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Oxadiazinones as chiral auxiliaries: diastereoselective aldol addition reactions of N_3-glycolyl-3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-ones☆

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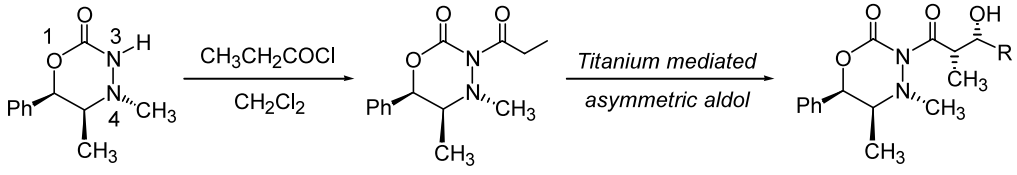
Abstract—Asymmetric aldol reactions have been conducted with a series of N_3-glycolyl-3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-ones derived from (1*R*,2*S*)-ephedrine. These reactions afford the non-Evans *syn*-adducts in 43–97% yield and diastereoselectivities ranging from 62:38 to 99:1. Oxadiazinone substrates substituted with either the phenoxyacetyl or *p*-methoxyphenoxyacetyl groups gave the best results whereas the methoxyacetyl substituted oxadiazinone afforded diastereoselectivities that were modest.

1. Introduction

The development and utilization of chiral auxiliaries in asymmetric reactions continues to evolve at an ever increasing rate.[1] Oxazolidinones have been among the most successfully exploited auxiliaries[2] and these compounds have given inspiration to the synthesis and application of a number of related auxiliaries.[3] Our efforts in this field led us to the development of 3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-ones (oxadiazinones) as potential candidates for asymmetric reactions (Scheme 1).[4a,b] We recently demonstrated the usefulness of N_3-propionyloxadiazinones in titanium mediated asymmetric aldol addition reactions.[4a] The chemical yields were good and the diastereoselectivities, directed by the N_4-methyl substituent, ranged from 3:1 to 99:1. We became interested in investigating the potential of the oxadiazinones as chiral auxiliaries for the related glycolate aldol reaction. Crimmins,[5] Davies,[6] and Evans[7] have successfully applied *N*-glycolyloxazolidin-2-ones and *N*-glycolyloxazolidine-2-thiones in asymmetric aldol reactions to selectively afford either *syn*- or *anti*-glycolate adducts. Andrus[8] has employed *N*-glycolyldioxanones in the preparation of *anti*-glycolate adducts with much success. Herein we report on our efforts in employing *N*-glycolyl-oxadiazinones in the asymmetric aldol reaction to afford *syn*-glycolate adducts.



Scheme 1. Asymmetric aldol reaction with a N_3-propionyl oxadiazinones.

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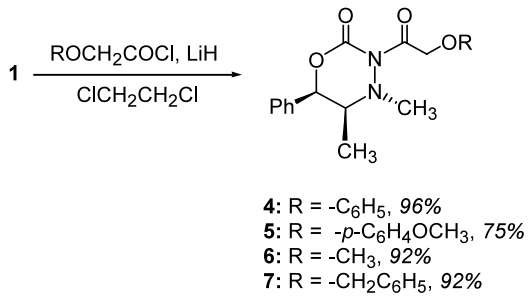


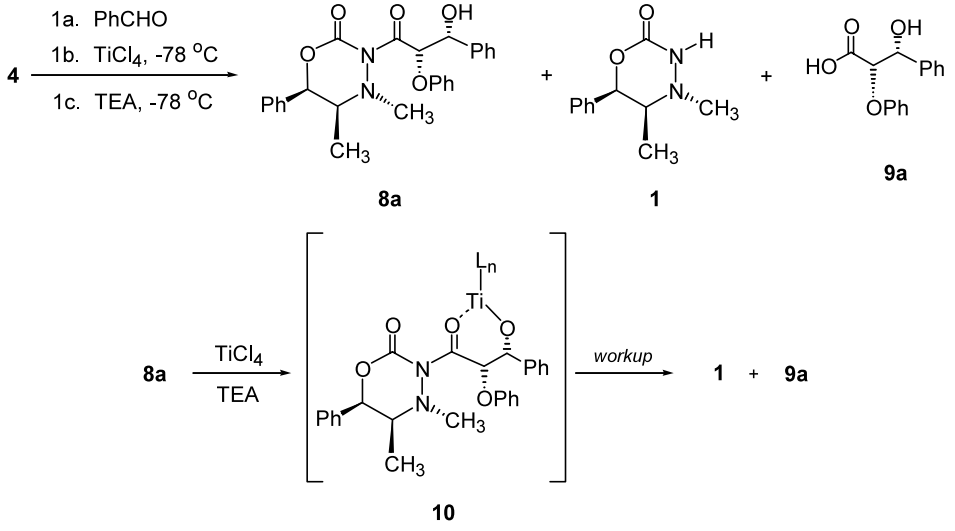
Scheme 2. Acylation of oxadiazinone **1**.

2. Results and discussion

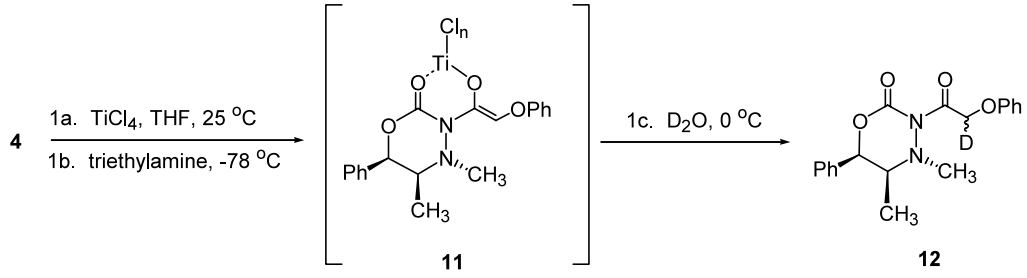
The (1*R*,2*S*)-ephedrine based oxadiazinone **1**[9] was acylated with a variety of substituted acetyl chloride derivatives ($ROCH_2COCl$: R = $-C_6H_5$, $-C_6H_4OCH_3$, $-CH_3$, and $-CH_2Ph$) to afford N_3-acylated oxadiazinones **4**–**7** in 75–96% yield (Scheme 2). The method of choice involved the addition of lithium hydride to a mixture of **1** and the substituted acetyl chloride in methylene chloride. The use of bases such as *n*-BuLi and HMDS proved to be inefficient in the acylation process.

