	yield[b] (%)	adduct
1	*n*-PrCHO	*c*	91	**3a**
2	(*E*)-MeCH=CHCHO	*c*	90	**3b**
3	PhCHO	*c*	94	**3c**
4	Me_2CHCHO	*c*	91	**3d**

[a] Ratio determined by 400-MHz ^{1}H NMR spectroscopy. [b] Isolated yield. [c] The *syn* aldol **3** was the only detected product by ^{1}H NMR analysis.

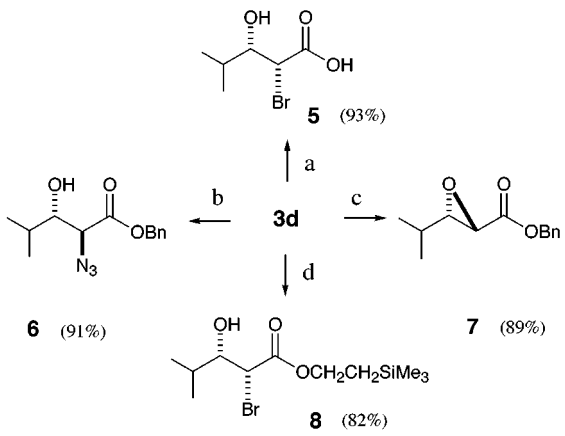
H), 4.52 (dd, J = 8.4, 4.0 Hz, 1 H), 2.91−1.21 (m, 7 H), 1.16 and 1.04 (2s, 6 H)] as the bromoacetate carboxthioimide.[10] Treatment of this intermediate, generated in situ, with an additional 1.2 equiv of diisopropylethylamine at −78 °C and subsequent aldolization of the resulting titanium bromoacetate enolate with *n*-butyraldehyde (1.3 equiv) at −78 °C led within 1.5 h to the bromohydrin **3a** in 94% yield (Scheme 1, Table 1, entry 1). We believe the enhanced electrophilicity of aldehyde carbonyl group, promoted by $TiCl_4$, is crucial to this high-yield asymmetric aldolization reaction. The crude aldol adduct showed a single set of peaks in the 400-MHz ^{1}H NMR spectrum suggestive of complete asymmetric induction. Assignment of the erythro configuration is based on the ^{1}H NMR vicinal coupling using the well-established fact that J_{threo} (7−9 Hz) > $J_{erythro}$ (3−6 Hz).[7a,11] The sense of asymmetric induction in this reaction is fully consistent with the observed stereochemical course of the previously reported titanium propionate thioimide enolate.[7] Having established the feasibility of the use of titanium acetate thioimide enolate to effect bromination−aldolization with excellent stereoselection, we established its generality with respect to the nature of the aldehyde. From the data in Table 1, it is clear that the reaction exhibits generality as well as extraordinary reactivity and asymmetric induction. Either the presence of conjugation (Table 1, entries 2 and 3) or α-methyl substitution (entry 4) in the aldehyde molecule does not appear to exert any influence on either the yield or the selectivity of the reaction. The absolute stereochemical assignment of the *syn* bromohydrin **3d** was made via nondestructive removal of the chiral auxiliary and correlation of the resultant benzyl epoxy ester (vide infra).[4b]

To promote further useful transformations of the initial aldol adducts without influencing the pendent functional groups, we sought to establish a very mild method for chiral auxiliary removal from thioimide **3**. Believing a nucleophilic catalysis route might be a useful method for the deacylation of thioimide, we initially explored DMAP-promoted transesterification of aldol **3a**. Exposing **3a** to 1.2 equiv of $PhCH_2OH$ in the presence of 25 mol % DMAP in CH_2Cl_2 at 0 °C for 8 h did indeed produce exclusively benzyl α-bromo-*β*-hydroxy ester **4a** in 98% yield with no apparent loss of stereochemistry (Scheme 3). Thioimide aldol **3b**, which by virtue of the acidity of its *β*-hydrogen is particularly prone to elimination, was also cleanly converted to the bromohydrin ester **4b**. Under our standard conditions, aldol adduct **3c** bearing a benzylic hydrogen led to exclusive deacylation to give α-bromo-*β*-hydroxy ester **4c** with no detectable elimination product. Transesterification of the hindered imide enolate/isobutyraldehyde aldol adduct **3d** can also lead to the corresponding ester **4d** in almost quantitative yield.

