***syn*-Diastereoselective glycolate aldol addition reactions of**

N₃-(*p*-methoxyphenoxy)acetyloxazolidine-2-thiones

Craig Haynes, Cassie A. Goodman, Juandah Bruce, Sarah C. Genin,
Brad J. Austermuehle, Victor L. Leong, Austin R. Leise, Robert Larson,
Christopher G. Hamaker and Shawn R. Hitchcock*

Department of Chemistry, Illinois State University, Normal, IL 61790-4160

Abstract-An N₃-(*p*-methoxyphenoxy)acetyloxazolidine-2-thione has been synthesized and employed in the glycolate asymmetric aldol addition reaction with aromatic and aliphatic aldehydes. The observed diastereoselectivities ranged from 62:38 to 80:20 when the reaction was conducted at -25 °C. The diastereoselectivities improved to 75:25 to 94:6 when the reaction was conducted at -78 °C. The absolute stereochemistry of the aldol adducts was determined by ¹H NMR spectroscopy and X-ray crystallography. The ¹H NMR spectra of the aldol adducts contained a signal (the α-proton of the glycolate position of the aldol sidechain) that was highly deshielded.

1. Introduction

The chiral auxiliary guided asymmetric glycolate aldol addition reaction has been proven to be a versatile reaction that has allowed for the synthesis of a diverse array of natural products.¹⁻³ The seminal efforts of Evans^{1a} and coworkers in this area employed an N₃-*p*-methoxybenzyloxyacetyl-oxazolidin-2-one auxiliary (**1**) in the synthesis of the polyether antibiotic X-206 (Chart 1).^{1a} This work would be followed by the works of Crimmins and Choy,² Hulme and Rosser,³ Davies and coworkers,⁴ and Roush Owens.⁵ and others. Seeberger and coworkers extended this work by the use of the more labile *para*-methoxybenzyl glycolate group.⁶ Crimmins and coworkers later employed oxazolidine-2-thiones as effective chiral auxiliaries for the aldol addition reaction^{7a-d} and the glycolate aldol reactions.^{7e-h} Romea, Urpí and coworkers⁸ developed highly stereoselective anti-aldol addition using a thiazolidine-2-thione system. These glycolate systems have all been used to great success as well as other chiral auxiliary systems.⁹⁻¹²

Evans, 1989^{1a}

Crimmins and Choy, 1997²

Hulme and Rosser, 2002³

Davies *et al.*, 2004⁴

Roush and Owen, 2005⁵

Seeberger *et al.*, 2008⁶

Crimmins *et al.*, 2008⁷

Romea, Urpí, *et al.*, 2012⁸

Chart 1. Oxazolidinone, oxazolidine-2-thione, and thiazolidine-2-thione glycolates.

A key component of interest is the glycolate protecting group. The benzyl group and the related *p*-methoxybenzyl group are the most commonly used (see Chart 1 references). The most commonly used protecting groups for the hydroxyl group in the glycolate series are the benzyl group and its derivatives; these protecting groups are ubiquitous in natural product synthesis.¹⁴ In contrast, the *p*-methoxyphenoxy group is a protecting group that has not been applied as often. It has the utility that it is a robust protecting group that can be orthogonally removed in the presence of a myriad of functional groups.¹⁵ We had previously used this protecting group in glycolate aldol addition reactions with *Ephedra* based oxadiazinones.¹⁶ Based on this work, we became interested in determining if the *p*-methoxy- phenoxy group would be useful in the Crimmins' based oxazolidine-2-thione based glycolate system. It is in this context that this work in the application of an N₃-*p*-methoxyphenoxyacetyl- oxazolidinone in the asymmetric glycolate aldol addition reaction, and the observation of a highly deshielded α -proton of the glycolate system is described.

2. Results and discussion

The oxazolidine-2-thione auxiliary (**10**) was prepared as described by Crimmins and coworkers by reacting (*S*)-phenylalanine with thiophosgene in dichloromethane in the presence of triethylamine.^{17a} This process was carried out on 15-gram scale and the product was purified by flash chromatography. This compound was then treated with *p*-methoxyphenoxyacetic acid

by reaction with EDC and catalytic DMAP^{17b} to afford the *N*₃-*p*-methoxyphenoxyacetyloxazolidine-2-thione (**11**) in 69% yield after chromatography and recrystallization (Scheme 1). Crystals suitable for x-ray crystallographic diffraction were grown by slow diffusion of hexanes into an ethyl acetate solution of **11**. The collected X-ray crystal data revealed the expected anti-parallel arrangement of the thione moiety and the N₃-carbonyl group (Scheme 1).

Scheme 1. Synthesis and X-ray crystal structure of oxazolidine-2-thione **11**.

With the oxazolidine-2-thione in hand, we conducted a series of titanium mediated glycolate aldol addition reactions using reaction conditions modified from those described by Crimmins

and coworkers.¹⁸ Thus, the acylated thione **11** was dissolved in dichloromethane, cooled to -25 °C and treated with TiCl₄ to cause complexation. Hünig's base was added to cause the formation of the titanium enolate, and this was followed by the addition of N-methylpyrrolidine (NMP). The aldehyde was then added to this mixture to afford the final aldol addition product after purification. The results of the addition reactions are illustrated in Table 1.

Table 1. Asymmetric glycolate aldol addition reaction with **11**.