Our initial efforts in applying the asymmetric aldol reaction to the N_3-glycolyloxadiazinones were not promising. Oxadiazinone **4** was combined with benzaldehyde, cooled to −78°C, treated with titanium tetrachloride, and finally reacted with triethylamine (Scheme 3). This process gave aldol adduct **8a**, the cleaved heterocycle **1**, and hydroxyacid **9a** in varying amounts (5–25% in situ deacylation). This was surprising as this phenomenon was not observed when these reaction conditions were applied to the corresponding N_3-propionyloxadiazinone.[4b] A possible explanation for this observation is associated with the fact that phenoxyacetyl group hydrolyzes nearly 50 times faster than the acetyl group under basic conditions.[10]

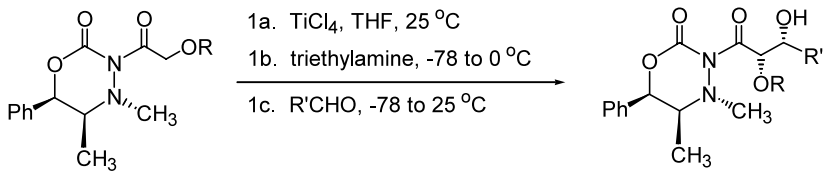
In order to improve the product distribution to favor the aldol adduct, the reaction conditions were modified to reflect our recent studies on improving the overall reactivity of N_3-propionyl-oxadiazinones in the asymmetric aldol reaction.[4a] Oxadiazinone **4** was dissolved in THF (0.33 M) and treated with titanium tetrachloride at 25°C for 25 min. This reaction mixture was cooled to −78°C, triethylamine was added, and the temperature was allowed to come to 0°C. At this time, D_2O was added to confirm successful deprotonation (Scheme 4).[11] The success of the deuteration experiment led us to modify the asymmetric aldol reaction conditions to allow for clean enolate formation (e.g. intermediate **11**) and subsequent carbon–carbon bond formation without significant concomitant product deacylation. Thus, oxadiazinones **4**–**6** were treated with titanium tetrachloride at 25°C for a period of 25 min, cooled to



Scheme 3. Initial attempt for asymmetric aldol reactions.



Scheme 4. Deuterium incorporation study of **4**.



Scheme 5. Asymmetric aldol reaction of oxadiazinones **4**–**6**.

Table 1. Diastereoselective aldol additions with oxadiazinones **4**–**6**

Entry	Substrate	R′CHO aldehyde	Dr[a]		Yield[b] [%]	Adduct
			Crude	Pure		
1	**4**	-C_6H_5	94:6	97:3	70	**8a**
2	**4**	-*p*-C_6H_4Cl	96:4	99:1	88	**8b**
3	**4**	-*p*-$C_6H_4OCH_3$	93:7	99:1	79	**8c**
4	**4**	-2-$C_{10}H_7$	91:9	99:1	43	**8d**
5	**4**	-*m*-$C_6H_4CH_3$	93:7	99:1	57	**8e**
6	**5**	-C_6H_5	95:5	99:1	82	**13a**
7	**5**	-*p*-C_6H_4Cl	91:9	96:4	66	**13b**
8	**5**	-*p*-$C_6H_4OCH_3$	93:7	98:2	76	**13c**
9	**5**	-2-$C_{10}H_7$	95:5	99:1	63	**13d**
10	**5**	-*m*-$C_6H_4CH_3$	97:3	99:1	76	**13e**
11	**6**	-C_6H_5	79:21[c]	85:15[c]	97	**14a**
12	**6**	-*p*-C_6H_4Cl	83:17[c]	90:10[c]	92[d]	**14b**
13	**6**	-*p*-$C_6H_4OCH_3$	62:38[c]	90:10[c]	46[d]	**14c**
14	**6**	-2-$C_{10}H_7$	86:14[c]	91:9[c]	99[d]	**14d**
15	**6**	-*m*-$C_6H_4CH_3$	74:26[c]	89:11[c]	64[d]	**14e**

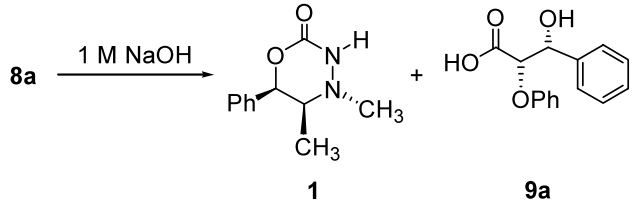
[a] Diastereomer ratios determined by HPLC.
[b] Chemical yield of the purified product after column chromatography.
[c] The ratio of diastereomers was determined by ^1H NMR.
[d] These products were contaminated with ~13% of oxadiazinone **1** which could not be removed by chromatography or resolved by HPLC; see Section 4.

−78°C, reacted with triethylamine, and warmed to 0°C over a span of 15 min. The reaction was then cooled to −78°C and the desired aldehyde was added. These conditions gave the aldol adducts **8a**–**e**, **13a**–**e**, and **14a**–**e**[12] in 43–97% chemical yield and good diastereoselectivity (Scheme 5, Table 1). Unfortunately, we were not able to successfully employ aliphatic aldehydes using this approach. The reactions gave mixtures of the desired aldol adduct, deacylation, and elimination.

We were disappointed to learn that the N_3-benzyloxyoxadiazinone **7** did not readily undergo the asymmetric aldol reaction. A series of control experiments were conducted in an effort to determine the source of the failure of this substrate to react. These experiments included variation of reaction temperature, stoichiometry, and molarity. Unfortunately, none of these conditions led to significant incorporation of deuterium.

