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Oxadiazinones as chiral auxiliaries: increased diastereoselectivities in the glycolate aldol reaction of oxadiazinones☆

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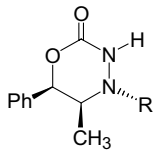
Abstract—Glycolate aldol reactions were conducted using a (1*R*,2*S*)-norephedrine based N_4-isopropyloxadiazinone as a chiral template to afford aldol adducts **8a**–**h**. The yields ranged from 57% to 99% while the diastereoselectivities ranged from 94:6 to 99:1. Adduct **8a** was hydrolyzed to afford the oxadiazinone auxiliary and β-hydroxyacid **9**, which was converted to the known methyl (2*S*,3*R*)-2,3-dihydroxy-3-phenylpropionate **12** with 95% ee as determined by chiral HPLC.

1. Introduction

The use of chiral, non-racemic oxadiazinones as chiral auxiliaries in aldol reactions has recently been investigated by our group.[1] The first reported asymmetric aldol applications of this class of auxiliary employed (1*R*,2*S*)-ephedrine as the chiral template **1** (Fig. 1).[1b,c] The stereochemical induction in the aldol addition reaction of this oxadiazinone is attributed to the conformational arrangement of the ring system and the positioning of the methyl substituent of the stereogenic nitrogen, that is the N_4-methyl group. The diastereoselectivities of the ephedrine based oxadiazinone mediated asymmetric aldol reactions were fair to very good.[1b,c]



1: R = -CH_3
2: R = -$CH(CH_3)_2$

Figure 1. Ephedrine and norephedrine based oxadiazinones.

In our ongoing efforts to develop oxadiazinones as chiral auxiliaries, we recently disclosed the synthesis and application of a novel N_4-isopropyloxadiazinone **2** derived from (1*R*,2*S*)-norephedrine.[1a] This auxiliary yielded better diastereoselectivities than the ephedrine based auxiliary in the aldol reaction involving either a propionate or thiophenylpropionate side chain.[1a] The enhanced diastereoselectivity was thought to originate from the increased steric demand of the N_4-substituent, that is, N_4–$CH(CH_3)_2$ versus N_4–CH_3.

With a superior oxadiazinone auxiliary in hand, we became interested in pursuing the asymmetric aldol reaction of glycolate substrates. The utility of the asymmetric glycolate reaction has been demonstrated in the synthesis of a variety of natural products.[2] An earlier study was carried out to determine the viability of the (1*R*,2*S*)-ephedrine based oxadiazinone **1** in the glycolate aldol reaction.[3] However, the chemical yields and observed diastereoselectivities were not optimal. Furthermore, aliphatic aldehydes were problematic, for example, low diastereoselectivity and incomplete reactivity. Herein we report our efforts in developing the (1*R*,2*S*)-norephedrine based N_4-isopropyloxadiazinone in the glycolate aldol reaction.

2. Results and discussion

N_4-isopropyloxadiazinone **2** was synthesized as described before (Scheme 1).[1a] (1*R*,2*S*)-Norephedrine was

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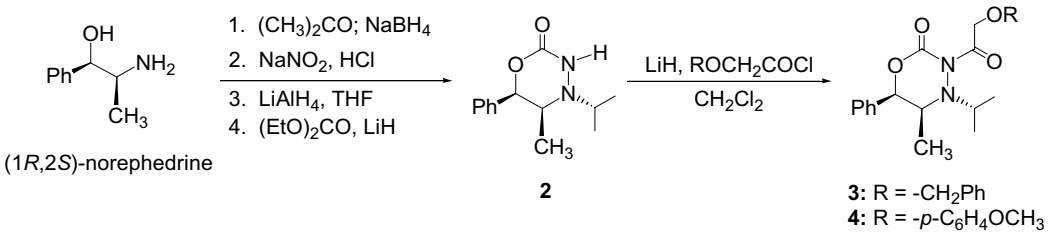


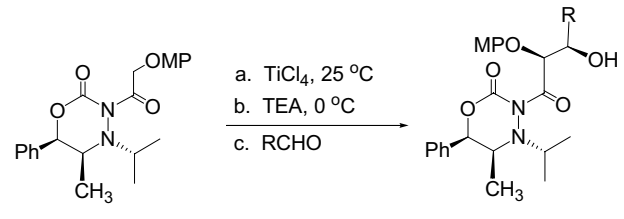
Scheme 1. Synthesis and acylation.

reductively alkylated with acetone and sodium borohydride, *N*-nitrosated,[4] reduced to the corresponding β-hydrazinoalcohol, and cyclized using diethyl carbonate and lithium hydride. Oxadiazinone **2** was subsequently acylated with either benzyloxyacetyl chloride or *p*-methoxyphenoxyacetyl chloride to afford N_3-acylated derivatives **3** and **4** in 83% and 92% yield, respectively.

These substrates were then used in the titanium mediated asymmetric aldol addition reaction (Scheme 2). Surprisingly, N_3-benzyloxyacetyloxadiazinone **3** failed to generate the desired aldol adduct in significant amounts (<10%). This same phenomenon was observed in the ephedrine based oxadiazinone **5**.[3] The reason for the failure of these two substrates to undergo the aldol addition is unknown at this time, but could be attributed to the interaction of the titanium tetrachloride ($TiCl_4$) with the N_3-side chain. In fact, when **3** was treated with a large excess of $TiCl_4$ (5 equiv), triethylamine (1 equiv), and benzaldehyde (5 equiv), aldol adduct **6** was obtained in 40% yield and 95:5 diastereoselectivity as determined by 400 MHz ^{1}H NMR spectroscopy. These unusual conditions were not satisfactory in terms of obtaining the product and so the benzyloxyacetyl substrates were abandoned.