11 $\xrightarrow[\text{CH}_2\text{Cl}_2, -25\text{ }^\circ\text{C}]{\text{TiCl}_4, i\text{-Pr}_2\text{NEt, NMP, RCHO}}$ **12**

entry	Aldehyde, RCHO	adduct	d.r. ^a	yield ^b
1	C ₆ H ₅ -	12a	80:20	89
2	<i>p</i> -ClC ₆ H ₄ -	12b	70:30	91
3	<i>p</i> -BrC ₆ H ₄ -	12c	73:27	69
4	<i>o</i> -FC ₆ H ₄ -	12d	71:29	65
5	<i>m</i> -NO ₂ C ₆ H ₄ -	12e	75:25	23
6	2-C ₁₀ H ₇ -	12f	76:24	69
7	(<i>E</i>)-PhCH=CH-	12g	74:26	98
8	(CH ₃) ₂ CHCH ₂ -	12h	73:27	91
9	(CH ₃) ₃ C-	12i	62:38	56

^aThe crude diastereomeric ratios were determined by ¹H NMR spectroscopy. ^bIsolated chemical yield after flash chromatography.

The isolated chemical yields ranged from 56 to 98%, and the diastereoselectivities ranged from 62:38 to 80:20 favoring the dominant stereoisomer. The low diastereoselectivities were attributed to the elevated temperature and so the reaction conditions were modified. In an effort to improve the outcome of the glycolate aldol reaction, the temperature was lowered from -25 °C to -78 °C, Hünig's base was replaced with triethylamine, and the solvent additive NMP was eliminated from the reaction. These changes afforded improved results in the crude diastereoselectivity, but not in the isolated yields (Table 2).

Table 2. Modified conditions for the asymmetric glycolate aldol addition reaction with **11**.

$$\mathbf{11} \xrightarrow[\text{CH}_2\text{Cl}_2, -78\text{ }^\circ\text{C}]{\text{TiCl}_4, \text{TEA}, \text{RCHO}} \mathbf{12}$$

entry	Aldehyde, RCHO	adduct	d.r. ^a	yield ^b
1	C ₆ H ₅ -	12a	93:7	71 ^c
2	<i>p</i> -ClC ₆ H ₄ -	12b	91:9	47
3	<i>p</i> -BrC ₆ H ₄ -	12c	94:6	83
4	<i>o</i> -FC ₆ H ₄ -	12d	75:25	86
5	<i>m</i> -NO ₂ C ₆ H ₄ -	12e	88:12	82
6	2-C ₁₀ H ₇ -	12f	93:7	52
7	(<i>E</i>)-PhCH=CH-	12g	94:6	89

8	(CH ₃) ₂ CHCH ₂ -	12h	87:13	95
9	(CH ₃) ₃ C-	12i	n/a ^d	n/a

^aThe crude diastereomeric ratios were determined by ¹H NMR spectroscopy. ^bIsolated chemical yield after flash chromatography. ^cReaction conducted on a 5 gram scale.

We were pleased with the improved results from the aldol addition reaction and conducted a stereochemical analysis of the products. In this context, analysis of the NMR spectrum of **12a** revealed that the ³J_{Ha/Hb} coupling constant between the glycolytic proton H_a and the benzylic proton H_b was 4.65 Hz (Scheme 2). This suggested a *syn*-configuration for **12a** and by correlation, for **12b-12i**. Methanolysis of **12a** with methanol and imidazole yielded the methyl ester in 87% yield. The ³J_{Ha/Hb} coupling constant of 5.29 Hz between the same two protons further suggested the *syn*-aldol relationship. The specific rotation of the methyl ester was determined to be [α]_D²⁴ = -28.6 (*c* = 0.688, CHCl₃). This was in agreement with the literature value of the (2*S*,3*R*)-enantiomer {[α]_D²⁴ = -25.0 (*c* = 0.35, CHCl₃)} that had been previously prepared by our group.¹⁶ The absolute stereochemistry of the glycolate aldol adduct **12a** was further confirmed by X-ray crystallographic analysis (Figure 1). Based on the observed (2*S*,3*R*)-stereochemistry of the product, the transition state model that was proposed by Crimmins and McDougall was invoked.

Scheme 2. Stereochemical determination.

Scheme 3: Proposed transition state of the major aldol product.

The origin of the deshielding effect was unclear, but was most likely be due to the glycolytic proton being in the deshielding cone of an aromatic system. A conformational evaluation of **12a** provided some insight into the unusual chemical shift value. The X-ray crystal structure of **12a** suggests that the N₃-amide carbonyl and the thiocarbonyl group share an anti-parallel arrangement. This same arrangement may well be present in the solution state due to favorable dipole minimization. Based on this configurational arrangement, the benzyl substituent of the oxazolidine-2-thione is not suspected as the origin of the deshielding effect; its proximity to the deshielded α -proton is not sufficient. The appendant phenyl ring of the N₃-aldol side chain in **12a** is not suspected as all of the aldol adducts (**12a-i**) share this deshielded proton, regardless of the presence of an aryl group (**12a-g**) or alkyl group (**12h-i**). Specifically, oxazolidine-2-thione **12h** possesses a *tert*-butyl group at the end of the N₃-aldol side chain, and the observed chemical shift of this deshielded proton is 7.13 ppm (Figure 2). Based on these observations, it is proposed that the aromatic ring of the *p*-methoxyphenoxy group is the source of the deshielding. This argument is supported by the fact that the methanolysis of **12a** to give **13** causes the glycolytic proton to appear at 5.07 ppm in the cleaved ester.

Figure 2. Comparison of the α -proton of glycolate aldol adducts.

