Chiral Auxiliary Mediated Conjugate Reduction and Asymmetric Protonation: Synthesis of High Affinity Ligands for HIV Protease Inhibitors

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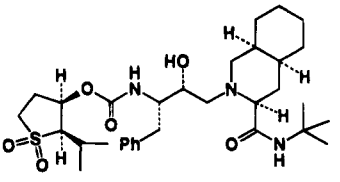
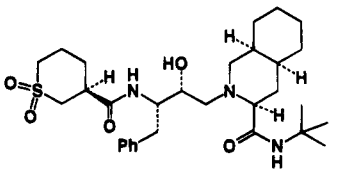
We recently reported the structure-based design and synthesis of a number of high affinity nonpeptidal P_2-ligands for the HIV protease substrate binding site.[1] As exemplified in **1** (Figure 1), urethanes of 3-hydroxy-2-alkylsulfolanes have effectively replaced both the P_2-asparagine and the P_3-quinoline of the Ro 31-8959 class of HIV protease inhibitors.[2] Subsequently, we found that the 1,1-dioxotetrahydro-2*H*-thiopyran-3-carboxamides can also effectively serve as high affinity P_2-ligands.[3] Incorporation of these ligands in the Ro 31-8959-based hydroxyethylamine isostere[2] has resulted in significant potency enhancement compared to the corresponding urethane derivatives. The (*S*)-1,1-dioxotetrahydro-2*H*-thiopyran-3-carboxamide derivative **2** has shown more than 190-fold inhibitory potency improvement over its corresponding 3(*R*) or 3(*S*) urethane derivatives.[1b] The corresponding inhibitor with 3(*R*)-carboxamide is 2-fold less potent compared to **2**. As described recently, the synthesis of optically active 3(*R*)-carboxylic acid **11** can be carried out efficiently by bakers' yeast reduction followed by Barton's deoxygenation sequence (Scheme 2).[3] However, access to the more potent 3(*S*) isomer **9** in optically pure form is only limited by its resolution from a racemic mixture. In order to further explore the biological properties of HIV protease inhibitors incorporating these P_2-ligands into other hydroxyethylamine isosteres,[4] we sought to develop an enantioselective route to these novel heterocycles. The concept of creation of new stereogenic centers at the α and β positions of chiral



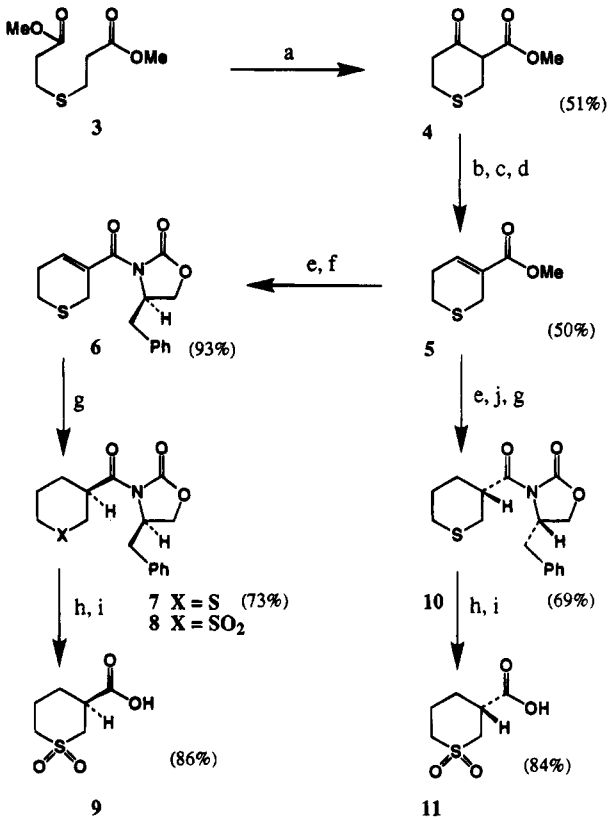
1 IC_{50} [HIV-1] = 3.5±0.8 nM (n=7)
CIC_{95} = 50±14 nM (n=7)



2 IC_{50} [HIV-1] = 9.2±0.2 nM (n=2)
CIC_{95} = 200 nM

Figure 1.