Scheme 3



Scheme 4



The efficiency of the method of general base and nucleophilic catalyst promoted thioimide deacylation for construction of useful α,*β*-difunctional compounds is illustrated by the additional examples provided below. Hindered thioimide aldol **3d** serves as our test substrate. Exposure of **3d** to $LiOH/H_2O_2$ produced bromohydrin acid **5** but also a second product readily identified as epoxy acid by its spectroscopic properties. Since more basic reagent LiOH enhances epoxide formation, replacing LiOH by a base like triethylamine may serve as a general base catalyst for promoting deacylation but inhibiting internal S_N2 displacement of bromide. Indeed, in the reaction of **3d** with H_2O (6 equiv) in the presence of NEt_3 (3 equiv) in CH_2Cl_2 at 0 °C, epoxide formation was completely suppressed and **5** was isolated in 93% yield (Scheme 4, path a). Bromohydrin **3d** can also be directed to form α-azido-*β*-hydroxy carboxylate via a deacylation−substitution protocol without any need to isolate the deacylation product and to protect the *β*-hydroxy group.[5a] Thus, exposing **3d** to $PhCH_2OH$ (1.2 equiv) in the presence of DMAP (0.25 equiv) in CH_2Cl_2 at 0 °C for 6 h, and subsequently adding NaN_3 (2.0 equiv) and n-Bu_4N^+-HSO_4^- (50 mol %) and warming to room temperature, led within 20 h to smooth S_N2 displacement of the bromide to give a 91% yield of azide **6** (Scheme 4, path b), a precursor of nonracemic 3-hydroxyleucine.[10] The NMR spectrum of the crude product showed it to be a single compound, free of the epoxide or the diastereomer at C-2. Switching the external nucleophile N_3^- to a base like F^- led to an internal S_N2 displacement of the bromide to give epoxide. Thus, exposure of the acyl-transfer

(10) This α-bromo thioimide intermediate is unstable at 0 °C. Attempts to obtain pure *N*-(α-bromoacetyl)oxazolidinethione from bromoacetyl chloride and oxazolidinethione **1** were not successful.

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product **4d**, generated in situ, to KF (5 equiv) and LiF (5 equiv) in the presence of n-$Bu_4N^+HSO_4^-$ (50 mol %) in CH_2Cl_2 at 25 °C for 36 h led to smooth epoxide formation to afford an 89% yield of the *cis*-benzyl α,β-epoxy ester **7**, $[\alpha]^{25}_D$ −35.5° (*c* 0.5, $CHCl_3$), with ≤1% of *trans*-epoxide being detected (Scheme 4, path c). The literature value for the rotation of the enantiomer of **7** ($[\alpha]^{25}_D$ +35.7°) confirms the stereochemical assignment.[4b] Finally, the utility of this nucleophilic catalyst promoted oxazolidinethione deacylation was examined in the transesterification of aldol **3d** with 2-(trimethylsilyl)ethanol (Scheme 4, path d), which participated equally well albeit in a somewhat slower reaction, giving the β-substituted ethyl ester **8** in 82% isolated yield.