3. Conclusion

In summary, the *p*-methoxyphenoxy group has much potential as a protecting group in glycolate chemistry as it is removed under conditions orthogonal to many alcohol protecting groups. We have prepared a N_3 -*p*-methoxyphenoxyacetyloxazolidine-2-thione and applied it in the asymmetric glycolate aldol addition reaction. The initial conditions employing titanium tetrachloride, Hünig's base, and NMP yielded moderate to excellent yields, but low diastereoselectivities. The optimized reaction conditions involving the lower temperature and the elimination of NMP proved afforded improved diastereoselection, but did not improve the yield. The absolute stereochemistry was determined and confirmed through a combination of ^1H NMR spectroscopy and X-ray crystallography. A ^1H NMR COSY revealed that the α -glycolytic proton was highly deshielded. The origin of the deshielding is postulated to be due to the presence of the highly deshielded glycolic α -proton in the aldol adducts was attributed to the presence of the *p*-methoxyphenoxy group.

4. Experimental section

4.1. General information

All chemical reagents were used as purchased. All reaction vessels were flame dried and purged under a nitrogen atmosphere. All NMR spectra were recorded in CDCl₃ and reported in parts per million (δ scale) with tetramethylsilane as an internal standard (δ = 0 ppm, ¹H) or deuterated chloroform as a standard (δ = 77.0 ppm, ¹³C). Optical rotation data was collected on a JASCO P-1010 digital polarimeter operating at 589 nm in an 8 × 100 mm cell. Melting points were determined using a Laboratory Devices Mel-Temp apparatus and are uncorrected.

4.2. (S)-4-Benzyl-3-[(*p*-methoxyphenoxy)acetyl]oxazolidine-2-thione (11)

In a 100 mL, flame dried, nitrogen purged round bottom flask equipped with a magnetic stir bar (*S*)-4-benzyl-1,3-oxazolidine-2-thione (15.0 g, 77.9 mmol), CH₂Cl₂ (312 mL), 1-ethyl-3-(3-dimethylamino propyl) carbodiimide (EDC, 16.4 g, 85.5 mmol), DMAP (2.38 g, 19.5 mmol), and *p*-methoxy-phenoxyacetic acid (14.2 g, 77.9 mmol) was added sequentially and stirred overnight. The reaction was quenched, extracted and the solvents removed *in vacuo*. The crude product was purified by flash column chromatography (hexanes: EtOAc, gradient: 80:20 to 65:35) to yield 19.3 g (69 %) of the title compound as an off-white solid. Melting Point: 86-88 °C. ¹H NMR (400 MHz, CDCl₃): δ 2.83 (dd, *J* = 10.0, 3.3 Hz, 1H), 3.33 (dd, *J* = 10.0, 3.3 Hz, 1H), 3.78 (s, 3H), 4.40-4.45 (m, 2H), 4.95-5.01 (m, 1H), 5.55 (q, *J* = 17.8 Hz, 2H), 6.83-6.89 (m, 2H), 6.91-6.95 (m, 2H), 7.21-7.24 (m, 2H), 7.28-7.37 (m, 3H). ¹³C NMR (125 MHz, CDCl₃): δ 37.54, 55.72, 59.90, 70.22, 71.65, 114.79, 116.04, 127.58, 129.12, 129.42, 134.90, 151.96,

154.51, 169.51, 184.85. IR (nujol mull): 1707, 1365, 1329, 1196, 754, 733, 700 cm^{-1} . $[\alpha]_{\text{D}}^{23} = +85.0$ (c 1.02, CHCl_3). ESI HRMS for $\text{C}_{19}\text{H}_{19}\text{NO}_4\text{S}$: calc ($\text{M} + \text{H}^+$) 358.1121, found 358.1113.

4.3. General procedure for the asymmetric glycolate aldol addition reaction.

Method A:

In a 250 mL, flame dried, nitrogen purged round bottom flask equipped with a magnetic stir bar, oxazolidine-2-thione **11** (0.500 g, 1.40 mmol), and CH_2Cl_2 (10 mL) were cooled to -25°C before the addition of TiCl_4 (0.160 mL, 1.54 mmol). The reactants were allowed stir for 30 minutes and then the addition of di-isopropylethylamine (0.61 mL, 3.5 mmol) followed. The mixture was stirred for one hour and *N*-methylpyrrolidinone (NMP) (0.13 mL 1.4 mmol) was added and the reaction stirred for 30 minutes. The aldehyde (2.1 mmol) was added and the reaction stirred for 4 hours at -25°C . The reaction was quenched by the addition of brine (3 mL). The reaction mixture was diluted with CH_2Cl_2 (50 mL) and treated with 1M HCl (30 mL), and subsequently treated with brine (30 mL). **Method B:** In a 250 mL, flame dried, nitrogen purged round bottom flask equipped with a magnetic stir bar was placed the oxazolidin-2-thione **11** (0.500 g, 1.40 mmol, 1 equiv), and CH_2Cl_2 (10 mL) were cooled to -78°C before the addition of TiCl_4 (0.160 mL, 1.54 mmol). The reactants were allowed stir for 30 minutes. Then the addition of TEA (0.50 mL, 3.50 mmol) occurred and was allowed to stir for one hour. The aldehyde (2.52 mmol) was added and allowed stir for 6 hours at -78°C . The reaction was quenched with brine (3 mL). The product was extracted by dilution with 50 mL CH_2Cl_2 with one treatment of 1M HCl (30 mL) and brine (30 mL). The crude product was purified by flash column chromatography (hexanes: EtOAc, 75:25). **Method C:** In a 1 L, flame dried, nitrogen purged round bottom flask equipped with a magnetic stir bar was placed **11** (5.00 g, 1.40 mmol), and CH_2Cl_2 (140 mL) were