The N_3-*p*-methoxyphenoxyacetyl side chain appended to the N_4-isopropyloxadiazinone proved to be more promising (Scheme 3). The optimized method for the aldol addition using oxadiazinone **4** involved treatment with $TiCl_4$ (2 equiv) at 25 °C, followed by reaction with triethylamine (1.05 equiv) at 0 °C, and treatment with a selected aldehyde (2 equiv). The yields ranged from fair to excellent and the observed diastereoselectivities ranged from 94:6 to greater than 99:1 as measured by HPLC (Table 1).

In addition, the glycolate aldol reactions for the norephedrine based auxiliary were successful for aliphatic aldehydes. These results were significantly improved over the results obtained with the ephedrine based oxadiazinone auxiliary.[3] This can be directly attributed to



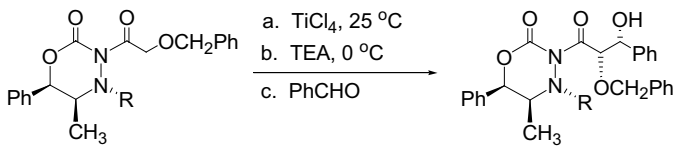
8a: R = -C_6H_5
8b: R = -*p*-C_6H_4Cl
8c: R = -*p*-$C_6H_4NO_2$
8d: R = -2-$C_{10}H_7$
8e: R = -$CH(CH_3)_2$
8f: R = -$C(CH_3)_3$
8g: R = -$CH_2OCH_2C_6H_5$
8h: R = -(*E*)-$CH{=}CHC_6H_5$

Scheme 3. Asymmetric aldol reaction.

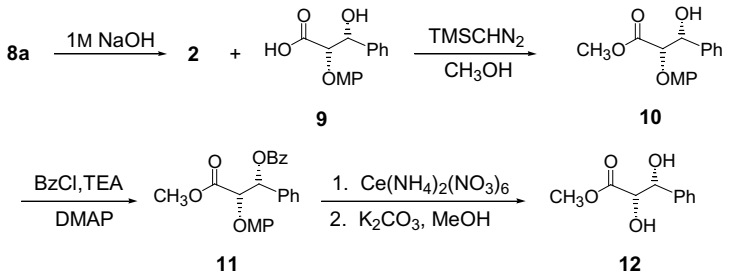
Table 1. Diastereoselectivity in the oxadiazinone mediated glycolate aldol reaction

Entry	Aldehyde	Adduct	Dr[a]	Yield[b] (%)
1	C_6H_5CHO	**8a**	97:3	97
2	*p*-ClC_6H_4CHO	**8b**	98:2	82
3	*p*-$NO_2C_6H_4CHO$	**8c**	94:6	66
4	2-$C_{10}H_7CHO$	**8d**	98:2	80
5	$(CH_3)_2CHCHO$	**8e**	98:2	57
6	$(CH_3)_3CCHO$	**8f**	98:2	98
7	$C_6H_5CH_2OCH_2CHO$	**8g**	99:1	87
8	(*E*)-$C_6H_5CHCHCHO$	**8h**	99:1	62

[a] All crude diastereomeric ratios were measured by HPLC using a Shimadzu SCL-10AVP system with a Dynamax Si-100 Å column (7:3, hexanes/ethyl acetate, flow rate = 1.5 mL/min). Diastereoselectivities are represented as major diastereomer:∑ all other diastereomers.
[b] Purified yields after column chromatography.



Scheme 2.



Scheme 4. Synthesis of the α,β-dihydroxyester **12**.

the introduction of the isopropyl group at the N_4-position via the primary amine of norephedrine. Based on earlier studies with the N_4-isopropyloxadiazinone, the stereochemistry of aldol adducts **8a**–**h** was tentatively assigned the (2*S*,3*R*)-configuration.[1a,3]

In order to confirm this assignment, we sought to hydrolyze adduct **8a** and convert the resultant β-hydroxyacid to the known methyl 2,3-dihydroxy-3-phenylpropionate and evaluate its enantiomeric purity (Scheme 4).[5] Thus, oxadiazinone **8a** was hydrolyzed to the β-hydroxyacid **9** (88%) and the N_4-isopropyloxadiazinone **2** (52%) by treatment with an aqueous solution of NaOH (1 M). The β-hydroxyacid **9** was esterified with trimethylsilyldiazomethane[6] in methanol to afford the β-hydroxyester **10** in 67% yield after column chromatography. At this stage it was not possible to remove the *p*-methoxyphenyl protecting group by reported methods[7] without significant decomposition, most likely due to presence of the benzylic alcohol. Thus, the β-hydroxy group was protected with benzoyl chloride to afford the corresponding benzoate ester **11** in 68% yield after chromatography.

The *p*-methoxyphenyl protecting group was then oxidatively removed by treatment of **11** with ceric ammonium nitrate $[Ce(NH_4)_2(NO_3)_6]$.[8] The resultant α-hydroxyester was not characterized as it was not possible to completely remove the quinone by-product. Consequently, the ester was directly treated with K_2CO_3 and methanol to effect cleavage of the benzoate ester[9] to yield the desired α,β-dihydroxyester **12** in 37% yield after chromatography for the two step process. This was determined to be the (2*S*,3*R*)-enantiomer based on the specific rotation: $[\alpha]_D^{25} = -9.3$ (*c* 0.175, $CHCl_3$); lit.[5c] = $[\alpha]_D^{25} = -8.8$ (*c* 1.0, $CHCl_3$), 82% ee.