Scheme 1[a]



[a] Key: (a) NaH, DME, 165 °C, 1 h; (b) $NaBH_4$, MeOH; (c) MsCl, Et_3N, 0–23 °C; (d) DBU, THF, 23 °C; (e) LiOH, aqueous THF, 23 °C, 12 h; (f) Me_3COCl, Et_3N, THF, −15 to 0 °C then *N*-lithio-(*R*)-(−)-4-benzyloxazolidinone, −78 °C; (g) L-Selectride, THF, −78 °C, 15 min; (h) Oxone, MeOH–H_2O, 23 °C, 6 h; (i) LiOH, H_2O_2, 0 °C; (j) Me_3COCl, Et_3N. THF, −15 to 0 °C and then *N*-lithio-(*S*)-(−)-4-benzyloxazolidinone, −78 °C.

α,β-unsaturated acyclic *N*-acyloxazolidinones[5] and *N*-enoylsultams[6] by Diels–Alder reactions and various conjugate additions has been well documented. Thus, conjugate hydride reduction of heterocyclic α,β-unsaturated chiral *N*-acyloxazolidinone followed by asymmetric

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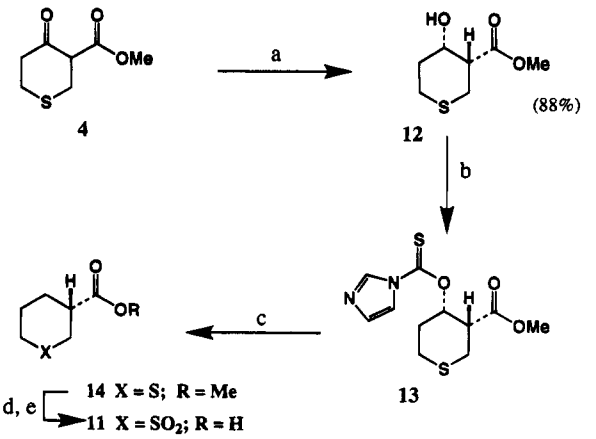
protonation of the resulting enolate is an attractive synthetic approach to the above heterocycles in optically active form. Herein we report an efficient enantioselective synthesis of (*R*)- and (*S*)-1,1-dioxotetrahydro-2*H*-thiopyran-3-carboxylic acids utilizing chiral oxazolidinone[7] mediated conjugate reduction and asymmetric protonation process.

Treatment of commercially available dimethyl 3,3′-thiodipropionate (**3**) with sodium hydride in refluxing DME for 1 h afforded the Dieckmann cyclization product **4** in 51% yield.[8] The ketoester **4** was subjected to sodium borohydride reduction in methanol at −78 to 23 °C for 2 h to provide the corresponding cis/trans mixture (1:1) of alcohols. The resulting alcohols were mesylated with mesyl chloride and triethylamine at 0−23 °C for 12 h, and subsequent elimination of the mesylate with DBU in THF at 23 °C for 1 h afforded the dihydrothiopyran **5** (50% from **4**).[9] Ester hydrolysis of **5** with aqueous lithium hydroxide followed by acidification provided the α,β-unsaturated acid which was converted to the α,β-unsaturated carboximide **6** with commercially available (*R*)-(+)-4-benzyl-2-oxazolidinone by standard protocol.[11] At first, hydrogenation of **6** was conducted to investigate the reactivity and diastereoselectivity. Since the ring sulfur of **6** is expected to deactivate the catalyst surface, the corresponding sulfone of **6** was exposed to hydrogenation conditions over 10% Pd−C under hydrogen-filled balloon for 12 h. Unfortunately, very little diastereoselectivity was observed. The sulfone derivative **8** and its corresponding diastereomer were obtained in a 1:1.5 mixture ratio (by 400 MHz ^{1}H NMR and HPLC) in 85% combined yield. We then investigated the well-known conjugate reduction[12] of the imide **6**. While direct hydrogenation did not provide any stereoselectivity, conjugate reduction with bulky lithium trialkylborohydride (L-Selectride, Aldrich)[13] followed by protonation resulted in excellent diastereocontrol. Reaction of **6** with 1.1 equiv of L-Selectride in THF at −78 °C for 15 min followed by quenching of the reaction with saturated aqueous NH_4Cl solution at −78 °C and warming to 23 °C provided the reduction product **7** in 73% yield after silica gel chromatography (selectivity 95:5 by HPLC before and after chromatography; 400 MHz ^{1}H NMR revealed only one isomer). Similarly, L-Selectride reduction and protonation of the corresponding (*S*)-4-benzyl-2-oxazolidinone derivative afforded **10** stereoselectively (selectivity >96:4 by HPLC; 400 MHz ^{1}H NMR revealed only one isomer) in 78% isolated yield. The enantiomeric excess of this asymmetric process was determined (>96% by ^{19}F NMR) by LAH reduction of oxazolidinone derivative **7** and **10** and subsequent formation of the Mosher ester[14] of the resulting hydroxymethyl tetrahydrothiopyran derivatives. Removal of the chiral auxiliaries of **7** and **10** with lithium hydroperoxide[15] was complicated by the formation of the diastereomeric sulfoxides. This problem was circumvented by initial oxidation of the ring sulfur to sulfone with oxone followed by removal of the chiral oxazolidinones by treatment with lithium hydroperoxide to provide enantiomerically pure acids **9** ($[\alpha]^{23}_D$ −5.1°, MeOH) and **11** ($[\alpha]^{23}_D$ +5.3°, MeOH) in 80−86% yields in the two-step sequence.