cooled to -78°C before the addition of TiCl₄ (1.60 mL, 1.54 mmol). The reactants were allowed stir for 45 minutes. Then the addition of TEA (0.50 mL, 3.50 mmol) occurred and was allowed to stir for 75 minutes. The benzaldehyde (2.60 mL, 2. mmol) was added and allowed stir for 6 hours at -78 °C. The reaction was quenched with brine (5 mL). The product was extracted by dilution with 80 mL CH₂Cl₂ and treated with 1M HCl (35 mL) and brine (35 mL). The extracted crude product was then dried(MgSO₄). The product was determined to have diastereoselectivity of 92:8 by ¹H NMR spectroscopy and was recrystallized from hexanes and ethyl acetate yielding 4.60 g (9.94 mmol, 71%) of white crystals of **12a**.

4.3.1. (2*S*,3*R*)-4-Benzyl-3-[(3-hydroxy-2-(*p*-methoxyphenoxy)-3-phenylpropanoyl]oxazolidine-2-thione (12a).

The title compound was purified by flash column chromatography (hexanes: EtOAc, 75:25) to yield 0.583 g (1.26 mmol, 89%) of white crystals via Method A. By Method C, the crude product was recrystallized to yield 4.60 g (9.94 mmol, 71%). Melting point: 154-157 °C. ¹H NMR (500 MHz, CDCl₃): δ 2.78 (dd, *J* = 13.4, 9.9 Hz, 1H), 3.19 (dd, *J* = 13.4, 3.1 Hz, 1H), 3.77 (s, 3H), 3.89 (dd, *J* = 8.5, 7.3 Hz, 1H), 4.24 (dd, *J* = 8.9, 1.3 Hz, 1H), 4.62-4.66 (m, 1H), 5.27 (d *J* = 4.65 Hz, 1H), 6.84 (d, *J* = 9.4 Hz, 2H), 6.99 (d, *J* = 8.45 Hz, 2H), 7.15 (d, *J* = 6.15 Hz, 1H), 7.24 (d, *J* = 4.65 Hz, 1H), 7.33 (m, 8H), 7.55 (d, *J* = 7.5 Hz, 1H). ¹³C NMR (125 MHz, CDCl₃) 3.41, 55.70, 61.01, 70.78, 75.46, 79.74, 114.78, 117.07, 126.71, 127.51, 128.33, 128.50, 129.00, 129.46, 134.79, 138.24, 151.17, 154.92, 170.75, 184.89. IR (nujol mull): 3550, 1720, 1231, 1062, 829, 742, 692 cm⁻¹. [α]_D²³ = +148 (*c* 1.00, CHCl₃). Melting point: 154-157 °C. ESI-HRMS for C₂₆H₂₅NO₅S: calc'd (M + H⁺) 464.1526; found 464.1522.

4.3.2. (2*S*,3*R*)-4-Benzyl-3-((*p*-chlorophenyl)-3-hydroxy-2-(*p*-methoxyphenoxy)propanoyl)

oxazolidine-2-thione (12b).

The title compound was purified by flash column chromatography (hexanes: EtOAc, 75:25) to yield yield of 0.641 g (1.33 mmol, 91%) of white crystals via Method A; Method B 0.331 g (0.667 mmol, 48%). Melting Point: 153-155 °C. ¹H NMR (500 MHz, CDCl₃): δ 2.77 (dd, *J* = 13.5, 9.9 Hz, 1H), 3.18 (dd, *J* = 13.5, 3.15 Hz, 1H), 3.74 (s, 3H), 4.05 (dd, *J* = 8.9, 6.5, 1H), 4.31 (dd, *J* = 9.3, 1.7 Hz, 1H), 4.71-4.75 (m, 1H), 5.28 (d, *J* = 3.8 Hz, 1H), 8.80 (d, *J* = 9.2 Hz, 2H), 6.90 (d, *J* = 9.2 Hz, 2H), 7.13 (d, *J* = 6.7 Hz, 1H), 7.18 (d, *J* = 3.6 Hz, 1 H), 7.26-7.33 (m, 7H), 7.48 (d, *J* = 8.7 Hz, 2H). ¹³C NMR (125 MHz, CDCl₃): δ 37.37, 55.68, 60.98, 70.96, 74.22, 79.50, 114.82, 115.01, 116.95, 127.589, 127.95, 128.48, 129.05, 129.45, 134.19, 134.66, 137.16, 151.01, 155.01, 170.34, 184.96. IR (CHCl₃): 3478, 2837, 1702, 1506, 1368, 1328, 1092, 822, 703 cm⁻¹. [α]_D²⁴ = +124 (*c* 1.00, CHCl₃). ESI HRMS for C₂₆H₂₄ClNO₅S: calc'd (M + H⁺) 498.1143, found 498.1136.

4.3.3. (2*S*,3*R*)-4-Benzyl-3-[(*p*-bromophenyl)-3-hydroxy-2-(*p*-methoxyphenoxy)propanoyl]oxazolidine-2-thione (12c).