Finally, chiral HPLC was used to accurately determine the enantiomeric purity of the diol. The enantiomeric purity of (2*S*,3*R*)-**12** was determined to be 95% ee by chiral HPLC analysis based on a comparison with the racemic α,β-dihydroxy ester **12**:[10] [Chiralcel OD column, 6% isopropanol in hexanes: t_R (2*R*,3*S*)-**12** = 16.0 min; t_R (2*S*,3*R*)-**12** = 18.0 min]. This work established the relative and absolute configurations of the aldol side chain of oxadiazinone **8a**. By analogy, the stereochemistry of aldol adducts **8b**–**h** were assigned to be in a (2*S*,3*R*)-*syn* relationship. This would suggest that the transition state of the aldol reaction closely resembles a chelated chair like Zimmerman–Traxler transition state (Fig. 2).

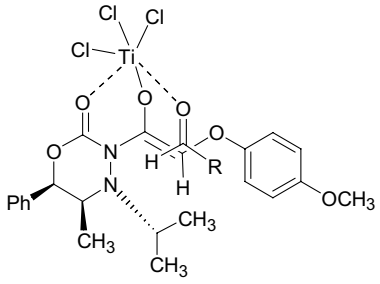


Figure 2. Proposed transition state.

3. Conclusion

In conclusion, we have demonstrated that the N_4-isopropyloxadiazinone is a viable chiral auxiliary for the glycolate aldol reaction. We have synthesized methyl (2*S*,3*R*)-2,3-dihydroxy-3-phenylpropionate **12** in a diastereomeric ratio of 19:1 favoring the *syn*-diastereomer and in an enantiomeric purity greater than 95% by means of an oxadiazinone mediated asymmetric aldol reaction. A limitation to the use of *p*-methoxyphenyl protecting group became evident as it could not be cleanly removed without further protection of the appendant β-hydroxy group. Studies directed toward the synthesis of HIV protease inhibitors nelfinavir and saquinavir are currently underway.

4. Experimental

4.1. General

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from a potassium/sodium alloy with benzophenone ketyl. Methylene chloride (CH_2Cl_2) was distilled from phosphorus pentoxide. All reactions were run under a nitrogen atmosphere. Unless otherwise noted, all ^1H and ^{13}C NMR spectra were recorded at 25 °C on a Varian spectrometer in $CDCl_3$ operating at 400 and 100 MHz, respectively. Chemical shifts are reported in parts per million (δ scale), and coupling constants (*J* values) are listed in hertz (Hz). Infrared spectra are

reported in reciprocal centimeters (cm^{-1}) and are measured either as a neat liquid or as a KBr window. Melting points were recorded on a Mel-Temp apparatus and are uncorrected.

4.2. (5*S*,6*R*)-3-Benzyloxyacetyl-3,4,5,6-tetrahydro-4-isopropyl-5-methyl-6-phenyl-2*H*-1,3,4-oxadiazin-2-one 3

In a flame-dried, nitrogen-purged 250 mL round bottom flask were placed N_4-isopropyloxadiazinone **2** (3.00 g, 12.8 mmol) and CH_2Cl_2 (12.8 mL). To this reaction mixture was added benzyloxyacetyl chloride (15.4 mmol) and the reaction heated to a gentle reflux (~39 °C). Lithium hydride (13.4 mmol) was then added to the reaction mixture in one portion. The reaction was allowed to run overnight and then quenched by the addition of saturated aqueous solution of ammonium chloride (NH_4Cl). This solution was diluted with CH_2Cl_2 and the layers separated, washed with brine, dried over $MgSO_4$, and the solvent removed via rotary evaporation. The resulting oil was purified via column chromatography using a 70/30 mixture of hexanes and ethyl acetate. The title compound was recovered in 92% yield (4.50 g): $[\alpha]_D^{25} = -40.7$ (*c* 0.39, $CHCl_3$); $R_f = 0.31$ (ethyl acetate/hexanes, 3:7). ^1H NMR: δ 0.79 (d, $J = 6.8$ Hz, 3H), 1.17 (d, $J = 6.4$ Hz, 3H), 1.37 (d, $J = 6.0$ Hz, 3H), 3.38 (septet, $J = 6.0$ Hz, 1H), 3.79 (septet, $J = 7.2$ Hz, 1H), 4.64 (s, 2H), 4.71 (*AB* quartet, $J = 18.0$ Hz, 2H), 5.94 (d, $J = 5.2$ Hz, 1H), 7.22–7.43 (m, 10H). ^{13}C NMR (the urethane carbonyl was not observed): 12.9, 20.3, 20.9, 51.4, 54.0, 70.9, 73.3, 78.8, 124.8, 127.9, 128.2, 128.4, 128.7, 135.6, 137.3, 149.0, 171.9. IR (neat): 1782, 1728, 1206 cm^{-1}. EI-HRMS calculated for $C_{22}H_{26}N_2O_4$: 382.1893, found: 382.1893.