Scheme 2[a]



[a] Key: (a) bakers' yeast, sugar, H_2O, 18 h; (b) 1,1′-(thiocarbonyl)diimidazole, pyridine, THF, 23 °C, 14 h; (c) nBu_3SnH, AIBN, dioxane, 104 °C, 2 h; (d) LiOH, aqueous THF, 23 °C, 6 h; (e) Oxone, MeOH−H_2O, 23 °C, 12 h.

The absolute configurations of the acids **9** and **11** were assigned based on the comparison of the optical rotation of the acid **11** prepared with known configuration according to Scheme 2. As shown, bakers' yeast reduction of **4** afforded the hydroxy ester **12**[16] with known configuration in 88% yield (88% ee).[17] The C_4-hydroxyl group was deoxygenated efficiently using Barton's procedures.[18] Thus, formation of thioimidazolide **13** with 1,1′-(thiocarbonyl)diimidazole in THF in the presence of pyridine followed by tri-*n*-butyltin hydride reduction of the imidazolide in refluxing dioxane in the presence of a catalytic amount of AIBN resulted in formation of the methyl ester **14**.[19] Ester hydrolysis of **14** with aqueous lithium hydroxide followed by oxidation of the ring sulfur to the corresponding sulfone afforded the (*R*)-1,1-dioxotetrahydro-2*H*-thiopyran-3-carboxylic acid (**11**) ($[\alpha]^{23}_D$ +3.8°, MeOH) in optically active form (88% ee).

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(9) Alternatively, following the procedure of Dupre and Meyers,[10] formation of vinyl triflate and subsequent reduction with tributyltin hydride in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0) in dry THF furnished a 34% yield of **5** in two steps.

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(19) Under the present reaction conditions (slow addition and at reflux), no elimination product **5** was obtained.

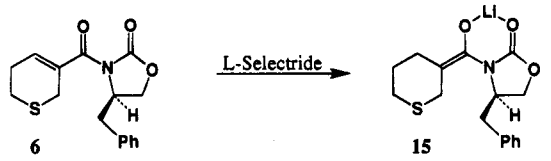

Figure 2.

The observed enantioselectivity in the above conjugate reduction and protonation process is in line with Evans' asymmetric alkylation model.[20] The ground state conformational preferences (s-cis, Figure 2) for the α,β-unsaturated imide derivative **6** will dictate the enolate geometry. The ground state conformational preferences for the related acyclic enones are well established due to the work of Chamberlin[21] and Oelichmann.[22] In imide conformation **6**, conjugate L-Selectride addition would lead to preferential formation of the chelated enolate **15**. Thus, *Re*-face protonation of the enolate **15** is preferred, and this will result in the formation of **7** selectively. While this model explains the present stereoselection, the evidence of such a model requires further experimentation which is currently in progress.