The titled product was purified by flash column chromatography (hexanes: EtOAc, 75:25) to yield 0.539 g (0.987 mmol, 69%) of viscous yellow oil of product via Method A and 0.625 g (1.16 mmol, 83%) of tan powder via Method B. Melting point: 147-150 °C. ¹H NMR (500 MHz, CDCl₃): δ 2.77 (dd, *J* = 13.4, 9.8, 1H), 3.18 (dd, *J* = 13.4, 2.9 Hz, 1 H), 3.74 (s, 3H), 4.05 (dd, *J* = 16.4, 8.2 Hz, 1 H), 4.31(d, *J* = 9.2 Hz, 1 H), 4.73 (t, *J* = 8.2 Hz, 1H), 5.26 (d, *J* = 3.7 Hz, 1 H), 6.81(d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 9.3 Hz , 2H), 7.13 (d, *J* = 6.7 Hz, 2 H), 7.18 (d, *J* = 3.65 Hz, 1H), 7.28 (m, 2H), 7.42 (d, *J* = 8.8 Hz, 2H), and 7.48 ppm (d, *J* = 8.3 Hz, 2H). ¹³C NMR (125 MHz, CDCl₃): δ 37.44, 55.76, 61.04, 71.02, 74.35, 79.48, 114.86, 116.95,

122.38, 127.62, 128.28, 129.09, 129.49, 131.49, 134.67, 137.70, 151.01, 155.08, 170.34, and 185.00 ppm. IR (CHCl₃): 3451, 2957, 1708, 1508, 1367, 1328, 1070, 829, 702 cm⁻¹. [α]_D²³ = +130 (*c* 1.00, CHCl₃). ESI HRMS for C₂₆H₂₄BrNO₅S: calc'd (M + H⁺) 542.0638, found 542.0632.

4.3.4. (2*S*,3*R*)-4-Benzyl-3-[(*o*-fluorophenyl)-3-hydroxy-2-(*p*-methoxyphenoxy)propanoyl] Oxazolidine-2-thione (12d).

The title compound was purified by flash column chromatography (hexanes: EtOAc, 75:25) to yield 0.469 g (0.975 mmol, 65%) of yellow viscous oil via Method A and 0.576 g (1.20 mmol, 86%) of white crystals via Method B. Melting Point: 122-124 °C. ¹H NMR (500 MHz, CDCl₃): δ 2.69 (dd, *J* = 10.2, 13.4, 1H), 3.11-3.16 (m, 2H), 3.68 (singlet, 3H), 3.93 (t, *J* = 8.0, 1H), 4.19 (d, *J* = 9.3, 1H), 4.65-4.69 (m, 1H), 5.44 (t, *J* = 5.65, 1H), 6.76 (d, *J* = 9.2, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 6.98-6.94 (m, 1H), 7.06-7.11 (m, 4H), 7.17-7.24 (m, 4H), 7.61 (t, *J* = 7.1 Hz, 1H). ¹³C NMR (125 MHz, CDCl₃): δ 37.29, 55.63, 61.16, 69.40 (d, *J*_{C-F} = 1.8 Hz), 78.69, 114.77, 114.92 (d, *J*_{C-F} = 21.8 Hz), 116.75, 124.36 (d, *J*_{C-F} = 2.6 Hz), 125.29 (d, *J*_{C-F} = 12.7 Hz), 127.42, 128.91, 129.38 (d, *J*_{C-F} = 3.64 Hz), 129.44, 130.11 (d, *J*_{C-F} = 8.2 Hz), 134.76, 154.04, 154.77, 159.95 (d, *J*_{C-F} = 247.1 Hz), 170.19, 184.68 ppm. IR (CHCl₃): 3414, 2837, 1705, 1507, 1365, 1329, 1108, 828, 702 cm⁻¹. [α]_D²⁴ = +16 (*c* 1.00, CHCl₃). ESI HRMS for C₂₆H₂₄FNO₅S: calc'd (M + H⁺) 482.1439, found 482.1426.

4.3.5. (2*S*,3*R*)-4-Benzyl-3-[(3-hydroxy-2-(*p*-methoxyphenoxy)-3-(*m*-nitrophenyl)propanoyl] oxazolidine-2-thione (12e).

The title compound was purified by flash column chromatography (hexanes: EtOAc, 75:25) to yield 0.167 g (0.337 mmol, 23%) of yellow oil via Method A and 0.586 (1.15 mmol, 82%) of light yellow crystals via Method B. Melting Point: 142-143 °C. ¹H NMR (500 MHz, CDCl₃): δ 2.58 (dd, *J* = 13.4, 9.8 Hz, 1H), 3.13-3.17 (m, 2H), 3.66 (s, 3H), 4.22 (dd, *J* = 8.9, 7.5 Hz, 2H), 4.33 (dd, *J* = 9.4, 2.1 Hz, 1H), 4.84-4.84 (m, 1H), 5.41 (dd, *J* = 8.2, 2.9 Hz, 1H), 6.71-6.77, (m, 4H), 7.07 (dd, *J* = 8.2, 1.9 Hz, 2H), 7.17-7.26 (m, 3H), 7.48, (t, *J* = 15.8, 7.9 Hz, 1H), 7.84 (d, *J* = 7.7 Hz, 1H), 8.09 (ddd, *J* = 5.1, 2.2, 0.9 Hz, 1H), and 8.37-8.38 (m, 1H). ¹³C NMR (125 MHz, CDCl₃): δ 37.36, 55.67, 60.92, 71.30, 72.99, 79.07, 114.88, 116.74, 121.58, 123.12, 127.66, 129.09, 129.33, 129.46, 132.35, 134.52, 141.57, 148.34, 150.84, 155.16, 169.56, 185.23 ppm. IR (CHCl₃): 3404, 2922, 1709, 1530, 1350, 1327, 1070, 827, 702 cm⁻¹. [α]_D²⁵ = +85 (c 1.10, CHCl₃). ESI HRMS for C₂₆H₂₄N₂O₇S: calc'd (M + H⁺) 498.1143, found 498.1136.