4.3. (5*S*,6*R*)-3,4,5,6-Tetrahydro-4-isopropyl-3-[2-(*p*-methoxyphenoxy)acetyl]-5-methyl-6-phenyl-2*H*-1,3,4-oxadiazin-2-one 4

In a flame-dried, nitrogen-purged 500 mL round bottom flask were added *p*-methoxyphenoxyacetic acid (43.1 mmol) and CH_2Cl_2 (103 mL). To this reaction mixture was added oxalyl chloride (51.7 mmol) and the solution then gently heated to reflux (~39 °C) for 2 h. At this time, 50% of the reaction solvent was distilled away. After removing the excess CH_2Cl_2, the N_4-isopropyloxadiazinone **2** (10.0 g, 34.5 mmol) was added in one portion. To this mixture was added lithium hydride (48.3 mmol) and the reaction allowed to run overnight. The reaction was quenched by the addition of an aqueous solution of NH_4Cl and diluted by the addition of CH_2Cl_2, separated, washed with brine, dried over $MgSO_4$, and the solvent removed via rotary evaporation. The resulting oil was purified via column chromatography using a 65/35 mixture of hexanes and ethyl acetate. The isolated product was collected in 83% (11.4 g) yield as an amber-colored oil. $[\alpha]_D^{25} = -31.6$ (*c* 0.19, $CHCl_3$); $R_f = 0.319$ (ethyl acetate/hexanes, 2:3). ^1H NMR: δ 0.82 (d, $J = 6.8$ Hz, 3H), 1.18 (d, $J = 6.0$ Hz, 3H), 1.37 (d, $J = 6.4$ Hz, 3H), 3.41 (septet, $J = 6.0$ Hz, 1H), 3.76 (s, 3H), 3.80 (dq, $J = 4.0$, 2.0 Hz, 1H), 5.18 (*AB* quartet, $J = 19.2$ Hz, 2H), 5.98 (d, $J = 4.8$ Hz, 1H), 6.79–6.84 (m, 2H), 6.88–6.92 (m, 2H), 7.26–7.28 (m, 3H), 7.32–7.43 (d, $J = 8.0$ Hz, 2H). ^{13}C NMR: δ 13.0, 20.4, 20.9, 51.5, 54.1, 55.6, 70.0, 79.0, 114.6, 116.2, 124.8, 128.3, 128.8, 135.6, 149.3, 152.1, 154.4, 170.3. IR (neat): 1728, 1204, 734 cm^{-1}. EI-HRMS calculated for $C_{22}H_{26}N_2O_5$ (M^++Na^+): 421.1743. found: 421.1739.

4.4. (2′*S*,3′*R*, 5*S*,6*R*)-3-(2-Benzyloxy-3-hydroxy-3-phenylpropionyl)-3,4,5,6-tetrahydro-4-isopropyl-5-methyl-6-phenyl-2*H*-1,3,4-oxadiazinan-2-one 6

In a flame-dried, nitrogen-purged 100 mL round bottom flask were placed oxadiazinone **3** (0.589 g, 1.54 mmol) and THF (4.5 mL). To this reaction mixture was added $TiCl_4$ (0.85 mL, 7.7 mmol) at 25 °C. This reaction mixture was allowed to react for 30 min. The reaction was then cooled to 0 °C and triethylamine (0.23 mL, 1.6 mmol) introduced and reacted for 1 h. At this point, the reaction was again cooled to 0 °C, and benzaldehyde added via syringe. After 4 h the reaction was quenched by the addition of a saturated solution of NH_4Cl and diethyl ether, separated, washed with brine, dried over $MgSO_4$, gravity filtered, and the solvent removed via rotary evaporation. The resulting compound was purified via column chromatography using a mixture of hexanes and ethyl acetate and recovered. Isolated product was collected in 40% yield as a yellow oil contaminated with 5% of an unidentified impurity. $[\alpha]_D^{25} = -79.1$ (*c* 0.172 in $CHCl_3$); $R_f = 0.26$ (ethyl acetate/hexanes, 2:3). ^1H NMR: δ 0.73 (d, $J = 6.4$ Hz, 3H), 1.23 (d, $J = 6.4$ Hz, 3H), 1.39 (d, $J = 5.6$ Hz, 3H), 3.00–3.19 (br s, 1H), 3.35–3.50 (m, 1H), 3.83 (septet, $J = 6.4$ Hz, 1H), 4.23 (d, $J = 11.6$ Hz, 1H), 4.44 (d, $J = 11.6$ Hz, 1H), 5.21 (s, 1H), 5.40 (s, 1H), 5.98 (d, $J = 4.8$ Hz, 1H), 6.99 (d, $J = 2.0$ Hz, 2H), 7.15–7.45 (m, 11H), 7.56 (d, $J = 7.6$ Hz, 2H). ^{13}C NMR: 12.7, 20.4, 20.7, 51.3, 54.3, 72.8, 73.4, 79.1, 82.7, 124.7, 125.9, 127.3, 127.8, 128.0, 128.1, 128.2, 128.3, 128.8, 135.6, 136.8, 141.3, 149.4, 171.6. IR (neat): 3478, 1725, 1245. EI-HRMS calculated for $C_{29}H_{32}N_2O_5$: 488.2303, found: 488.2311.

4.5. General procedure for the synthesis of aldol adducts 8a–h

Method A **8a** *and* **8b**: In a flame-dried, nitrogen-purged 100 mL round bottom flask were placed N_4-isopropyloxadiazinone **2** (0.4–0.6 g) and THF (0.33 M). To this 25 °C solution was added $TiCl_4$ (1 equiv) via syringe. After 30 min, the reaction was cooled to 0 °C and 1.05 equiv of triethylamine introduced and reacted for 1 h. At this time, the reaction was again cooled to 0 °C, and the desired aldehyde (1.10 equiv) added via syringe. The reaction was allowed to stir for 4 h and then quenched by the addition of a saturated solution of NH_4Cl and diluted with diethyl ether. The layers were separated and the organic layer was washed with brine, dried over $MgSO_4$, and the solvent removed via rotary evaporation. The resulting compounds were purified via column chromatography using a mixture of hexanes and ethyl acetate and then recovered. *Method B* **8c**–**h**: In this procedure, 2 equiv of $TiCl_4$ and 2 equiv of the desired aldehyde were employed. Diastereomeric ratios were determined by HPLC using a Shimadzu SCL-10AVP

system with a Dynamax Si-100 Å column (7:3, hexanes/ethyl acetate, flow rate = 1.5 mL/min). Diastereoselectivities are represented as the observed major diastereomer versus the minor diastereomers. The chromatographic peaks that were assigned as the minor diastereomers have not been rigorously established, but the diastereoselectivities were determined so that they would not overstate the success of the formation of the major diastereomer.