In summary, chiral auxiliary-mediated conjugate reduction and protonation of α,β-unsaturated carboximide provides a convenient synthetic route to optically active (*R*)- and (*S*)-1,1-dioxotetrahydro-2*H*-thiopyran-3-carboxylic acids. The usefulness of these novel heterocycles as high affinity nonpeptidal P_2-ligands for the HIV-1 substrate binding site has been reported.[3,23] Further application of these ligands as well as the scope and utility of the present asymmetric synthesis are the subjects of ongoing investigations in our laboratory.

Experimental Section

All melting points are uncorrected. Analytical HPLC analyses were performed on a μBondapak C-18 column, 4.6 mm × 25 cm, 50% EtOAc/hexanes as solvent, flow rate 2.0 mL/min. Anhydrous solvents were obtained as follows: methylene chloride, distillation from P_4O_{10}; tetrahydrofuran, distillation from sodium/benzophenone; dimethoxyethane and pyridine, distillation from CaH_2. All other solvents were HPLC grade. Column chromatography was performed with Whatman 240–400 mesh silica gel under low pressure of 5–10 psi. Thin-layer chromatography (TLC) was carried out with E. Merck silica gel 60 F-254 plates.

Methyl 4-Oxotetrahydro-2*H*-thiopyran-3-carboxylate (4). To a stirred solution of commercially available (Lancaster) dimethyl 3,3'-thiopropionate (30 g, 145.6 mmol) in DME (200 mL) under nitrogen was suspended NaH (60%, 7 g) and the resulting mixture was refluxed for 1 h. The reaction was cooled to 23 °C, and saturated $NaHCO_3$ solution was added to the reaction mixture carefully. The mixture was concentrated under reduced pressure, and the residue was extracted with EtOAc (2 × 150 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution followed by saturated NaCl solution. The organic layer was dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure provided a residue which was chromatographed (5% EtOAc/Hexanes) on silica gel to give 13.1 g of **4** (51% yield) as colorless oil: ^{1}H NMR ($CDCl_3$) δ 3.77 (s, 3 H), 3.34 (s, 2 H), 2.69–2.82 (t, J = 5.7 Hz, 2 H), 2.54–2.64 (m, 2 H).

Methyl 5,6-Dihydro-2*H*-thiopyran-3-carboxylate (5). To a solution of β-keto ester **4** (2.69 g, 15.4 mmol) in methanol (100 mL) at −78 °C was added solid $NaBH_4$ (730 mg, 19.3 mmol). The resulting mixture was stirred at −78 °C for 10 min, and then the dry ice bath was removed and the mixture was allowed to warm to 23 °C for 2 h. After this period, the reaction was quenched with saturated $NaHCO_3$ solution and the mixture was concentrated under reduced pressure. The residue was extracted with EtOAc (2 × 100 mL). The combined organic extracts were washed with 1 N HCl solution and saturated $NaHCO_3$ solution followed by saturated NaCl solution. The organic layer was dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure provided a residue which was chromatographed (50% EtOAc/hexanes) on silica gel to give the corresponding β-hydroxy ester (2.12 g, 79% yield) as a colorless oil.

To a stirred solution of the above β-hydroxy ester (2.12 g, 12.1 mmol) at 0 °C in CH_2Cl_2 (25 mL) were added methanesulfonyl chloride (2.22 mL, 29.0 mmol) and triethylamine (5 mL, 36.2 mmol). The resulting mixture was stirred at 0–23 °C for 12 h. After this period, the reaction was quenched with saturated $NaHCO_3$ solution (15 mL), and the mixture was diluted with CH_2Cl_2 (25 mL). The layers were separated, and the organic layer was washed with NaCl solution, dried over anhydrous Na_2SO_4, and concentrated to dryness. The crude mesylate was used for the next reaction without further purification.