4.3.6. (2*S*,3*R*)-4-Benzyl-3-[(3-hydroxy-2-(*p*-methoxyphenoxy)-3-(2-naphthyl)propanoyl]oxazolidine -2-thione (12f).

The title compound was purified by flash column chromatography (hexanes: EtOAc, 75:25) to give a 69% yield (0.498 g, 0.970 mmol) of small white crystals via Method A. For Method B, the product was recrystallization from ethyl acetate and hexanes. (0.723 mmol, 52%) of white crystals. Melting Point: 160-162 °C. ¹H NMR (500 MHz, CDCl₃): δ 2.66 (dd, *J* = 13.4, 9.8 Hz, 1H), 3.06 (dd, *J* = 13.4, 3.16 Hz, 1H), 3.10 (d, *J* = 6.3 Hz, 1H), 3.41 (dd, *J* = 8.9, 7.5 Hz, 1H), 3.66 (s, 3H), 4.01 (dd, *J* = 9.2, 1.6 Hz, 1H), 4.49-4.53 (m, 1H), 5.33-5.36 (m, 1H), 6.73 (d, *J* = 9.2 Hz, 2H), 6.90 (d, *J* = 9.2 Hz, 2H), 7.16-7.22 (m, 3H), 7.25 (d, *J* = 4.6 Hz, 1H), 7.38-7.41 (m, 2H), 7.73-7.77 (m, 3H), 7.86 (s, 1H) ppm. ¹³C NMR (125 MHz, CDCl₃): δ 37.40, 55.67, 60.95, 10.60, 75.56, 79.84, 114.78, 117.10, 124.42, 125.71, 126.36, 126.44, 127.49, 127.69, 128.03, 128.16, 128.97, 129.43, 132.87, 133.28, 134.71, 135.75, 151.16, 154.93, 170.75, 184.85

ppm. IR (CHCl₃): 3444, 2930, 1704, 1507, 1364, 1328, 1108, 825, 702 cm⁻¹. [α]_D²³ = +166 (*c* 1.00, CHCl₃). ESI HRMS for C₃₀H₂₇NO₅S: calc'd (M + H⁺) 514.1688, found 514.1689.

4.3.7. (2*S*,3*R*,*E*)-1-[(*S*)-4-Benzyl-(3-hydroxy-2-(*p*-methoxyphenoxy)-5-phenyl-4-pentenoyl)oxazolidine-2-thione (12g).

The title compound was purified by flash column chromatography (hexanes: EtOAc, 75:25) to yield 0.682 g (1.39 mmol, 98%) orange viscous oil via Method A and 0.680 g (1.24 g, 89%) of white crystals via Method B. Melting point: 128-130 °C. ¹H NMR (500 MHz, CDCl₃): δ 2.69 (dd, *J* = 13.4, 9.8 Hz, 1H), 3.08 (dd, *J* = 13.4, 3.1 Hz, 1H), 3.65 (s, 1H), 3.94 (dd, *J* = 9.1, 7.5 Hz, 1H), 4.17 (dd, *J* = 9.3, 1.7 Hz, 1H), 4.70-4.75 (m, 1H), 4.79-4.81 (m, 1H), 6.36 (dd, *J* = 16.1, 7.1 Hz, 1H), 6.61 (d, *J* = 15.9 Hz, 1H), 6.75 (d, *J* = 9.2 Hz, 2H), 6.90 (d, *J* = 9.1 Hz, 2H), 7.02-7.04 (m, 2H), 7.09 (d, *J* = 4.1 Hz, 1H), 7.13-7.15 (m, 1H), 7.16-7.21 (m, 5H), 7.27 (d, *J* = 7.3 Hz, 2H). ¹³C NMR (125 MHz, CDCl₃): δ 37.45, 55.72, 60.89, 71.02, 74.19, 78.98, 114.91, 116.82, 126.38, 126.73, 127.53, 128.24, 128.73, 129.02, 129.47, 132.95, 134.79, 135.98, 151.36, 154.91, 170.36, 185.44 ppm. IR (CHCl₃): 3417, 1710, 1507, 1366, 1328, 1071, 828, 702 cm⁻¹. [α]_D²⁴ = +205 (*c* 1.00, CHCl₃). ESI HRMS (C₂₈H₂₇NO₅S): calc'd (M + H⁺) 490.1689, found 490.1682.

4.3.8. (2*S*,3*R*)-4-Benzyl-3-(3-hydroxy-2-(*p*-methoxyphenoxy)-4,4-dimethylpentanoyl)oxazolidine-2-thione (12h).