In order to determine the stereochemical outcome of the asymmetric aldol addition reaction, aldol adduct **8a** was hydrolyzed to the corresponding β-hydroxyacid **9a** by treatment with 1 M NaOH in THF (Scheme 6). This process afforded **9a** (74%) and the heterocycle **1** was recovered (96%).[13,14] The crude ^1H NMR spectrum suggested that the diastereomeric purity of the adduct was retained under the hydrolytic conditions.

The relative stereochemistry of **9a**[15] was determined to be the *syn*-configuration based on the observed vicinal coupling constant between the benzylic methine proton and the α-methine of the carboxyl group ($J_{a\text{-}b}$ = 4.0 Hz) from the 400 MHz ^1H NMR spectrum.[15] The absolute stereochemistry of **9a** was determined by optical rotation to have the (2*S*,3*R*)-geometry {$[\alpha]_D$ −41.3 (ee≈ 91%), (*c* 1.73, ethanol); lit.[15] (2*R*,3*S*)-isomer: $[\alpha]_D$+44.3 (ee = 98%), (*c* 2.1, ethanol)}.[15] This suggested that the transition state for the formation of the 'non-Evans' *syn*-adduct is a closed Zimmerman–Traxler transition state[16] in which the *si*-face of the aldehyde is directed by the stereogenic N_4-methyl substituent to the *re*-face of the enolate (Fig. 1).[17]



Scheme 6. Hydrolysis oxadiazinone adduct **8a**.

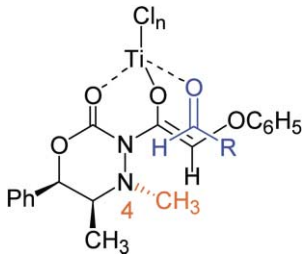


Figure 1. Proposed transition state for the *syn*-glycolate aldol addition.

3. Conclusion

In summary, we have synthesized a series of N_3-glycolyl-3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-ones and have employed them in the asymmetric aldol reaction to afford non-Evans *syn*-glycolate adducts. The reactions with the glycolyl substrates (*O*-phenyl, *O*-anisyl, *O*-methyl) afforded glycolate aldol adducts in fair to good chemical yield and good diastereoselectivities. Research is underway to refine the asymmetric aldol reaction of N_3-glycolyl-oxadiazinones for extension of this method to the use of aliphatic aldehydes.[12] Studies focused on the reactivity of N_3-benzyloxy-oxadiazinone **7** are also underway.

4. Experimental

4.1. General remarks

Tetrahydrofuran (THF) was distilled from a potassium/sodium alloy with benzophenone ketyl. Methylene chloride (CH_2Cl_2) and ethylene chloride were distilled from calcium hydride. All reactions were run under a nitrogen atmosphere. Flash chromatography was conducted with silica gel (32–63 mesh). ^{1}H 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). Tetramethylsilane (tms) was used as an internal standard ($\delta = 0.00$ ppm). Infrared spectra are reported in reciprocal centimeters (cm^{-1}) and are measured either as a neat solution of dissolved in CCl_4. Melting points were recorded on a Mel-Temp apparatus and are uncorrected. High-resolution mass spectra were obtained from the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois, Urbana-Champaign. Elemental analyses were conducted by the Microanalytical Laboratory, School of Chemical Sciences, University of Illinois, Urbana-Champaign.

4.2. General procedure for the preparation of compounds 4–7

In a flame-dried, nitrogen purged, 250 mL round bottomed flask equipped with a condenser was placed the (1*R*,2*S*)-ephedrine heterocycle **1** (7.0 g, 34 mmol), freshly distilled ethylene chloride (34 mL), and the appropriate acyl halide (41 mmol). The reaction mixture was heated to reflux, and lithium hydride (0.28 g, 36 mmol) was added. The reaction was allowed to stir overnight and was then cooled to 0°C and quenched by the addition of a saturated solution of ammonium chloride (75 mL). The solution was extracted with EtOAc (2×75 mL), washed with a saturated solution of brine, dried over $MgSO_4$, and the solvent was removed via rotary evaporation.

4.2.1. (4*R*,5*S*,6*R*)-3,4,5,6-Tetrahydro-4,5-dimethyl-3-(2-phenoxyacetyl)-6-phenyl-2*H*-1,3,4-oxadiazin-2-one 4. Isolated product recrystallized from EtOAc to yield **4** (96%) as a white powder. $[\alpha]_D^{25} = -41.8$ (c 1.14, methanol). $R_f = 0.35$ (50:50, hexanes:EtOAc). Mp: 124–126°C. ^{1}H NMR ($CDCl_3$): δ 0.90 (d, 3H, $J = 6.9$ Hz), 3.02 (s, 3H), 3.41–3.47 (m, 1H), 5.17 (d, 1H, $J = 17.6$ Hz), 5.27 (d, 1H, $J = 17.6$ Hz), 6.07 (d, 1H, $J = 4.03$ Hz), 6.95–7.45 (m, 10H). ^{13}C NMR ($CDCl_3$): 12.3, 43.3, 56.9, 69.4, 77.7, 114.9, 121.6, 124.9, 128.4, 128.8, 129.5, 135.1, 148.6, 157.9, 169.0. IR (CCl_4): 1782, 1366, 1245, 1211, 784, 755 cm^{-1}. Anal. calcd for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.92; N, 8.23. Found: C, 67.00; H, 5.80; N, 8.21. HRMS calcd for $C_{19}H_{21}N_2O_4$: 341.1501. Found: 341.1503.

4.2.2. (4*R*,5*S*,6*R*)-3,4,5,6-Tetrahydro-3-[2-(4-methoxyphenoxy)acetyl]-4,5-dimethyl-6-phenyl-2*H*-1,3,4-oxadiazin-2-one 5. Product isolated by column chromatography (60:40, hexanes:EtOAc, $R_f = 0.20$, column dimensions = 5.5×15 cm) to yield **5** (75%) as an oil. $[\alpha]_D^{25} = -40.5$ (c 1.66, methanol). ^{1}H NMR ($CDCl_3$): δ 0.89 (d, 3H, $J = 6.9$ Hz), 3.01 (s, 3H), 3.41–3.47 (m, 1H), 3.77 (s, 3H), 5.12 (d, 1H, $J = 17.6$ Hz), 5.21 (d, 1H, $J = 17.6$ Hz), 6.07 (d, 1H, $J = 4.0$ Hz), 6.82–6.94 (m, 4H), 7.30–7.44 (m, 5H). ^{13}C NMR ($CDCl_3$): 12.3, 43.3, 55.6, 56.8, 70.4, 77.7, 114.6, 116.3, 124.9, 128.4, 128.8, 135.1, 148.6, 152.1, 154.5, 169.3. IR (neat): 1786, 804, 747 cm^{-1}. HRMS calcd for $C_{20}H_{23}N_2O_5$: 371.1607. Found: 371.1607.