4.5.1. (2′*S*,3′*R*,5*S*,6*R*)-3-[3-Hydroxy-2-(*p*-methoxyphenoxy)-3-phenylpropionyl]-4-isopropyl-5-methyl-6-phenyl-2*H*-1,3,4-oxadiazin-2-one 8a. Isolated product was collected in 99% yield as a yellow oil. $[\alpha]_D^{25} = -31.6$ (*c* 0.33, $CHCl_3$); $R_f = 0.34$ (ethyl acetate/hexanes, 1:1). ^{1}H NMR (the alcohol proton, RO*H*, was not observed): δ 0.66 (d, $J = 7.2$ Hz, 3H), 1.21 (d, $J = 6.0$ Hz, 3H), 1.38 (d, $J = 5.6$ Hz, 3H), 3.42 (septet, $J = 6.4$ Hz, 1H), 3.67 (s, 3H), 3.81 (dq, $J = 7.2$, 1.8 Hz, 1H), 5.53 (s, 1H), 5.85 (s, 1H), 6.00 (d, $J = 4.8$ Hz, 1H), 6.64 (dd, $J = 7.2$, 4.0 Hz, 4H), 7.23–7.44 (m, 8H), 7.64 (d, $J = 8.0$ Hz, 2H). ^{13}C NMR: δ 12.6, 20.5, 20.6, 51.3, 54.3, 55.5, 73.6, 79.3, 84.0, 114.4, 118.2, 124.7, 126.1, 127.6, 128.26, 128.28, 128.7, 135.5, 140.6, 149.6, 151.7, 155.0, 170.7. IR (neat): 3412, 1723, 1243, 699 cm^{-1}. EI-HRMS calculated for $C_{29}H_{32}N_2O_6$ (M^+): 504.2260, found: 504.2254.

4.5.2. (2′*S*,3′*R*,5*S*,6*R*)-3-[3-(*p*-Chlorophenyl)-3-hydroxy-2-(*p*-methoxyphenoxy)propionyl]-3,4,5,6-tetrahydro-4-isopropyl-5-methyl-6-phenyl-2*H*-1,3,4-oxadiazin-2-one 8b. Isolated product was collected in 82% yield as a yellow wax. $[\alpha]_D^{25} = -20.5$ (*c* 0.34, $CHCl_3$); $R_f = 0.23$ (ethyl acetate/hexanes, 2:3). ^{1}H NMR: δ 0.65 (d, $J = 7.2$ Hz, 3H), 1.20 (d, $J = 5.6$ Hz, 3H), 1.37 (d, $J = 6.4$ Hz, 3H), 3.16 (br s, 1H), 3.41 (septet, $J = 6.4$ Hz, 1H), 3.67 (s, 3H), 3.81 (septet, $J = 6.4$ Hz, 1H), 5.49 (br s, 1H), 5.78 (d, $J = 2.0$ Hz, 1H), 6.00 (d, $J = 4.8$ Hz, 1H), 6.62–6.68 (m, 4H), 7.24 (d, $J = 8.0$ Hz, 2H), 7.25–7.26 (m, 2H), 7.33–7.43 (m, 3H), 7.58 (d, $J = 7.2$ Hz, 2H). ^{13}C NMR: δ 12.6, 20.5, 20.6, 51.3, 54.3, 55.6, 73.1, 79.3, 83.6, 114.5, 118.2, 124.7, 127.6, 128.3, 128.4, 128.8, 133.4, 135.4, 139.3, 149.7, 151.4, 155.1, 170.4. IR (neat): 3433, 1723, 1243, 828, 732 cm^{-1}. EI-HRMS calculated for $C_{29}H_{31}ClN_2O_6$: 538.1871 (M^+), found: 538.1857.

4.5.3. (2′*S*,3′*R*,5*S*,6*R*)-3,4,5,6-Tetrahydro-3-[3-hydroxy-2-(*p*-methoxyphenoxy)-3-(*p*-nitrophenyl)propionyl]-4-isopropyl-5-methyl-6-phenyl-2*H*-1,3,4-oxadiazin-2-one 8c. Isolated product was collected in 66% yield as a yellow wax. $[\alpha]_D^{25} = -18.0$ (*c* 0.22, $CHCl_3$); $R_f = 0.26$ (ethyl acetate/hexanes, 1:1). ^{1}H NMR: δ 0.67 (d, $J = 6.8$ Hz, 3H), 1.23 (d, $J = 6.4$ Hz, 3H), 1.38 (d, $J = 6.4$ Hz, 3H), 3.36 (d, $J = 9.2$ Hz, 1H), 3.46 (septet, $J = 7.6$ Hz, 1H), 3.66 (s, 3H), 3.82 (septet, $J = 6.8$ Hz, 1H), 5.62 (d, $J = 8.4$ Hz, 1H), 5.81 (s, 1H) 6.02 (d, $J = 4.4$, 1H), 6.58–6.67 (m, 4H), 7.24–7.44 (m, 5H), 7.83 (d, $J = 8.8$ Hz, 2H), 8.25 (d, $J = 8.8$ Hz, 2H). ^{13}C NMR: δ 12.6, 20.5, 20.7, 51.3, 54.4, 55.5, 72.9, 79.4, 83.2, 114.5, 118.0, 123.5, 124.7, 127.0, 128.4, 128.8, 135.2, 147.4, 148.3, 149.8, 151.0, 155.2, 170.0. IR (neat): 3467, 1723, 1244, 833, 733 cm^{-1}. EI-HRMS calculated for $C_{29}H_{31}N_3O_8$: 549.2111, found: 549.2099.