The title compound was purified by flash column chromatography (hexanes: EtOAc, 75:25) to yield 0.348g (0.784 mmol, 56%) of a viscous oil for Method A. The use of Method B failed in the preparation of this compound. ¹H NMR (500 MHz, CDCl₃): δ 0.99 (s, 9H), 2.26 (d, *J* = 8.71 Hz, 1H), 2.62 (dd, *J* = 13.47 Hz, 9.80, 1H), 3.02 (dd, *J* = 13.44 Hz, 3.24, 1H), 3.73 (t, *J* =

8.75 Hz, 1H), 4.23-4.26 (m, 2H), 4.87-4.92 (m, 1H), 6.79 (d, $J = 9.13$ Hz, 2H), 6.92 (d, $J = 9.11$ Hz, 2H), 7.03 (d, $J = 6.50$ Hz, 2H), 7.13 (d, $J = 8.30$ Hz, 1H), 7.16-7.22 (m, 5H) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ 26.57, 35.80, 37.66, 55.70, 60.67, 71.00, 74.88, 80.82, 114.88, 116.32, 127.45, 128.99, 129.41, 134.91, 150.44, 154.64, 173.72, 186.30 ppm. IR (CHCl_3): 3499, 2965, 1704, 1507, 1367, 1324, 1045, 827, 702 cm^{-1} . $[\alpha]_D^{25} = +76$ (c 1.50, CHCl_3). ESI HRMS for $\text{C}_{24}\text{H}_{29}\text{NO}_5\text{S}$: calc'd ($\text{M} + \text{H}^+$) 444.1846, found 444.1832.

4.3.9. (2*S*,3*R*)-4-Benzyl-3-[(3-hydroxy-2-(*p*-methoxyphenoxy)-5-methylhexanoyl]oxazolidine-2-thione (12i).

The title product was purified by flash column chromatography (hexanes: EtOAc, 75:25) to yield 0.567 g (91%) of the title compound as a mixture of diastereomers as an orange oil at -25°C. By Method B, 0.590 g (1.33 mmol, 95%) of white crystals were collected. Melting point: 49-51 °C. ^1H NMR (400 MHz, CDCl_3): 0.93 (d, $J = 6.6$ Hz, 3H), 0.97 (d, $J = 6.6$ Hz, 3H), 1.47-1.54 (m, 1H), 1.73-1.92 (m, 2H), 2.12 (d, $J = 11.0$ Hz, 1H), 2.79 (dd, $J = 10.0, 3.3$ Hz, 1H), 3.26 (dd, $J = 10.0$ Hz, 3.1 Hz, 1H), 3.77 (s, 3H), 4.29-4.41 (m, 3H), 4.88-4.94 (m, 1H), 6.84-6.88 (m, 3H), 6.90-6.94 (m, 2H), 7.15-7.17 (m, 2H), 7.27-7.33 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 21.98, 23.66, 24.62, 37.37, 43.16, 55.71, 60.94, 70.47, 71.23, 79.14, 114.89, 116.40, 127.50, 129.00, 129.49, 134.92, 151.54, 154.70, 170.63, 185.42. IR (neat): 3420, 1729, 1474, 1444, 1366, 1326, 1038, 126, 752, 702 cm^{-1} . $[\alpha]_D^{23} = +9.43$ (c 1.10, CHCl_3). ESI HRMS for $\text{C}_{24}\text{H}_{29}\text{NO}_5\text{S}$: calc'd ($\text{M} + \text{H}^+$) 444.1841, found 444.1845.

4.4. Methyl 3-hydroxy-2-(*p*-methoxyphenoxy)-3-phenylpropanoate (13)

In a 500 mL, flame dried, nitrogen purged round bottom flask equipped with a magnetic stir bar was added imidazole (2.316 g, 34.0 mmol, 3 equiv), anhydrous methanol (30 mL) and THF (20 mL). Compound **12a** (4.602g, 9.94 mmol, 1 equiv) was then added and allowed to stir overnight. The MeOH was removed via rotary evaporation and the crude product was then extracted with CH₂Cl₂ (80 mL) and sequentially treated with 1M HCl (35 mL) and brine (35 mL). The solvent was removed by rotary evaporation to yield a viscous oil. This product was then purified by flash column chromatography (hexanes: EtOAc, 75:25) to yield a viscous oil (2.613 g, 8.64 mmol, 87%). ¹H NMR (500 MHz, CDCl₃): δ 2.99 (s, 1H), 3.54 (s, 3H), 3.65 (s, 3H), 4.56 (d, *J* = 5.3 Hz, 1H), 5.07 (d, *J* = 5.3 Hz, 1H), 6.68-6.72 (m, 4H), 7.22-7.30 (m, 3H), 7.33-7.35 (m, 2H) ppm. ¹³C NMR: δ 52.25, 55.64, 74.84, 83.10, 114.74, 117.14, 126.61, 128.41, 128.46, 138.74, 151.75, 155.03, 170.12 ppm. IR: 3569, 2964, 1748, 1507, 1393, 1052, 828, 701 cm⁻¹. [α]_D²³ = +146 (*c* 0.50, CHCl₃).

Acknowledgements

The authors acknowledge Zachary Lawton and Prof. C. Mulligan for their technical assistance in the collection of ESI-HRMS data. Structural elucidations were made with assistance from high resolution MS instrumentation acquired through support by the National Science Foundation MRI Program under Grant No. CHE 1337497.