4.2.3. (4*R*,5*S*,6*R*)-3-(2-Methoxyacetyl)-4,5-dimethyl-6-phenyl-2*H*-1,3,4-oxadiazin-2-one 6. The product was recrystallized from EtOAc to yield **6** (92%) as a white powder. $R_f = 0.26$ (20:80, hexanes:EtOAc). Mp: 100–102°C. $[\alpha]_D^{25} = -70.9$ (c 1.86, methanol). ^{1}H NMR ($CDCl_3$): δ 0.87 (d, 3H, $J = 6.9$ Hz), 3.00 (s, 3H), 3.40–3.46 (m, 1H), 3.51 (s, 3H), 4.56 (d, 1H, $J = 17.9$ Hz), 4.68 (d, 1H, $J = 17.9$ Hz), 6.05 (d, 1H, $J = 4.04$ Hz), 7.29–7.43 (m, 5H). ^{13}C NMR ($CDCl_3$): 12.2, 43.3, 56.8, 59.3, 73.9, 77.6, 124.9, 128.3, 128.8, 135.2, 148.5, 170.6. IR (CCl_4): 1781, 1258, 1219, 793, 784, 766 cm^{-1}. Anal. calcd for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.08; H, 6.40; N, 9.97. HRMS calcd for $C_{14}H_{18}N_2O_4$: 279.1345. Found: 279.1345.

4.2.4. (4*R*,5*S*,6*R*)-3-(2-Benzyloxyacetyl)-3,4,5,6-tetrahydro-4,5-dimethyl-6-phenyl-2*H*-1,3,4-oxadiazin-2-one 7. Yellow oil purified by column chromatography on silica gel (50:50, hexanes:EtOAc, $R_f = 0.21$, column dimensions = 5.5×15 cm) to yield **7** (92%) as a clear oil. $[\alpha]_D^{25} = -55.7$ (c 2.15, methanol). ^{1}H NMR ($CDCl_3$): δ

0.85 (d, 3H, $J=6.9$ Hz), 3.00 (s, 3H), 3.39–3.45 (m, 1H), 4.64 (d, 1H, $J=17.9$ Hz), 4.68 (d, 1H, $J=2.2$ Hz), 4.75 (d, 1H, $J=17.9$ Hz), 6.03 (d, 1H, $J=4.0$ Hz), 7.28–7.44 (m, 10H). ^{13}C NMR ($CDCl_3$): 12.3, 43.3, 56.8, 71.3, 73.3, 77.6, 124.9, 127.9, 128.2, 128.3, 128.4, 128.7, 135.2, 137.2, 148.4, 170.8. IR (neat): 1786, 1732, 1202, 1136, 738, 699 cm^{-1}. HRMS calcd for $C_{20}H_{23}N_2O_4$: 355.1658. Found: 355.1659.

4.3. Procedure for the synthesis of (2′*S*,3′*R*,4*R*,5*S*,6*R*)-3,4,5,6-tetrahydro-3-(3-hydroxy-2-phenoxy-3-phenylpropionyl)-4,5-dimethyl-6-phenyl-2*H*-1,3,4-oxadiazin-2-one 8a

In a nitrogen-purged, flame-dried 100 mL, round bottomed flask was placed **4** (0.75 g, 2.20 mmol), freshly distilled THF (6.60 mL), and titanium tetrachloride (0.25 mL, 2.3 mmol). The solution was stirred for 25 min and was then cooled to −78°C for 15 min. Triethylamine (0.61 mL, 4.4 mmol) was then added, and the reaction was brought to 0°C over a period of 15 min. The reaction mixture was again cooled to −78°C and benzaldehyde (0.44 mL, 4.4 mmol) was added. The reaction stirred for 4 h and was quenched by the addition of a saturated solution of ammonium chloride (50 mL). The resulting mixture was then extracted with EtOAc (3×50 mL), washed with a saturated solution of brine, dried over $MgSO_4$, and the solvent was removed via rotary evaporation. This process afforded a yellow oil purified by column chromatography on silica gel (40:60, hexanes:EtOAc, $R_f=0.27$, column dimensions = 3×40 cm) to yield **8a** (70%) as an oil. $[\alpha]_D^{25}=-6.0$ (*c* 2.46, methanol). ^{1}H NMR ($CDCl_3$): δ 0.79 (d, 3H, $J=6.9$ Hz), 2.91 (s, 3H), 3.38–3.44 (m, 1H), 5.41 (d, 1H, $J=2.2$ Hz), 6.05 (d, 1H, $J=3.6$ Hz), 6.10 (d, 1H, $J=2.6$ Hz), 6.77–7.60 (m, 15H). ^{13}C NMR ($CDCl_3$): 11.9, 42.9, 56.5, 73.8, 77.8, 82.1, 115.9, 122.1, 124.7, 126.3, 127.8, 128.1, 128.2, 128.7, 129.3, 135.0, 139.7, 148.8, 157.3, 169.5. IR (neat): 3460, 3063, 1716, 1599, 1186, 732, 700 cm^{-1}. HRMS calcd for $C_{26}H_{27}N_2O_5$: 447.1920. Found: 447.1922.