The above mesylate was dissolved in dry THF (100 mL), and DBU (2.1 mL, 14.4 mmol) was added. The resulting mixture was stirred at 23 °C for 1 h. The reaction was diluted with ethyl acetate (100 mL), and the organic solution was washed with saturated NH_4Cl solution (2 × 40 mL) and saturated NaCl solution and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue which was chromatographed (10% EtOAc/hexane) over silica gel to afford the title α,β-unsaturated ester **5** (1.2 g, 63%) as an oil: ^{1}H NMR ($CDCl_3$) δ 7.1 (m, 1 H), 3.72 (s, 3 H), 3.3–3.4 (dd, J = 2.3, 4.4 Hz, 2 H), 2.65 (t, J = 5.7 Hz, 2 H), 2.41–2.57 (m, 2 H).

1-[5,6-Dihydro-2*H*-thiopyran-3-yl]-4(*R*)-(phenylmethyl)-2-oxazolidinone (6). To a stirred mixture of **5** (1.21 g, 7.64 mmol) in THF (6 mL) and water (30 mL) was added solid $LiOH·H_2O$ (640 mg, 15.2 mmol). The resulting mixture was stirred at 23 °C for 12 h. After this period, the THF was removed under reduced pressure, and the remaining aqueous mixture was acidified with 6 N aqueous HCl solution (pH = 1). The mixture was extracted with EtOAc (2 × 100 mL). The combined extracts were dried over anhydrous Na_2SO_4 and concentrated to give the corresponding acid (1.1 g) as an oil.

To a stirred solution of 5,6-dihydro-2*H*-thiopyran-3-carboxylic acid (1.1 g, 7.64 mmol) in dry THF at −15 °C were added triethylamine (1.6 mL) and then trimethylacetyl chloride (1.0 mL, 8.4 mmol). After 15 min at −15 °C, the reaction slurry was warmed to 0 °C slowly over a period of 15 min and then recooled to −78 °C. In a separate flask, 4(*R*)-(phenylmethyl)-2-oxazolodinone (2.43 g, 13.7 mmol) was dissolved in dry THF (25 mL), and the resulting solution was cooled to −60 °C. To this solution was added *n*-butyllithium in hexanes (1.6 M, 8.6 mL) over a period of 15 min. This cold solution was taken up in a syringe and added to the white slurry prepared as described above. After the mixture was stirred for 1 h at −78 °C, sodium bisulfate (1 N, 10 mL) was added. The THF was removed under reduced pressure, and the remaining aqueous mixture was extracted with EtOAc (3 × 50 mL). The combined extracts were washed with saturated $NaHCO_3$ solution and then dried over anhydrous Na_2SO_4 and concentrated to dryness. The residue was purified by silica gel chromatography (25% EtOAc/hexanes) to provide oxazolidinone derivative **6** (2.16 g, 93%) as solid (mp 71–72 °C): ^{1}H NMR ($CDCl_3$) δ 7.1–7.4 (m, 5 H), 6.47 (m, 1 H), 4.75 (m,1 H), 4.35 (t, J = 8.5 Hz, 1 H), 4.15 (dd, J = 5.7, 8.8 Hz, 1H), 3.5 (dd, J = 1.8, 6.7 Hz, 1H), 3.20–3.41 (m, 2 H), 2.70–2.89 (m, 3 H), 2.52 (m, 2 H); IR ($CHCl_3$) 2920–3019, 1785, 1693, 1389 cm^{-1}; $[\alpha]^{23}_D$ −95.3° (*c* 0.87, MeOH); HRMS calcd for $C_{16}H_{17}NO_3S$ 303.0929, found 303.0931. Anal. Calcd for $C_{16}H_{17}NO_3S$: C, 63.34; H, 5.65; N, 4.62. Found: C, 63.79; H, 5.88; N, 4.53.

