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TETRAHEDRON: *ASYMMETRY*

An efficient method for the synthesis of enantiopure *cis*-α,β-epoxy acids

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Abstract

Enantiopure *cis*-α,β-epoxy acids were prepared via a modified Darzen's reaction employing the titanium-mediated bromination–aldolization of chiral acetate thioimide enolate.

The great importance of chiral α,β-epoxy carboxylic acids as precursors to enantiopure α,β-epoxy lactone and α-amino-β-hydroxy acids make their easy availability desirable.[1] While Sharpless epoxidation,[2] asymmetric nucleophilic epoxidation[3] and modified Darzen's epoxidation reactions[4] are facile approaches to chiral epoxides such as epoxy alcohols and α,β-epoxy esters, progress in the synthesis of enantiopure epoxy acids and epoxy carboxylate salts has been sporadic.[1,5] Although the asymmetric epoxidation procedure reported by Sharpless has been demonstrated to be a useful approach to chiral epoxy alcohols needed for the synthesis of enantiomerically pure α,β-epoxy acids, this method does not generally extend to *cis*-epoxy acids and γ,δ-unsaturated α,β-epoxy acids.[6] Herein we report an efficient route to enantiomerically pure *cis*-α,β-epoxy acids and γ,δ-unsaturated α,β-epoxy carboxylate salts by a modified Darzen's reaction. Such a modification involves the use of one-pot bromination–aldolization of *N*-acetyloxazolidinethione **1**[7] and then converting the resulting bromohydrin aldol adducts to epoxy acids. The reaction of thioimide **1** with $TiCl_4$ (2.0 equiv.), diisopropylethylamine (2.2 equiv.) and bromine (1.0 equiv.) in dichloromethane at −78°C for 0.5 h led to the bromoacetate titanium enolate. Addition of representative aldehydes (1.5 equiv.) and reaction at −78°C for 2 h followed by extractive isolation and silica gel purification gave bromohydrin aldols **2a**–**2d** in excellent yields (90%) with complete asymmetric induction (Scheme 1).[8]

Can the initial thioimide aldol adducts be directed toward epoxy acids? Exposure of a mixture of α-bromo-β-hydroxy thioimide aldols **2a** (1 mmol) and 10 equiv. of H_2O in CH_3CN (4 mL) to NEt_3 (5 mmol) at 0°C for 4 h, and subsequently adding MeOH (1 mL)/saturated aqueous potassium carbonate (1 mL) and stirring at 25°C led to hydrolysis and epoxide formation to give α,β-epoxy acid **3a** in 91% yield

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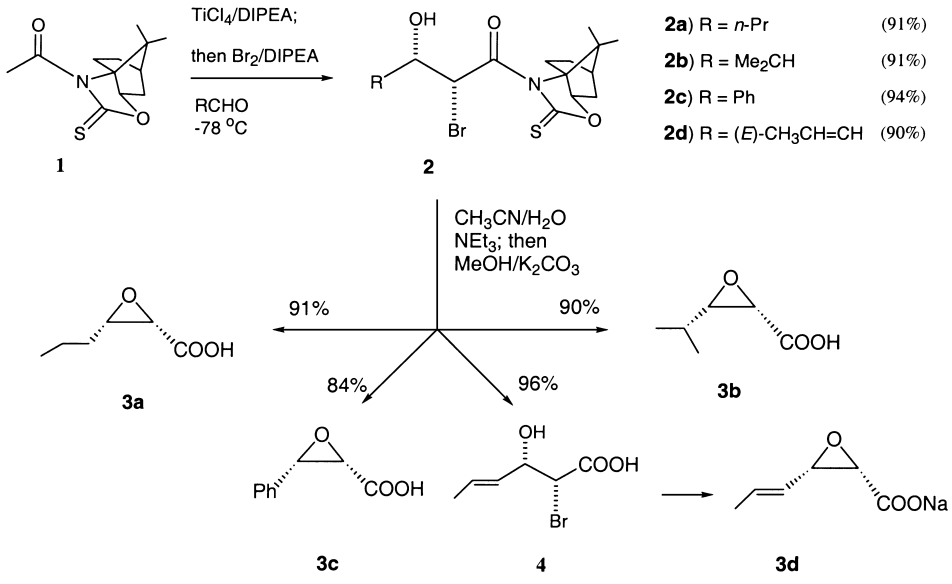

Scheme 1.