4.4. General procedure for the preparation of 8b–e

In a nitrogen-purged, flame-dried 100 mL, round bottomed flask was placed **4** (1.00 g, 2.93 mmol), freshly distilled tetrahydrofuran (8.80 mL), and the appropriate aldehyde (5.86 mmol). The solution was then cooled to −78°C for 10 min. To this solution was added titanium tetrachloride (0.34 mL, 3.1 mmol) and the reaction stirred for 15 min. Triethylamine (0.81 mL, 5.86 mmol) was then added. The reaction was allowed to run for 4 h and was quenched by the addition of a saturated solution of sodium bicarbonate (50 mL) at 25°C. The resulting mixture was then extracted with EtOAc (3×50 mL), washed with a saturated solution of brine, dried over $MgSO_4$, and the solvent was removed via rotary evaporation.

4.4.1. (2′*S*,3′*R*,4*R*,5*S*,6*R*)-3-[3-(4-Chlorophenyl)-3-hydroxy-2-phenoxypropionyl]-3,4,5,6-tetrahydro-4,5-dimethyl-6-phenyl-2*H*-1,3,4-oxadiazin-2-one 8b

Yellow oil purified by column chromatography on silica gel (40:60, hexanes:EtOAc, $R_f=0.27$, column dimensions = 3×40 cm) to yield **8b** (88%) as an oil. $[\alpha]_D^{25}=-1.4$ (*c* 2.22, methanol). ^{1}H NMR ($CDCl_3$): δ 0.80 (d, 3H, $J=6.96$ Hz), 2.96 (s, 3H), 3.40–3.46 (m, 1H), 5.41 (s, 1H), 6.01 (d, 1H, $J=2.20$ Hz), 6.08 (d, 1H, $J=4.04$ Hz), 6.74–7.55 (m, 14H). ^{13}C NMR ($CDCl_3$): 11.8, 42.8, 56.3, 72.9, 77.8, 81.8, 115.7, 122.1, 124.6, 127.6, 128.1, 128.2, 128.6, 129.3, 133.2, 134.9, 138.5, 148.9, 157.1, 169.2. IR (neat): 3438, 3064, 1700, 1598, 1134 cm^{-1}. HRMS calcd for $C_{26}H_{26}N_2O_5Cl$: 481.1530. Found: 481.1532.

4.4.2. (2′*S*,3′*R*,4*R*,5*S*,6*R*)-3,4,5,6-Tetrahydro-3-[3-hydroxy-3-(4-methoxyphenyl)-2-phenoxypropionyl]-4,5-dimethyl-6-phenyl-2*H*-1,3,4-oxadiazin-one 8c

Yellow oil purified by column chromatography on silica gel (40 hexanes: 60 EtOAc, $R_f=0.24$, column dimensions = 3×40 cm) to yield **8c** (79%) as an oil. $[\alpha]_D^{25}=-20.8$ (*c* 2.29, methanol). ^{1}H NMR ($CDCl_3$): δ 0.74 (d, 3H, $J=6.9$ Hz), 2.74 (s, 3H), 3.31–3.37 (m, 1H), 3.49 (d, 1H, $J=7.3$ Hz), 3.72 (s, 3H), 5.33 (d, 1H, $J=4.0$ Hz), 5.95 (d, 1H, $J=4.03$ Hz), 6.09 (d, 1H, $J=2.9$ Hz), 6.78–7.50 (m, 14H). ^{13}C NMR ($CDCl_3$): 11.7, 42.6, 54.9, 56.3, 73.5, 77.7, 81.9, 113.4, 115.7, 121.8, 124.6, 127.6, 128.1, 128.5, 129.2, 131.7, 135.0, 148.7, 157.3, 159.0, 169.4. IR (neat): 3455, 2936, 1717, 1599, 740, 700 cm^{-1}. HRMS calcd for $C_{27}H_{29}N_2O_5$: 477.2026. Found: 477.2026.

4.4.3. (2′*S*,3′*R*,4*R*,5*S*,6*R*)-3,4,5,6-Tetrahydro-3-(3-hydroxy-3-naphthalen-2-yl-2-phenoxypropionyl)-4,5-dimethyl-6-phenyl-2*H*-1,3,4-oxadiazin-2-one 8d

Yellow oil purified by column chromatography on silica gel (50:50, hexanes:EtOAc, $R_f=0.19$, column dimensions = 3×40 cm) to yield **8d** (43%) as an oil. $[\alpha]_D^{25}$ +10.3 (*c* 2.00, methanol). ^{1}H NMR ($CDCl_3$): δ 0.79 (d, 3H, $J=6.6$ Hz), 2.87 (s, 3H), 3.32 (d, 1H, $J=6.6$ Hz), 3.36–3.42 (m, 1H), 5.59 (s, 1H), 5.99 (d, 1H, $J=3.7$ Hz), 6.20 (d, 1H, $J=2.7$ Hz), 6.76–8.01 (m, 17H). ^{13}C NMR ($CDCl_3$): 11.9, 42.8, 56.4, 73.8, 77.7, 82.0, 115.8, 122.0, 124.2, 124.7, 125.3, 125.8, 125.9, 127.5, 127.9, 128.0, 128.2, 128.6, 129.3, 132.8, 132.9, 135.0, 137.3, 148.9, 157.3, 169.5. IR (neat): 3446, 3013, 1716, 1600, 751 cm^{-1}. HRMS calcd for $C_{30}H_{29}N_2O_5$: 497.2076. Found: 497.2070.

4.4.4. (2′*S*,3′*R*,4*R*,5*S*,6*R*)-3,4,5,6-Tetrahydro-3-(3-hydroxy-2-phenoxy-3-*m*-tolylpropionyl)-4,5-dimethyl-6-phenyl-2*H*-1,3,4-oxadiazin-2-one 8e

Yellow oil purified by column chromatography on silica gel (40:60, hexanes:EtOAc, $R_f=0.30$, column dimensions = 3×40 cm) to yield **8e** (57%) as an oil. $[\alpha]_D^{25}=-6.0$ (*c* 1.28, methanol). ^{1}H NMR ($CDCl_3$): δ 0.79 (d, 3H, $J=6.9$ Hz), 2.34 (s, 3H), 2.84 (s, 3H), 3.22 (d, 1H, $J=7.7$ Hz), 3.35–3.41 (m, 1H), 5.37 (d, 1H, $J=5.5$ Hz), 6.00 (d, 1H, $J=4.0$ Hz), 6.10 (d, 1H, $J=2.6$ Hz), 6.77–7.43 (m, 14H). ^{13}C NMR ($CDCl_3$): 11.8, 21.3, 42.7, 56.4, 73.8, 77.7, 82.0, 115.8, 121.9, 123.3, 124.6, 127.0, 128.0, 128.1, 128.4, 128.6, 129.2, 135.0, 137.6, 139.5, 148.7, 157.3, 169.4. IR (neat): 3464, 2976, 1718, 1239, 788, 752 cm^{-1}. HRMS calcd for $C_{27}H_{29}N_2O_5$: 461.2076. Found: 461.2074.