We have demonstrated, to our knowledge, the first example of employing titanium-mediated bromination−aldolization of *N*-acetyloxazolidinethione to develop a general chiral α-substituted acetate enolate synthon. Synthetically, the remarkable facility of nucleophilic catalyst and general base promoted oxazolidinethione deacylation not only expands the scope of asymmetric aldol addition method by providing direct access to a variety of optically active α,β-difunctional acids and esters but also opens the question of the importance of the nature of the chiral auxiliary on further useful transformations of the initial chiral adducts. In addition, the preceding studies highlight the unexpected reactivity and stereoselection of bromoacetate titanium enolate aldolizations, which offer a practical alternative to the use of other expensive metalloids such as boron to achieve excellent yield as well as exceptional stereocontrol. Further studies will determine whether this DMAP-promoted deacylation will be generally useful for other adducts derived from chiral carboximides. At present we know that the DMAP-promoted transesterification of standard thioimide aldol adducts is also easily effected without recemization of either center.

Experimental Section

General. Diisopropylamine 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 400-MHz ^{1}H NMR.

General Procedure for the $TiCl_4$-Mediated Bromination−Aldolization of Thioimide 2. To a solution of **2** (10 mmol) in 40 mL of CH_2Cl_2 cooled to 0 °C was added 16 mL (1 M in CH_2Cl_2, 16 mmol, 1.6 equiv) of $TiCl_4$. After stirring at 0 °C for 3 min, slow addition of diisopropylethylamine (1 M in CH_2Cl_2, 12 mL, 12 mmol) and further stirring for 10 min at 0 °C, the reaction mixture was cooled to −78 °C. To the above reaction mixture was slowly added a solution of Br_2 (10 mmol) in 10 mL of CH_2Cl_2. After stirring at −78 °C for 10 min, a second equivalent of diisopropylethylamine (1 M in CH_2Cl_2, 12 mL, 12 mmol) was added and stirred for 10 min at −78 °C. To the above enolate solution was slowly added a solution of freshly distilled aldehyde (13 mmol) in 13 mL of CH_2Cl_2. The reaction mixture was stirred at −78 °C for 1.5 h and quenched with 40 mL of aqueous phosphate buffer (pH = 7). The aqueous layer was extracted with 60 mL of CH_2Cl_2. The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexane, silica gel, 0−5 °C) afforded pure aldol adduct **3**.

***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).** As described above, 2.39 g (10 mmol) of **2** was converted to its chlorotitanium enolate. Condensation with *n*-butyraldehyde (14 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 3.54 g (91%) of **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-(*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 (3b).** As described above, 2.39 g (10 mmol) of **2** was converted to its chlorotitanium enolate. Condensation with crotonaldehyde (14 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 3.49 g (90%) of **3b**: 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-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).** As described above, 2.39 g (10 mmol) of **2** was converted to its chlorotitanium enolate. Condensation with benzaldehyde (14 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, 5 °C) afforded 3.98 g (94%) of **3c** as a white solid: 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-methylpentanoyl]-(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, 2.39 g (10 mmol) of **2** was converted to its chlorotitanium enolate. Condensation with isobutyraldehyde (14 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 3.54 g (91%) of **3d** as a white solid: 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.

General Procedure for the Deacylation Reaction Promoted by DMAP. To a solution of aldol adduct **3** (1 mmol) and $PhCH_2OH$ (1.2 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C was added a solution of DMAP (0.2 mmol) in 0.5 mL of CH_2Cl_2. After stirring

at that temperature for 8−12 h, the reaction mixture was quenched with HCl (1 N, 2 mL) and diluted with CH_2Cl_2 (10 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The pale yellow oil was purified by chromatography on silica gel (using eluent gradient 15% ethyl acetate/hexane to 50% ethyl acetate/hexane) to afford bromohydrin ester and recovered oxazolidinethione auxiliary.