1-[(*S*)-Tetrahydro-2*H*-thiopyran-3-yl]-4(*R*)-(phenylmethyl)-2-oxazolidinone (7). To a stirred solution of **6** (220 mg, 0.73 mmol) in dry THF (10 mL) at −78 °C was added L-Selectride (1.0 M in THF, 0.8 mL, 0.8 mmol). The resulting mixture continued to stir at −78 °C, and after 15 min, the

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(23) Protease inhibitors incorporating these ligands have also been reported by others recently; see: Getman, D. et al. Abstract, 208th Meeting of the American Chemical Society, Washington, DC, Aug 27, 1994.

reaction was quenched with saturated NH_4Cl solution at −78 °C and then allowed to warm slowly to 23 °C over a period of 1 h. The THF was removed under reduced pressure, and the remaining aqueous mixture was extracted with EtOAc (2 × 50 mL). The combined extracts were washed with brine solution, dried over anhydrous Na_2SO_4, and concentrated to dryness. The residue was purified by silica gel chromatography (25% EtOAc/hexanes) to furnish the saturated oxazolidinone derivative **7** (162 mg, 73% yield) as colorless oil: ^1H NMR ($CDCl_3$) δ 7.12−7.40 (m, 5 H), 4.61 (m,1 H), 4.18 (m, 2 H), 3.82 (m, 1 H), 3.15−3.28 (dd, J = 3.3, 13.4, 1 H), 2.97 (dd, J = 1.1, 13.2 Hz, 1 H), 2.76 (dd, J = 9.4, 13.2 Hz, 1 H), 2.5−2.72 (m, 3 H), 2.07−2.19 (d, J = 11.2, 2 H), 1.76−1.95 (m, 1 H), 1.48−1.55 (m, 1 H), 0.9 (m, 1H); IR ($CHCl_3$) 3022−2918, 1780, 1690, 1375 cm^{-1}; $[\alpha]^{23}_D$ −151.9° (*c* 0.77, MeOH); HRMS calcd for $C_{16}H_{19}NO_3S$, 305.1086, found 305.1077. Anal. Calcd for $C_{16}H_{19}NO_3S$: C, 62.92; H, 6.27; N, 4.58. Found: C, 62.85; H, 6.54; N, 4.89.

1-[(*S*)-1,1-Dioxotetrahydro-2*H*-thiopyran-3-yl]-4(*R*)-(phenylmethyl)-2-oxazolidinone (8). To stirred solution of **7** (80 mg, 0.26 mmol) in methanol (8 mL) and water (3 mL), was added oxone (800 mg, 1.32 mmol). The resulting mixture was stirred at 23 °C for 6 h. The methanol was removed under reduced pressure, and the remaining aqueous mixture was extracted with EtOAc (2 × 50 mL). The combined extracts were washed with brine solution, dried over anhydrous Na_2SO_4, and concentrated to dryness to furnish the corresponding sulfone derivative **8** (87 mg, 100%) as an oil: ^1H NMR($CDCl_3$) δ 7.15−7.40 (m, 5 H), 4.65 (m, 1 H), 4.10−4.32 (m, 3 H), 3.05−3.45 (m, 4 H), 2.94 (m, 1 H), 2.77 (m, 1 H), 2.17−2.35 (m, 3 H), 1.5 (m,1 H); IR ($CHCl_3$) 3034−2922, 1780, 1697, 1386 cm^{-1}; $[\alpha]^{23}_D$ −106.4° (*c* 0.7, MeOH); MS (EI) 337, 161, 143; HRMS calcd for $C_{16}H_{19}NO_5S$ 337.0984, found 337.0975.

(*S*)-1,1-Dioxotetrahydro-2*H*-thiopyran-3-carboxylic Acid (9). To a stirred solution of **8** (77 mg, 0.23 mmol) in a mixture of THF (6 mL) and H_2O (2 mL) at 0 °C were added solid $LiOH·H_2O$ (19 mg, 0.46 mmol) and H_2O_2 (30%, 0.1 mL). The resulting mixture was stirred at 0 °C for 1 h and then at 23 °C for 5 h. After this period, the reaction was treated with aqueous Na_2SO_3 (1.5 M, 0.2 mL) solution, followed by saturated aqueous $NaHCO_3$ solution. The mixture was concentrated under reduced pressure, and the remaining residue was extracted with CH_2Cl_2 (2 × 50 mL) to remove the chiral auxiliary. The aqueous phase was acidified to pH 1−2 with 6 N HCl and extracted with EtOAc (3 × 50 mL). The combined EtOAc extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated to give a residue which was chromatographed over silica gel to afford **9** (35 mg, 86%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 3.12−3.42 (m, 2 H), 2.87−3.12 (m, 3 H), 1.74−2.22 (m, 3 H), 1.43−1.68 (m, 1 H); IR (neat) 3216−2934, 1706, 1446, cm^{-1}; $[\alpha]^{23}_D$ −5.1° (*c* 1.42, MeOH); MS 179 (M^+ + 1), 134 (M^+ − 44). Anal. Calcd for $C_6H_{10}O_4S$: C, 40.44; H, 5.65. Found: C, 40.05; H, 5.68.