4.5. (+)-(2*S*,3*R*)-3-Hydroxy-2-phenoxy-3-phenylpropionic acid 9a

In a 100 mL, round bottomed flask was placed **8a** (1.00g, 2.24 mmol), tetrahydrofuran (6.70 mL), and NaOH (1 M, 6.72 mL). The resulting solution was stirred overnight. A saturated solution of sodium bicarbonate (50 mL) was then added. The mixture was then extracted with EtOAc (2×50 mL), washed with a saturated solution of brine, dried over $MgSO_4$, and the solvent was removed via rotary evaporation. The aqueous layer was acidified with 1 M HCl. This solution was extracted with EtOAc (2×50 mL), washed with a saturated solution of brine, dried over $MgSO_4$, and the solvent was removed via rotary evaporation. This process afforded **9a** (79%) as an oil. R_f=0.13 (50:50, hexanes:EtOAc). $[\alpha]_D^{25}$=−41.3 (*c* 1.73, ethanol). ^{1}H NMR ($CDCl_3$): δ 3.63 (s, 1H), 4.81 (d, 1H, J=4.03 Hz), 5.27 (d, 1H, J=4.03 Hz), 6.82–7.49 (m, 10H). ^{13}C NMR ($CDCl_3$): 74.3, 80.8, 115.5, 122.3, 126.6, 128.4, 129.5, 133.8, 138.7, 157.3, 173.8. IR (neat): 3408, 3064, 1732, 1599, 753, 700 cm^{-1}. HRMS calcd for $C_{15}H_{15}O_4$: 259.0970. Found: 259.0970.

4.6. (2′*S*,3′*R*,4*R*,5*S*,6*R*)-3,4,5,6-Tetrahydro-4,5-dimethyl-3-(2-deuterio-2-phenoxyacetyl)-6-phenyl-2*H*-1,3,4-oxadiazin-2-one 12

In a nitrogen-purged, flame-dried 100 mL, round bottomed flask was placed **4** (0.75 g, 2.2 mmol), freshly distilled tetrahydrofuran (6.60 mL), and titanium tetrachloride (0.25 mL, 2.31 mmol). The solution was stirred for 25 min and was then cooled to −78°C for 15 min. Triethylamine (0.61 mL, 4.4 mmol) was then added, and the reaction was brought to 0°C over a period of 15 min and D_2O was added. Then, a saturated solution of ammonium chloride (50 mL) was added. The resulting mixture was then extracted with EtOAc (3×50 mL), washed with a saturated solution of brine, dried over $MgSO_4$, and the solvent was removed via rotary evaporation. Isolated product recrystallized from EtOAc to yield **12** (40%) as a white powder. R_f=0.36 (50 hexanes:50 EtOAc). Mp: 125–126°C. ^{1}H NMR ($CDCl_3$): δ 0.90 (d, 3H, J=6.9 Hz), 3.02 (s, 3H), 3.41–3.47 (m, 1H), 5.16 (s, 1H), 5.24 (s, 1H), 6.08 (d, 1H, J=4.0 Hz), 6.95–7.45 (m, 10H). ^{13}C NMR ($CDCl_3$): 12.3, 43.3, 56.9, 68.8, 69.1, 69.3, 77.7, 114.9, 121.6, 124.9, 128.4, 128.8, 129.5, 135.1, 148.6, 157.8, 169.0. IR (CCl_4): 3011, 1770, 1210, 786, 760 cm^{-1}. HRMS calcd for $C_{19}H_{21}DN_2O_4$: 342.1564. Found: 342.1564.

4.7. General procedure for the preparation of 13a–e

In a nitrogen-purged, flame-dried, 100 mL round bottomed flask was placed **5** (1.00 g, 2.70 mmol), freshly distilled tetrahydrofuran (8.10 mL), and titanium tetrachloride (0.31 mL, 2.8 mmol). The solution was stirred for 25 min and was then cooled to −78°C for 15 min. Triethylamine (0.75 mL, 5.4 mmol) was then added and the reaction was brought to 0°C over a period of 15 min. The reaction mixture was again cooled to −78°C, and the appropriate aldehyde (5.40 mmol) was then added. The reaction stirred for 4 h and was quenched by the addition of a saturated solution of ammonium chloride (50 mL). The resulting mixture was then extracted with EtOAc (3×50 mL), washed with a saturated solution of brine, dried over $MgSO_4$, and the solvent was removed via rotary evaporation.

4.7.1. (2′*S*,3′*R*,4*R*,5*S*,6*R*)-3,4,5,6-Tetrahydro-3-[3-hydroxy-2-(4-methoxyphenoxy)-3-phenylpropionyl]-4,5-dimethyl-6-phenyl-2*H*-1,3,4-oxadiazin-2-one 13a. Yellow oil purified by column chromatography on silica gel (30:70, hexanes:EtOAc, R_f=0.24, column dimensions=3×40 cm) to yield **13a** (82%) as an oil. $[\alpha]_D^{25}$=−13.7 (*c* 2.10, methanol). ^{1}H NMR ($CDCl_3$): δ 0.74 (d, 3H, J=6.9 Hz), 2.91 (s, 3H), 3.37–3.43 (m, 1H), 3.39 (s, 3H), 5.38 (d, 1H, J=2.6 Hz), 5.95 (d, 1H, J=2.9 Hz), 6.03 (d, 1H, J=4.0 Hz), 6.69 (s, 4H), 7.25–7.60 (m, 10H). ^{13}C NMR ($CDCl_3$): 11.8, 42.8, 55.3, 56.3, 73.8, 77.7, 83.7, 114.3, 117.7, 124.6, 126.2, 127.6, 128.0, 128.1, 128.5, 135.0, 139.8, 148.6, 151.2, 154.7, 169.8. IR (neat): 3458, 1720, 1258, 745, 700 cm^{-1}. HRMS calcd for $C_{27}H_{29}N_2O_6$: 477.2026. Found: 477.2025.