4.5.4. (2′*S*,3′*R*,5*S*,6*R*)-3,4,5,6-Tetrahydro-3-[3-hydroxy-2-(*p*-methoxyphenoxy)-3-naphthalen-2-yl-propionyl]-4-isopropyl-5-methyl-6-phenyl-2*H*-1,3,4-oxadiazin-2-one 8d. Isolated product was collected in 80% yield as a amber oil. $[\alpha]_D^{25} = -18.4$ (*c* 0.37, $CHCl_3$); $R_f = 0.24$ (ethyl acetate/hexanes, 2:3). ^{1}H NMR: δ 0.67 (d, $J = 6.8$ Hz, 3H), 1.22 (d, $J = 6.0$ Hz, 3H), 1.38 (d, $J = 6.4$ Hz, 3H), 1.58 (s, 1H), 3.43 (septet, $J = 6.8$ Hz, 1H), 3.65 (s, 3H), 3.82 (septet, $J = 6.8$ Hz, 1H), 5.70 (s, 1H), 5.97 (s, 1H), 6.01 (d, $J = 4.8$ Hz, 1H), 6.63 (s, 4H), 7.20–7.52 (m, 6H), 7.78–7.92 (m, 5H), 8.07 (s, 1H). ^{13}C NMR: δ 12.6, 20.5, 20.7, 51.3, 54.3, 55.5, 73.7, 79.3, 83.9, 114.4, 118.2, 124.2, 124.7, 125.2, 125.8, 126.0, 127.6, 128.0, 128.2, 128.3, 128.8, 133.0, 133.2, 135.5, 138.1, 149.6, 151.6, 155.0, 170.7. IR (neat): 3466, 1724, 1244, 733 cm^{-1}. EI-HRMS calculated for $C_{33}H_{34}N_2O_6$: 554.2417, found: 554.2425.

4.5.5. (2′*S*,3′*R*,5*S*,6*R*)-3,4,5,6-Tetrahydro-3-[3-hydroxy-2-(*p*-methoxyphenoxy)-4-methylpentanoyl]-4-isopropyl-5-methyl-6-phenyl-2*H*-1,3,4-oxadiazin-2-one 8e. Isolated product was collected in 57% yield as a yellow wax. $[\alpha]_D^{25} = -16.2$ (*c* 0.31, $CHCl_3$); $R_f = 0.38$ (ethyl acetate/hexanes, 1:1). ^{1}H NMR (the alcohol proton, RO*H*, was not observed): 0.69 (d, $J = 6.8$ Hz, 3H), 1.06 (d, $J = 7.2$ Hz, 3H), 1.13 (d, $J = 6.8$ Hz, 3H), 1.20 (d, $J = 6.4$ Hz, 3H), 1.34 (d, $J = 6.0$ Hz, 3H), 2.09 (dq, $J = 7.2$, 2.0 Hz, 1H), 3.38 (septet, $J = 6.0$ Hz, 1H), 3.71 (s, 3H), 3.79 (dq, $J = 7.2$, 1.6 Hz, 1H), 3.92 (d, $J = 8.4$ Hz, 1H), 5.87 (d, 0.8 Hz, 1H), 5.98 (d, $J = 4.8$ Hz, 1H), 6.72–6.82 (m, 4H), 7.25–7.45 (m, 5H). ^{13}C NMR: δ 12.5, 19.0, 19.4, 20.5, 20.7, 32.4, 51.4, 54.3, 55.6, 79.1, 79.7, 114.5, 116.8, 124.7, 128.2, 128.8, 135.6, 149.5, 151.5, 154.6, 171.3. IR (neat): 3466, 1725, 1228, 730 cm^{-1}. EI-HRMS calculated for $C_{26}H_{34}N_2O_6$: 470.2417, found: 470.2413.

4.5.6. (2′*S*,3′*R*,5*S*,6*R*)-3,4,5,6,-Tetrahydro-3-[3-hydroxy-2-(*p*-methoxyphenoxy)-4,4-dimethylpentanoyl]-4-isopropyl-5-methyl-6-phenyl-2*H*-1,3,4-oxadiazin-2-one 8f. Isolated product was collected in 98% yield as a yellow wax. $[\alpha]_D^{25} = -12.6$ (*c* 0.38, $CHCl_3$); $R_f = 0.23$ (ethyl acetate/hexanes, 2:3). ^{1}H NMR: δ 0.69 (d, $J = 6.4$ Hz, 3H), 1.12 (s, 9H), 1.20 (d, $J = 6.4$ Hz, 3H), 1.35 (d, $J = 6.4$ Hz, 3H) 2.50 (d, $J = 11.2$ Hz, 1H), 3.40 (septet, $J = 6.0$ Hz, 1H), 3.71 (s, 3H), 3.80 (septet, $J = 4.8$ Hz, 1H), 3.96 (d, $J = 10.8$ Hz, 1H), 5.99 (d, $J = 4.4$ Hz, 1H), 6.02 (s, 1H), 6.74–6.79 (m, 4H), 7.25–7.45 (m, 5H). ^{13}C NMR: δ 12.5, 20.6, 20.7, 26.9, 36.3, 51.4, 54.4, 55.6, 78.0, 79.1, 114.6, 116.2, 124.7, 128.2, 128.8, 135.7, 149.4, 150.8, 154.5, 171.5. IR (neat): 1727, 1229, 732 cm^{-1}. EI-HRMS calculated for $C_{27}H_{36}N_2O_6$: 484.2573, found: 484.2577.