References

1. (a) Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506-2526. (b) Keck, G. E.; Palani, A.; McHardy, S. F. *J. Org. Chem.*, **1994**, *59*, 3113-3122. (c) Jones, T. K.; Reamer, R. A.; Desmond, R.; Mills, S. G. *J. Am. Chem. Soc.* **1990**, *112*, 2998-3017.
2. (a) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653-5660. (b) Crimmins, M. T.; She, J. *J. Am. Chem. Soc.* **2004**, *126*, 12790-12791. (c) Crimmins, M. T. Ellis, J. M. *J. Org. Chem.* **2008**, *73*, 1649-1660.
3. Hulme, A. N; Rosser, E. M. *Org. Lett.* **2002**, *4*, 265-267. For the lesser used N₃-methoxy acetyloxazolidinone, please see: (a) Crimmins, M. T.; Christie, H. S.; Chaudhary, K.; Long, A. *J. Am. Chem. Soc.* **2005**, *127*, 13810-13812. (b) Andrus, M. B.; Meredith, E. L.; Hicken, E. J.; Simmons, B. L.; Glancey, R. R.; Ma, W. *J. Org. Chem.* **2003**, *68*, 8162-8169.
4. Davies, S. G.; Nicholson, R. L.; Smith, A. D. *Org. Biomol. Chem.* **2004**, *2*, 3385-3400.
5. Owen, R. M.; Roush, W. R. *Org. Lett.* **2005**, *7*, 3941-3944.
6. Stallforth, P.; Adibekian, A.; Seeberger, P. H. *Org. Lett.* **2008**, *10*, 1573-1576.
7. (a) Crimmins, M. T.; Shamszad, M. *Org. Lett.* **2007**, *9*, 149-152. (b) Guz, N. R.; Phillips, A. J. *Org. Lett.* **2002**, *4*, 2253-2256. (c) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K.; *J. Org. Chem.* **2001**, *66*, 894-902. (d) Crimmins, M. T.; King, B. W.; Tabet, E. A. *J. Am. Chem. Soc.* **1997**, *119*, 7883-7884. (e) Crimmins, M. T. Ellis, J. M. *J. Org. Chem.* **2008**, *73*, 1649-1660. (f) Crimmins, M. T. Ellis, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 17200-17201. (g) Crimmins, M. T.; Long, A. *Org. Lett.* **2005**, *7*, 4157-4160. (h) Crimmins, M. T.; McDougall, P. J. *Org. Lett.* **2003**, *5*, 591-594.
8. Baiget, J.; Caba, M.; Gálvez, E.; Romea, P.; Urpí, F.; Font-Bardia, M. *J. Org. Chem.* **2012**, *77*, 8809-8814.

9. Giampietro, N. C.; Kampf, J. W.; Wolfe, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 12556-12557.
10. Fanjul, S.; Hulme, A. N. *J. Org. Chem.* **2008**, *73*, 9788-9791
11. (a) Andrus, M. B.; Meredith, E. L.; Hicken, E. J.; Simmons, B. L.; Glancey, R.; Ma, W. *J. Org. Chem.* **2003**, *68*, pp 8162-8169. (b) Andrus, M. B.; Meredith, E. L.; Soma Sekhar, B. B. V. *Org. Lett.* **2001**, *3*, pp 259-262. (c) Andrus, M. B.; Soma Sekhar, B. B. V.; Meredith, E. L.; Dalley, N. K. *Org. Lett.* **2000**, *2*, pp 3035-3037.
12. (a) Pearson, W. H.; Cheng, M. C. *J. Org. Chem.* **1987**, *52*, 3176-3178. (b) Pearson, W. H.; Cheng, M. C. *J. Org. Chem.*, **1986**, *51*, pp 3746-3748.
13. (a) Wuts, P. G. M.; Greene, T. W. *Protecting Groups in Organic Synthesis*, 4th Ed., John Wiley & Sons, Inc. 2007.
14. (a) Yadav, J. S.; Dutta, P. *J. Org. Chem.* **2016**, *81*, 1786-1797. (b) Liu, Q.; An, C.; TenDyke, K.; Cheng, H.; Shen, Y. Y.; Hoye, A. T. Smith III, A. B. *J. Org. Chem.* **2016**, *81*, 1930-1942. (c)
15. (a) Castelli, R.; Overkleeft, H. S.; van der Marel, G. A.; Codee, J. D. C. *Org. Lett.* **2013**, *15*, 2270-2273. (b) Iacobucci, S.; Filippova, N.; d'Alarcao, M. *Carbohydrate Res.* **1995**, *277*, 321-325. (c) Jacob III, P.; Callery, P. S.; Shulgin, A. T.; Castagnoli, Jr., N. *J. Org. Chem.* **1976**, *41*, 3627-3629.
16. Vaughn, J. F.; Hitchcock, S. R. *Tetrahedron: Asymm.* **2004**, *15*, 3449-3455.
17. (a) Wu, Y.; Y. Y.-Q.; Hu, Q. *J. Org. Chem.* **2004**, *69*, 3990-3992. (b) Andrade, C. K. Z.; Rocha, R. O.; Vercillo, O. E.; Silva, W. A.; Matos, R. A. F. *SynLett* **2003**, 2351-2352.
18. Crimmins and coworkers had developed a reaction protocol employing (-)-sparteine. Please see Crimmins, M. T.; She, J. *SynLett* **2004**, 1371-1374. Our initial results with (-)-

sparteine were not successful. These initial efforts were not optimized due to the uncertain availability and increasing cost of (-)-sparteine as a stoichiometric reagent.

Graphical Abstract

for

syn-Diastereoselective glycolate aldol addition reactions of an *N*(3)-(4-methoxyphenoxy)acetyloxazolidine-2-thione

Craig Haynes, Cassie A. Goodman, Juandah Bruce, Sarah C. Genin,

Brad Austermeuhle, Victor L. Leong, Austin R. Leise, Robert Larson,

Christopher G. Hamaker and Shawn R. Hitchcock*

Department of Chemistry, Illinois State University, Normal, IL 61790-4160