Phenylmethyl (2*R*,3*S*)-2-Bromo-3-hydroxyhexanoate (4a). Bromohydrin aldol **3a** (390 mg, 1 mmol) was converted to its corresponding benzyl ester **4a** (295 mg, 98%) as described in the general protocol. Diastereomer analysis (400 MHz ^{1}H NMR) of the unpurified mixture revealed the presence of essentially a single *syn* bromohydrin **4a**: IR (neat) 3479, 1730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (bs, 5 H), 5.20 (2d, J = 12.0 Hz, 2 H), 4.30 (d, J = 3.6 Hz, 1 H), 3.91 (dt, J = 4.2, 4.0 Hz, 1 H), 2.71 (bs, 1 H). 1.58−1.30 (m, 4 H), 0.89 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 168.61, 134.55, 128.41, 128.25, 128.07, 70.69, 67.79, 52.41, 36.18, 18.72, 13.85; $[\alpha]^{25}_D$ +67.2° (*c* 4.3, CH_2Cl_2); high-resolution MS *m*/*e* calcd for $C_{13}H_{17}O_3Br$: 300.0361, found: 300.0355. Anal. Calcd for $C_{13}H_{17}O_3Br$: C, 51.82; H, 5.69. Found: C, 51.86; H, 5.67.

Phenylmethyl (2*R*,3*S*)-2-Bromo-3-hydroxy-(*E*)-4-hexenoate (4b). Bromohydrin aldol **3b** (390 mg, 1 mmol) was converted to its corresponding benzyl ester **4b** (283 mg, 95%) as described in the general protocol. Diastereomer analysis (400 MHz ^{1}H NMR) of the unpurified mixture revealed the presence of essentially a single *syn* bromohydrin **4b**: IR (neat) 3481, 1731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (bs, 5 H), 5.69 (dq, J = 15.6, 6.8 Hz, 1 H), 5.34 (dd, J = 15.6, 6.4 Hz, 1 H), 5.09 (2d, J = 12.0 Hz, 2 H), 4.35 (t, J = 6.4 Hz, 1 H), 4.17 (d, J = 6.4 Hz, 1 H), 2.75 (bs, 1 H). 1.54 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 167.77, 134.57, 130.98, 128.33, 128.28, 128.06, 127.56, 72.45, 67.60, 51.64, 17.74; $[\alpha]^{25}_D$ +5.6° (*c* 3.5, CH_2Cl_2); high-resolution MS *m*/*e* calcd for $C_{13}H_{15}O_3Br$: 298.0204, found: 298.0208. Anal. Calcd for $C_{13}H_{15}O_3Br$: C, 52.17; H, 5.06. Found: C, 52.36; H, 5.11.

Phenylmethyl (2*R*,3*S*)-2-Bromo-3-hydroxy-3-phenylpropanoate (4c). Bromohydrin aldol **3c** (390 mg, 1 mmol) was converted to its corresponding benzyl ester **4c** (320 mg, 96%) as described in the general protocol. Diastereomer analysis (400 MHz ^{1}H NMR) of the unpurified mixture revealed the presence of essentially a single *syn* bromohydrin **4c**: IR (neat) 3477, 1732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29−7.09 (ms, 10 H), 5.02 (d, J = 6.8 Hz, 1 H), 5.01 (s, 2 H), 4.42 (d, J = 6.8 Hz, 1 H), 1.56 (bs, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 167.78, 137.91, 134.32, 128.48, 128.30, 128.22, 128.04, 127.93, 126.51, 73.80, 67.61, 52.69; $[\alpha]^{25}_D$ +33.9° (*c* 0.8, CH_2Cl_2); high-resolution MS *m*/*e* calcd for $C_{16}H_{15}O_3Br$: 334.0204, found: 334.0209. Anal. Calcd for $C_{16}H_{15}O_3Br$: C, 57.31; H, 4.51. Found: C, 57.54; H, 4.55.