(>99% ee)[9] along with recovered oxazolidinethione.[10] **3a** Showed a single set of absorptions in the 400 MHz NMR spectrum suggestive of stereospecific epoxide-formation. Hindered saturated aldol adduct **2b** gave a similar result. Enantioselectivity was confirmed by chiral HPLC to be >99% by comparison to racemic samples.[10] The utility of this protocol was examined in the conversion of **2c** to the corresponding epoxy acids, which demands very mild conditions for workup due to the high propensity of phenyl substituted epoxide functionality to rearrange in the presence of acid. Thus, under the workup conditions described above, **3c** was produced only in less than 10% yield. Replacing HCl by oxalic acid remarkably avoided this problem and increased the yield to 84% (>99% ee).[9,10] The appearance of only one set of signals indicates no concurrent epimerization before cyclization. In the case of bromohydrin aldol **2d**, all attempts to isolate the desired epoxy acid led to decomposition or bromohydrin acid **4** (96% yield), depending on the conditions. However, adding 2.5 equiv. of sodium carbonate to a solution of **4** in CH_3CN:H_2O (3:1, 4 mL) and stirring at 25°C for 10 h led to smooth epoxide formation to give sodium epoxy carboxylate **4d**, which was characterized by NMR spectroscopy.[10]

In conclusion, diastereopure *syn*-α-bromo-β-hydroxy thioimide aldols can be conveniently prepared and serve as precursors to chiral *cis*-α,β-epoxy acids or sodium epoxy carboxylate.

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8. 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) [Ref. 7a and (a) House, H. O.; Crumrine, D. S.; Olmstead, H. D. *J. Am. Chem. Soc*. **1973**, *95*, 3310. (b) Kleschick, W. A.; Buse, C. T.; Heathcock, C. H. *J. Am. Chem. Soc*. **1977**, *99*, 247. (c) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A. *J. Org. Chem*. **1980**, *45*, 1066]. The *syn*-aldol adduct **2** was the only detected product in the 400 MHz ^{1}H NMR analysis. The crude aldol adduct showed a single set of peaks in the 400 MHz ^{1}H NMR spectrum suggestive of complete asymmetric induction.
9. Enantiomeric excesses were determined by HPLC using a Chiralcel OD column (Daicel Chemical Industries), hexane:*i*PrOH:CF_3COOH (370:20:1), at 23°C with detection at 254 nm; elution times (1 mL/min flow) were 7.64 min and 10.14 min.
10. New compounds have been characterized spectroscopically. Selected data for **3a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.54 (d, *J*=4.0 Hz, 1H, CHC*H*C=O), 3.22–3.18 (m, 1H, C*H*CHC=O), 1.69–1.37 (m, 4H, $CH_3CH_2CH_2$), 0.92 (t, *J*=6.0 Hz, 1H, $CH_3CH_2CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.38, 58.02, 52.51, 29.21, 19.53, 13.79; $[\alpha]_D^{25}$ −6.5 (*c* 2.4, CH_2Cl_2); high-resolution MS m/e calcd for $C_6H_{11}O_3$: 131.0717. Found: 131.0718. **3b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.58 (d, *J*=4.4 Hz, 1H, CHC*H*C=O), 2.92 (dd, 1H, *J*=9.2, 4.4 Hz, C*H*CHC=O), 1.72–1.56 (m, 1H, $(CH_3)_2CHCH$), 1.30 and 0.94 (2d, *J*=7.2 Hz, 1H, $(CH_3)_2CH$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.12, 63.64, 53.01, 27.25, 20.18, 18.39; HPLC (hexane:*i*PrOH:CF_3COOH 370:20:1) 9.47 min (>99%); $[\alpha]_D^{25}$ −4.3 (*c* 0.5, CH_2Cl_2); high-resolution MS m/e calcd for $C_6H_{11}O_3$: 131.0717. Found: 131.0715. **3c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.28 (m, 5H, C_6H_5), 4.27 (d, *J*=4.4 Hz, 1H, CHC*H*C=O), 3.80 (d, *J*=4.4 Hz, 1H, C*H*CHC=O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.37, 132.02, 128.54, 128.04, 126.47, 57.95, 55.30; HPLC (hexane:*i*PrOH:CF_3COOH 370:20:1) 9.76 min (>99%); $[\alpha]_D^{25}$ −22.3 (*c* 1.1, CH_2Cl_2); high-resolution MS m/e calcd for $C_9H_8O_3$: 164.0473. Found: 164.0474. **4d**: ^{1}H NMR (400 MHz, D_2O) δ 6.25 (dq, *J*=15.2, 6.8 Hz, 1H, CH_3HC=CH), 5.32 (dd, *J*=15.2, 7.2 Hz, 1H, CH_3HC=C*H*), 3.72 (bs, 2H, C*H*C*H*C=O), 1.79 (d, *J*=6.8 Hz, 3H, CH_3CH=CH); ^{13}C NMR (100 MHz, D_2O) δ 174.67, 136.63, 123.35, 57.29, 57.15, 17.74.