4.7.2. (2′*S*,3′*R*,4*R*,5*S*,6*R*)-3-[3-(4-Chlorophenyl)-3-hydroxy-2-(4-methoxyphenoxy)propionyl]-3,4,5,6-tetrahydro-4,5-dimethyl-6-phenyl-2*H*-1,3,4-oxadiazin-2-one 13b. Yellow oil purified by column chromatography on silica gel (30:70, hexanes:EtOAc, R_f=0.28, column dimensions=3×40 cm) to yield **13b** (66%) as an oil. $[\alpha]_D^{25}$=−6.5 (*c* 2.20, methanol). ^{1}H NMR ($CDCl_3$): δ 0.75 (d, 3H, J=6.9 Hz), 2.95 (s, 3H), 3.38–3.45 (m, 1H), 3.69 (s, 3H), 5.37 (d, 1H, J=1.8 Hz), 5.86 (d, 1H, J=2.2 Hz), 6.05 (d, 1H, J=4.0 Hz), 6.69 (d, 4H, J=2.2 Hz), 7.28–7.55 (m, 9H). ^{13}C NMR ($CDCl_3$): 11.8, 42.8, 55.3, 56.3, 72.9, 77.7, 83.4, 114.3, 117.6, 124.6, 127.6, 128.1, 128.11, 128.5, 133.1, 134.9, 138.7, 148.7, 151.3, 154.7, 169.5. IR (neat): 3456, 1724, 757 cm^{-1}. HRMS calcd for $C_{27}H_{28}N_2O_6Cl$: 511.1636. Found: 511.1636.

4.7.3. (2′*S*,3′*R*,4*S*,5*S*,6*R*)-3,4,5,6-Tetrahydro-3-[3-hydroxy-2-(4-methoxyphenoxy)-3-(4-methoxyphenyl)propionyl]-4,5-dimethyl-6-phenyl-2*H*-1,3,4-oxadiazin-2-one 13c. Yellow oil purified by column chromatography on silica gel (30:70, hexanes:EtOAc, R_f=0.20, column dimensions=3×40 cm) to yield **13c** (76%) as an oil. $[\alpha]_D^{25}$=−14.5 (*c* 2.58, methanol). ^{1}H NMR ($CDCl_3$): δ 0.73 (d, 3H, J=6.9 Hz), 2.88 (s, 3H), 3.36–3.42 (m, 1H), 3.70 (s, 3H), 3.81 (s, 3H), 5.32 (d, 1H, J=2.9 Hz), 5.95 (d, 1H, J=2.9 Hz), 6.01 (d, 1H, J=4.0 Hz), 6.69–6.75 (m, 4H), 6.91 (d, 4H, J=8.4 Hz), 7.29–7.51 (m, 5H). ^{13}C NMR ($CDCl_3$): 11.7, 42.7, 55.0, 55.3, 56.3, 73.5, 77.6, 83.6, 113.4, 114.3, 117.6, 124.6, 127.6, 128.1, 128.5, 131.8, 135.0, 148.6, 151.5, 154.6, 158.9, 169.8. IR (neat): 3466, 3012, 1720, 1252, 750 cm^{-1}. HRMS calcd for $C_{28}H_{31}N_2O_6$: 507.2131. Found: 507.2131.

4.7.4. (2′*S*,3′*R*,4*R*,5*S*,6*R*)-3,4,5,6-Tetrahydro-3-[3-hydroxy-2-(4-methoxyphenoxy)-3-naphthalen-2-yl-propionyl]-4,5-dimethyl-6-phenyl-2*H*-1,3,4-oxadiazin-2-one 13d. Yellow oil purified by column chromatography on silica gel (30:70, hexanes:EtOAc, R_f=0.28, column dimensions=3×40 cm) to yield **13d** (63%) as an oil.

$[\alpha]_D^{25} = +2.2$ (*c* 1.92, methanol). ^{1}H NMR ($CDCl_3$): δ 0.74 (d, 3H, $J = 6.9$ Hz), 2.89 (s, 3H), 3.36–3.42 (m, 1H), 3.66 (s, 3H), 5.56 (d, 1H, $J = 2.6$ Hz), 6.00 (d, 1H, $J = 4.0$ Hz), 6.06 (d, 1H, $J = 2.6$ Hz), 6.64–6.71 (m, 4H), 7.28–8.02 (m, 12H). ^{13}C NMR ($CDCl_3$): 11.6, 42.6, 55.2, 56.1, 73.7, 77.5, 83.6, 114.1, 117.5, 124.2, 124.5, 125.2, 125.6, 125.8, 127.3, 127.7, 127.8, 128.0, 128.4, 132.7, 132.8, 134.9, 137.5, 148.7, 151.5, 154.5, 169.7. IR (neat): 3452, 3013, 1720, 750 cm^{-1}. HRMS calcd for $C_{31}H_{31}N_2O_6$: 527.2182. Found: 527.2180.

4.7.5. (2′*S*,3′*R*,4*R*,5*S*,6*R*)-3,4,5,6-Tetrahydro-3-[3-hydroxy-2-(4-methoxyphenoxy)-3-*m*-tolylpropionyl]-4,5-dimethyl-6-phenyl-2*H*-1,3,4-oxadiazin-2-one 13e

Yellow oil purified by column chromatography on silica gel (30:70, hexanes:EtOAc, $R_f = 0.22$, column dimensions = 3×40 cm) to yield **13e** (76%) as an oil. $[\alpha]_D^{25} = -10.4$ (*c* 2.71, methanol). ^{1}H NMR ($CDCl_3$): δ 0.74 (d, 3H, $J = 6.9$ Hz), 2.37 (s, 3H), 2.89 (s,3H), 3.36–3.43 (m, 1H), 3.69 (s, 3H), 5.34 (d, 1H, $J = 2.6$ Hz), 5.96 (d, 1H, $J = 2.9$ Hz), 6.02 (d, 1H, $J = 4.0$ Hz), 6.70 (s, 4H), 7.10–7.43 (m, 9H). ^{13}C NMR ($CDCl_3$): 11.6, 21.2, 42.6, 55.2, 56.2, 73.7, 77.6, 83.6, 114.1, 117.5, 123.2, 124.5, 126.8, 127.8, 128.0, 128.2, 128.4, 134.9, 137.4, 139.6, 148.5, 151.5, 154.5, 169.8. IR (neat): 3458, 3008, 1720, 754 cm^{-1}. HRMS calcd for $C_{28}H_{31}N_2O_6$: 491.2182. Found: 491.2184.