1-[(*R*)-Tetrahydro-2*H*-thiopyran-3-yl]-4(*S*)-(phenylmethyl)-2-oxazolidinone (10). As described above, from **5** (1.03 g, 6.5 mmol) the title compound **10** was obtained (1.36 g, 69%) as an oil: ^1H NMR ($CDCl_3$) δ 7.1−7.4 (m, 5 H), 4.65 (m, 1 H), 4.12−4.29 (m, 2 H), 3.80 (m, 1 H), 3.12−3.3 (dd, J = 3.3, 13.4 Hz, 1 H), 2.5−3.01 (m, 5 H), 2.05−2.25 (m, 2 H), 1.86 (m, 1 H); 1.5 (m, 1 H); IR ($CHCl_3$) 3024−2921, 1782, 1690, 1381 cm^{-1}; $[\alpha]^{23}_D$ +148° (*c* 0.7, MeOH); HRMS calcd for $C_{16}H_{19}NO_3S$ 305.1086, found 305.1079.

(*R*)-1,1-Dioxotetrahydro-2*H*-thiopyran-3-carboxylic Acid (11). As described above, the oxidation of **10** (95 mg, 0.28 mmol) with oxone followed by LiOOH-mediated hydrolysis of the oxazolidinone afforded the title acid **11** (42 mg, 84%) after purification by silica gel chromatography (50% ethyl acetate/hexanes): ^1H NMR ($CDCl_3$) δ 3.12−3.42 (m, 2 H), 2.87−3.12 (m, 3 H), 1.74−2.22 (m, 3 H), 1.43−1.68 (m, 1 H); IR (neat) 3216−2934, 1706, 1446, cm^{-1}; $[\alpha]^{23}_D$ +5.3° (*c* 1.2, MeOH); MS 179 (M^+ + 1), 134 (M^+ − 44).

(3*R*,4*S*)-Methyl-4-hydroxytetrahydro-2*H*-thiopyran-3-carboxylate (12). To a stirred solution of sucrose (100 g) in water (450 mL) was added wet bakers' yeast (57 g), and the resulting mixture was stirred at 23 °C for 4 h. After this period, methyl 4-oxo-5,6-dihydrothiopyran-3-carboxylate (**4**) (2.86 g) was added to the suspension. The reaction mixture was stirred for 14 h. The mixture was then filtered through a Celite pad, and the aqueous layer was thoroughly extracted with EtOAc (3 × 400 mL). The combined EtOAc extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated to give a residue which was chromatographed (25% EtOAc/hexanes) over silica gel to afford **12** (2.54 g, 88%) as colorless oil: $[\alpha]^{23}_D$ +39.7° (*c* 2.7, MeOH); ^1H NMR ($CDCl_3$) δ 4.18 (m, 1 H), 3.72 (s, 3 H), 3.18 (dd, J = 10.5, 13.5 Hz, 1 H), 2.96 (m, 1 H), 2.84 (m,1 H), 2.57 (dd, J = 2.0, 13.4 Hz, 1 H), 2.34 (m, 1 H), 2.17 (m, 1 H), 1.9 (m, 1 H); IR ($CHCl_3$) 3019−2925, 1718, 1437 cm^{-1}. MS (EI) 176 (M^+), 158 ($M^+ - H_2O$).