4.5.7. (2′*S*,3′*R*,5*S*,6*R*)-3-[4-Benzyloxy-3-hydroxy-2-(*p*-methoxyphenoxy)butyryl]-3,4,5,6-tetrahydro-4-isopropyl-5-methyl-2*H*-1,3,4-oxadiazin-2-one 8g. Isolated product was collected in 87% yield as a yellow wax. $[\alpha]_D^{25} = -20.4$ (*c* 0.29, $CHCl_3$); $R_f = 0.34$ (ethyl acetate/hexanes, 1:1). ^{1}H NMR: δ 0.66 (d, $J = 7.2$ Hz, 3H), 1.19 (d, $J = 6.4$ Hz, 3H), 1.34 (d, $J = 6.0$ Hz, 3H), 2.57 (br s, 1H), 3.38 (septet, $J = 6.8$ Hz, 1H), 3.72 (s, 3H), 3.77–3.80 (m, 3H), 4.57–4.70 (m, 3H), 5.85 (s, 1H),

5.97 (d, $J = 4.4$ Hz, 1H), 6.73–6.85 (m, 4H), 7.24–7.43 (m, 10H). ^{13}C NMR: δ 0.0, 12.6, 20.5, 20.7, 51.4, 54.3, 55.6, 70.5, 71.0, 73.3, 74.4, 79.2, 79.5, 114.5, 117.5, 124.7, 127.6, 127.7, 128.3, 128.4, 128.8, 135.6, 138.0, 149.4, 151.5, 154.8, 170.7. IR (neat): 1725, 1229, 750, 700 cm^{-1}. HRMS (EI) calculated for $C_{31}H_{36}N_2O_7$: 548.2523, found: 548.2520.

4.5.8. (2′*S*,3′*R*,5*S*,6*R*)-3,4,5,6-Tetrahydro-3-[3-hydroxy-2-(*p*-methoxyphenoxy)-5-phenylpent-4-enoyl]-4-isopropyl-5-methyl-6-phenyl-2*H*-1,3,4-oxadiazin-2-one 8h. Isolated product was collected in 62% yield as a yellow wax. $[\alpha]_D^{25} = -2.8$ (c 0.29, $CHCl_3$); $R_f = 0.25$ (ethyl acetate/hexanes, 9:11). ^{1}H NMR (the alcohol proton, RO*H*, was not observed): δ 0.62 (d, $J = 6.8$ Hz, 3H), 1.18 (d, $J = 6.4$ Hz, 3H), 1.34 (d, $J = 6.4$ Hz, 3H), 3.37 (septet, $J = 6.0$ Hz, 1H), 3.70 (s, 3H), 3.77 (septet, $J = 6.0$ Hz, 1H), 5.00 (br s, 1H), 5.81 (d, $J = 2.4$ Hz, 1H), 5.97 (d, $J = 4.8$ Hz, 1H), 6.50 (dd, $J = 16.0$, 6.0 Hz, 1H), 6.73–6.88 (m, 5H), 7.20–7.45 (m, 10H). ^{13}C NMR: 12.6, 20.5, 20.7, 51.3, 54.3, 55.6, 73.2, 79.3, 82.2, 114.5, 117.9, 124.7, 126.7, 127.8, 127.9, 128.3, 128.5, 128.8, 132.3, 135.5, 136.5, 149.6, 151.5, 155.0, 170.4. IR (neat): 1724, 1243, 732 cm^{-1}. EI-HRMS calculated for $C_{31}H_{34}N_2O_6$: 530.2417 (M^+), found: 530.2421.

4.6. 3-Hydroxy-2-(*p*-methoxyphenoxy)-3-phenylpropionic acid 9

Aldol adduct **8a** (5.01 g, 10.1 mmol) was placed in a 100 mL round bottom flask and dissolved in THF (50 mL), and then reacted with NaOH (150 mL, 1.0 M). The reaction was allowed to run for 20 h, after which point the reaction was diluted by the addition of diethyl ether, washed with brine, dried over $MgSO_4$, and the solvent removed via rotary evaporation. This process afforded the parent heterocycle **2** in 52% yield (1.21 g). The combined aqueous layers were then acidified using HCl, diluted with diethyl ether, separated, washed with brine, dried over $MgSO_4$, and the solvent removed via rotary evaporation. This process afforded the crude carboxylic acid in 88% yield (2.52 g) contaminated with a small amount of benzaldehyde presumably arising from a retro-aldol reaction. This material was not purified and was directly esterified: ^{1}H NMR (CO_2H not observed): δ 3.74 (s, 3H), 4.30–5.20 (br s, 1H), 4.71 (d, $J = 3.6$ Hz, 1H), 5.25 (d, $J = 4.0$ Hz, 1H), 6.76 (s, 4H), 7.26–7.47 (m, 5H). ^{13}C NMR: δ 55.6, 74.4, 82.4, 114.7, 117.2, 126.5, 128.5, 128.6. IR (neat): 3062, 1733, 1225, 1031, 826, 700 cm^{-1}. HRMS (EI) calculated for $C_{16}H_{16}O_5$: 288.0998, found: 288.0996.