Phenylmethyl (2*R*,3*S*)-2-Bromo-3-hydroxy-4-methylpentanoate (4d). Bromohydrin aldol **3d** (390 mg, 1 mmol) was converted to its corresponding benzyl ester **4d** (288 mg, 96%) as described in the general protocol. Diastereomer analysis (400 MHz ^{1}H NMR) of the unpurified mixture revealed the presence of essentially a single *syn* bromohydrin **4d**: IR (neat) 3481, 1730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (bs, 5 H), 5.20 (2d, J = 12.0 Hz, 2 H), 4.47 (d, J = 3.6 Hz, 1 H), 3.53 (dd, J = 7.2, 3.6 Hz, 1 H), 1.87 (bs, 1 H), 1.78 (octet, J = 7.2 Hz, 1 H), 1.00 (d, J = 6.8 Hz, 3 H), 0.91 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.18, 134.67, 128.60, 128.48, 128.25, 75.91, 67.94, 51.07, 31.61, 18.90, 17.60; $[\alpha]^{25}_D$ +15.5° (*c* 0.9, CH_2Cl_2); high-resolution MS *m*/*e* Calcd for $C_{13}H_{17}O_3Br$: 300.0361, found: 300.0355. Anal. calcd for $C_{13}H_{17}O_3Br$: C, 51.82; H, 5.69. Found: C, 51.80; H, 5.65.

(2*R*,3*S*)-2-Bromo-3-hydroxy-4-methylpentanoic Acid (5). To a solution of aldol adduct **3d** (390 mg, 1 mmol) and H_2O (6 mmol) in CH_3CN (1.5 mL) at 0 °C was added a solution of NEt_3 (3 mmol) in 0.5 mL of CH_3CN. After stirring at that temperature for 8 h, the reaction was quenched with HCl (1 N, 3 mL) and diluted with CH_2Cl_2 (10 mL). The organic layer was washed with 1 N aqueous $NaHCO_3$ (5 mL × 2). The aqueous phases were combined, cooled to 0 °C, neutralized with HCl, and extracted with three portions of CH_2Cl_2. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford pure bromohydrin acid **5** (196 mg, 93%): IR (neat) 3509, 3400−2411 (br COOH), 1703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.49 (d, J = 3.6 Hz, 1 H), 3.54 (dd, J = 6.8, 3.6 Hz, 1 H), 3.45 (bs, 2 H), 1.85 (octet, J = 6.8 Hz, 1 H), 1.04 (d, J = 6.8 Hz, 3 H), 0.92 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.80, 76.17, 51.06, 31.87, 18.71, 17.73; $[\alpha]^{25}_D$ +22.2° (*c* 1.2, CH_2Cl_2); high-resolution MS *m*/*e* calcd for $C_6H_{12}O_3Br$ (FAB, MH^+): 210.9970, found: 210.9977. Anal. Calcd for $C_6H_{11}O_3Br$: C, 34.13; H, 5.25. Found: C, 34.07; H, 5.24.

Phenylmethyl (2*S*,3*S*)-2-Azido-3-hydroxy-4-methylpentanoate (6). To a solution of aldol adduct **3d** (390 mg, 1 mmol) and $PhCH_2OH$ (1.2 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added a solution of DMAP (0.2 mmol) in 0.2 mL of CH_2Cl_2. After stirring for 8−10 h at 0 °C, NaN_3 (2.0 mmol) and n-$Bu_4N^+HSO_4^-$ (25 mol %) were added and stirring was continued for 20 h at room temperature. The product was extracted with 20 mL of CH_2Cl_2 and washed with H_2O (5 mL x 6) and brine (5 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrateed in vacuo. The pale yellow oil was purified by chromatography on silica gel (using eluent gradient 20% ethyl acetate/hexane to 50% ethyl acetate/hexane) to afford recovered auxiliary and azido ester **6** (239 mg, 91%): IR (neat) 3481, 1740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (bs, 5 H), 5.25 and 5.23 (2d, J = 12.0 Hz, 2 H), 3.92 (d, J = 6.0 Hz, 1 H), 3.65 (t, J = 6.0 Hz, 1 H), 1.88 (octet, J = 6.0 Hz, 1 H), 0.95 (d, J = 6.4 Hz, 3 H), 0.93 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.18, 134.65, 128.54, 128.51, 128.27, 76.38, 67.70, 63.89, 30.26, 19.42, 16.59; $[\alpha]^{25}_D$ −18.7° (*c* 1.7, CH_2Cl_2); high-resolution MS *m*/*e* Calcd for $C_{13}H_{17}O_3N_3$: 263.1269. Found: 263.1275. Anal. Calcd for $C_{13}H_{17}O_3N_3$: C, 59.28; H, 6.51. Found: C, 59.34; H, 6.49.