Thioimidazolide 13. To a stirred solution of **12** (316 mg, 1.8 mmol) in dry THF (15 mL) under nitrogen were added 1,1'-(thiocarbonyl)diimidazole (636 mg, 3.6 mmol) and pyridine (0.2 mL). The resulting mixture was stirred for 14 h at 23 °C. After this period, the reaction mixture was diluted with EtOAc (100 mL), and the organic mixture was washed with saturated $NaHCO_3$ aqueous solution and saturated NaCl solution. The layers were separated, and the organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated to give a residue which was chromatographed (25% EtOAc/hexanes) over silica gel to furnish **13** (251 mg, 49%) as colorless oil: ^1H NMR ($CDCl_3$) δ 8.30 (s, 1 H), 7.57 (s, 1 H), 7.04 (s, 1 H), 6.15 (m, 1 H), 3.66 (s, 3 H), 3.02−3.22 (m, 2 H), 2.61−3.00 (m, 3 H), 2.40−2.57 (m, 1 H), 2.02 (m, 1 H).

(3*R*)-Methyl Tetrahydro-2*H*-thiopyran-3-carboxylate (14). To a stirred solution of tributyltin hydride (470 mg, 1.6 mmol) under nitrogen in the presence of a catalytic amount of AIBN (25 mg) in dioxane (20 mL) at reflux was added a solution of **13** (216 mg, 0.8 mmol) in dioxane (2 mL) over a period of 2 h. The reaction mixture was refluxed for an additional 30 min and then cooled to 23 °C. The dioxane was removed under reduced pressure, and the residue was partitioned between CH_3CN and hexanes. The layers were separated, and the CH_3CN layer was washed with hexane (20 mL) and concentrated to provide **14** (128 mg) as an oil: ^1H NMR ($CDCl_3$) δ 3.65 (s, 3 H), 2.71−2.77 (d, J = 6.97, 2 H), 2.65 (m, 1 H), 2.45−2.60 (m, 2 H), 2.1 (m, 2 H), 1.71 (m, 1 H), 1.51 (m, 1 H).

Bakers' Yeast Route: (*R*)-1,1-Dioxotetrahydro-2*H*-thiopyran-3-carboxylic Acid (11). To a stirred solution of above crude **14** in THF (2 mL) and water (6 mL) at 23 °C was added solid $LiOH·H_2O$ (67mg, 1.6 mmol). The resulting mixture was stirred at 23 °C for 8 h. After this period, the reaction mixture was concentrated by rotary evaporation, and the remaining aqueous layer was diluted with brine (5 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The aqueous layer was acidified to pH 1−2 with 6 N HCl solution and was extracted with EtOAc (3 × 15 mL). The combined EtOAc layers were dried over anhydrous Na_2SO_4 and concentrated to provide the corresponding acid (71 mg, 61% from **13**) as a colorless oil: $[\alpha]^{23}_D$ −8.8° (*c* 1.82, MeOH); ^1H NMR ($CDCl_3$) δ 2.60−2.85 (m, 3 H), 2.45−2.60 (m, 2 H), 2.0−2.2 (m, 2 H), 1.42−1.85 (m, 2 H); IR ($CHCl_3$) 3019−2912, 1703, 1519 cm^{-1}; MS (EI) 146 (M^+), 101 (M^+ − COOH).

To a stirred solution of the above acid (65 mg, 0.45 mmol) in methanol (6 mL) and water (2 mL) was added Oxone (1.37 g, 2.23 mmol). The resulting reaction mixture was stirred at 23 °C for 6 h. The reaction mixture was then concentrated by rotary evaporation, and the remaining aqueous layer was diluted with brine (5 mL) and extracted with EtOAc (3 × 50 mL). The combined EtOAc layers were dried over anhydrous Na_2SO_4 and concentrated to provide a residue which was chromatographed (50% ethyl acetate/hexanes) over silica gel to furnish the acid **11** (79 mg, 99%) as solid: $[\alpha]^{23}_D$ +3.8° (*c* 1.7, MeOH); ^1H NMR (D_2O) δ 3.39 (br d, J = 14.2 Hz, 1 H), 3.21 (t, J = 11.4 Hz, 1 H), 2.90−3.14 (m, 3 H), 1.78−2.20 (m, 3 H), 1.46−1.64 (m, 1 H); IR ($CHCl_3$) 3216−2929, 1714, 1446 cm^{-1}; MS (EI) 178 (M^+), 160 ($M^+ - H_2O$). Anal. Calcd for $C_6H_{10}O_4S$: C, 40.44; H, 5.65. Found: C, 40.81; H, 5.31.

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