4.7. (2*S*,3*R*)-Methyl 3-hydroxy-2-(*p*-methoxyphenoxy)-3-phenylpropionate 10

The crude carboxylic acid **9** (1.12 g) was placed in a 100 mL round bottom flask and dissolved in THF (15.5 mL) and CH_3OH (7.8 mL). To this reaction mixture was added trimethylsilyldiazomethane (4 equiv). The reaction was allowed to run overnight, quenched by the addition of a saturated solution of NH_4Cl. The reaction mixture was then diluted with diethyl ether and extracted. The combined organic layers were washed with brine, dried over $MgSO_4$, gravity filtered, and the solvent removed via rotary evaporation. The resulting ester was purified via column chromatography using a 70/30 mixture of hexanes and ethyl acetate and recovered in a 67% yield (0.787 g) as a yellow oil. $[\alpha]_D^{25} = -25.0$ (c 0.35, $CHCl_3$). ^{1}H NMR: δ 2.98 (br s, 1H), 3.63 (s, 3H), 3.74 (s, 3H), 4.63 (d, $J = 5.2$ Hz, 1H), 5.15 (s, 1H), 6.78 (s, 4H), 7.26–7.43 (m, 5H). ^{13}C NMR: δ 52.3, 55.6, 74.8, 82.9, 114.7, 117.0, 126.6, 128.5, 138.5, 151.6, 155.0, 170.1. IR (neat): 3462, 1748, 1226, 701 cm^{-1}. EI-HRMS calculated for $C_{17}H_{18}O_5$: 302.1154, found: 302.1163.

4.8. (2*S*,3*R*)-Methyl 3-benzoyl-2-(*p*-methoxyphenoxy)-3-phenylpropionate 11

Methyl ester **10** (0.7785 g, 1.92 mmol) was placed in a 100 mL round bottom flask and dissolved in CH_2Cl_2 (5.15 mL). To this reaction mixture was added DMAP (1.2 mmol), followed by triethylamine (3.1 mmol). The reaction was cooled to 0 °C and benzoyl chloride (3.6 mmol) was added. The reaction allowed to run overnight, quenched by the addition of HCl (1 M), extracted via CH_2Cl_2, separated, washed with brine, dried over $MgSO_4$, and the solvent removed via rotary evaporation. The resulting ester was purified via column chromatography using a 90/10 mixture of hexanes and ethyl acetate and recovered in a 68% yield (0.7151 g) as a yellow oil. $[\alpha]_D^{25} = +24.7$ (c 0.25, $CHCl_3$); $R_f = 0.14$ (ethyl acetate/hexanes, 1:9). ^{1}H NMR: δ 3.64 (s, 3H), 3.73 (s, 3H), 4.88 (d, $J = 5.2$ Hz, 1H), 6.48 (d, $J = 4.8$ Hz, 1H), 6.72–6.78 (m, 4H), 7.32–7.58 (m, 8H), 8.10 (d, $J = 7.2$ Hz, 1H). ^{13}C NMR: δ 52.5, 55.6, 75.9, 81.6, 114.6, 117.4, 127.2, 128.4, 128.5, 128.8, 129.6, 129.9, 133.3, 135.8, 152.2, 154.9, 165.3, 169.2. IR (neat): 1724, 1507, 1107, 1027, 743 cm^{-1}. EI-HRMS calculated for $C_{24}H_{22}O_6$: 406.1416, found: 406.1416.

4.9. (2*S*,3*R*)-Methyl (2*S*,3*R*)-2,3-dihydroxy-3-phenylpropionate 12

Compound **11** (0.7780 g, 1.9 mmol) was placed in a 50 mL round bottom flask and dissolved in acetonitrile (4.8 mL). To this reaction mixture was added ceric ammonium nitrate (5.7 mmol) dissolved in water (4.8 mL). The reaction was allowed to run for 2 h, after which point it was quenched using water and chloroform. The compound was then extracted into the chloroform, washed with brine, dried ($MgSO_4$), and the solvent removed via rotary evaporation. This material was then measured and placed in a 50 mL round bottom flask and dissolved in methanol (17.4 mL), to which 1.00 equiv (1.9 mmol) of K_2CO_3 was added. The reaction was allowed to run for 3 h, quenched by the addition of a saturated solution of $NaHCO_3$, extracted via $CHCl_3$, separated, washed with brine, dried over $MgSO_4$, gravity filtered, and the solvent removed via rotary evaporation. The resulting ester diol was purified via column chromatography using a 60/40 mixture of hexanes and ethyl acetate and recovered in 37% yield (140.2 mg). $[\alpha]_D^{25} = -9.3$ (c 0.46, $CHCl_3$); $R_f = 0.20$ (ethyl acetate/hexanes, 2:3). ^{1}H NMR: δ 3.81 (s, 3H), 4.37 (d,

$J = 2.4$ Hz, 1H), 5.02 (d, $J = 2.4$ Hz, 1H), 7.24–7.40 (m, 5H). ^{13}C NMR: δ 53.1, 74.4, 74.7, 126.2, 128.1, 128.5, 138.9, 173.1. IR (neat): 3449, 1737, 1212, 768 cm^{-1}. EI-HRMS calculated for $C_{10}H_{12}O_4$: 196.0736, found: 196.0745.

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