Phenylmethyl (2*S*,3*S*)-2,3-Epoxy-4-methylpentanoate (7). To a solution of aldol adduct **3d** (390 mg, 1 mmol) and $PhCH_2OH$ (1.2 mmol) in CH_2Cl_2 (1 mL) at 0 °C was added a solution of DMAP (0.2 mmol) in 1 mL of CH_2Cl_2. The resulting mixture was stirred for 8−10 h at 0 °C. A solution of LiF (5 mmol), KF (5 mmol), and n-$Bu_4N^+HSO_4^-$ (25 mol %) in 2 mL of CH_2Cl_2 was added in one portion. After stirring for 36 h at room temperature, the reaction mixture was partitioned between CH_2Cl_2 (10 mL) and HCl (1 N, 5 mL). The aqueous phase was washed with CH_2Cl_2 (5 mL × 2). The organic layer was combined, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford crude epoxy ester **7**. Diastereomer analysis (400 MHz ^{1}H NMR) of the unpurified mixture revealed a >98:2 ratio of cis and trans epoxides. The pale yellow oil was purified by chromatography on silica gel (using eluent gradient 6% ethyl acetate/hexane to 50% ethyl acetate/hexane) to afford recovered oxazolidinethione auxiliary and epoxy ester **7** (196 mg, 89%): IR (neat) 1733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (bs, 5 H), 5.21 and 5.19 (2d, J = 12.0 Hz, 2 H), 3.54 (d, J = 4.8 Hz, 1 H), 2.82 (dd, J = 9.2, 4.8 Hz, 1 H), 1.71−1.50 (m, 1 H), 1.08 (d, J = 6.8 Hz, 3 H), 0.78 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 167.94, 135.03, 128.46, 128.44, 128.43, 67.09, 63.24, 53.25, 27.12, 20.21, 18.34; $[\alpha]^{25}_D$ −35.5° (*c* 0.5, $CHCl_3$); high-resolution MS *m*/*e* calcd for $C_{13}H_{16}O_3$: 220.1099, found: 220.1095.

2-(Trimethylsilyl)ethyl (2*R*,3*S*)-2-Bromo-3-hydroxy-4-methylpentanoate (8). Bromohydrin aldol **3d** (390 mg, 1 mmol) was converted to its corresponding β-(trimethylsilyl)ethyl ester **8** (254 mg, 82%) as described in the general protocol. Diastereomer analysis (400 MHz ^{1}H NMR) of the unpurified mixture revealed the presence of essentially a single *syn* bromohydrin **8**: IR (neat) 3490, 1736 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39 (d, J = 4.0 Hz, 1 H), 4.25 (m, 2 H), 3.50 (dd, J = 4.8, 4.0 Hz, 1 H), 1.94 (bs, 1 H), 1.81 (m, 1 H), 1.02 (m, 2 H), 1.01 (d, J = 6.8 Hz, 3 H), 0.90 (d, J = 6.8 Hz, 3H), 0.03 (s, 9 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.46, 75.83, 64.83, 51.24, 31.53, 18.94, 17.57, 17.06, −1.60; $[\alpha]^{25}_D$ +21.5° (*c* 1.0, CH_2Cl_2); high-resolution MS *m*/*e* calcd for $C_{11}H_{23}O_3BrSi$: 310.0599, found: 310.0595. Anal. Calcd for $C_{11}H_{23}O_3BrSi$: C, 42.44; H, 7.44. Found: C, 42.12; H, 7.33.

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