4.8. General procedure for the preparation of 14a–e

In a nitrogen-purged, flame-dried, 100 mL, round bottomed flask was placed **6** (0.75 g, 2.70 mmol), freshly distilled tetrahydrofuran (8.60 mL), and titanium tetrachloride (0.33 mL, 3.00 mmol). The solution was stirred for 25 min, and was then cooled to −78°C for 15 min. Triethylamine (0.79 mL, 5.70 mmol) was then added, and the reaction was brought to 0°C over a period of 1 h. The reaction mixture was again cooled to −78°C, and the appropriate aldehyde (5.70 mmol) was then added. The reaction stirred for 4 h and was quenched by the addition of a saturated solution of ammonium chloride (50 mL). The resulting mixture was then extracted with EtOAc (3×50 mL), washed with a saturated solution of brine, dried over $MgSO_4$, and the solvent was removed via rotary evaporation.

4.8.1. (2′*S*,3′*R*,4*R*,5*S*,6*R*)-3,4,5,6-Tetrahydro-3-(3-hydroxy-2-methoxy-3-phenylpropionyl)-4,5-dimethyl-6-phenyl-2*H*-1,3,4-oxadiazin-2-one 14a

Yellow oil purified by column chromatography on silica gel (20:80, hexanes:EtOAc, $R_f = 0.20$, column dimensions = 3×40 cm) to yield **14a** (97%) as a white powder. A second purification was carried out: white powder recrystallized from CH_2Cl_2 to yield **14a** (34%). Crude product contained 6.5% ephedrine heterocycle **1**. Mp: 148–149°C. $[\alpha]_D^{25} = -60.8$ (*c* 1.98, methanol). ^{1}H NMR ($CDCl_3$): δ 0.87 (d, 3H, $J = 6.9$ Hz), 2.91 (s, 3H), 3.31 (s, 3H), 3.40–3.46 (m, 1H), 5.17 (d, 1H, $J = 2.6$ Hz), 5.22 (d, 1H, $J = 2.2$ Hz), 6.04 (d, 1H, $J = 4.4$ Hz), 7.29–7.54 (m, 10H). ^{13}C NMR ($CDCl_3$): 11.8, 42.7, 56.1, 58.4, 73.4, 77.4, 84.9, 124.5, 126.0, 127.2, 127.8, 127.9, 128.4, 135.0, 140.3, 148.5, 170.7. IR (CCl_4): 3450, 1728, 1720, 1258, 1134, 786, 762 cm^{-1}. HRMS calcd for $C_{21}H_{24}N_2O_5$: 385.1763. Found: 385.1762.

4.8.2. (2′*S*,3′*R*,4*R*,5*S*,6*R*)-3-[3-(4-Chlorophenyl)-3-hydroxy-2-methoxypropionyl]-3,4,5,6-tetrahydro-4,5-dimethyl-6-phenyl-2*H*-1,3,4-oxadiazin-2-one 14b

Yellow oil purified by column chromatography on silica gel (20:80, EtOAc:hexanes $R_f = 0.22$, column dimensions = 3×40 cm) to yield **14b** (92%) as an oil. Crude product contained 13.2% ephedrine heterocycle **1**, and the purified product contained 13.2% ephedrine heterocycle. The contaminant could not be separated by column chromatography or HPLC. $[\alpha]_D^{25} = -44.1$ (*c* 2.45, methanol). ^{1}H NMR ($CDCl_3$): δ 0.88 (d, 3H, $J = 6.9$ Hz), 3.00 (s, 3H), 3.29 (s, 3H), 3.43–3.49 (m, 1H), 5.11 (d, 1H, $J = 2.2$ Hz), 5.17 (s, 1H), 6.07 (d, 1H, $J = 4.0$ Hz), 7.29–7.49 (m, 9H). ^{13}C NMR ($CDCl_3$): 11.7, 42.6, 55.9, 58.3, 72.5, 77.4, 84.7, 124.4, 127.3, 127.7, 127.9, 128.3, 132.6, 134.8, 139.2, 148.5, 170.3. IR (neat): 3450, 2994, 1720, 750, 700 cm^{-1}. HRMS calcd for $C_{21}H_{24}N_2O_5Cl$: 419.1374. Found: 419.1375.

4.8.3. (2′*S*,3′*R*,4*R*,5*S*,6*R*)-3,4,5,6-Tetrahydro-3-[3-hydroxy-2-methoxy-3-(4-methoxyphenyl)propionyl]-4,5-dimethyl-6-phenyl-2*H*-1,3,4-oxadiazin-2-one 14c

Yellow oil purified by column chromatography on silica gel (20:80, hexanes:EtOAc, $R_f = 0.18$, column dimensions = 3×40 cm) to yield **14c** (46%) as an oil. Crude product contained 18% ephedrine heterocycle **1**, and the purified product contained 29.2% ephedrine heterocycle. The contaminant could not be efficiently separated by column chromatography or HPLC. $[\alpha]_D^{25} = -41.8$ (*c* 2.33, methanol). ^{1}H NMR ($CDCl_3$): δ 0.87 (d, 3H, $J = 6.9$ Hz), 2.88 (s, 3H), 3.34 (s, 3H), 3.40–3.46 (m, 1H), 3.81 (s, 3H), 5.10 (d, 1H, $J = 2.6$ Hz), 5.20 (d, 1H, $J = 2.6$ Hz), 6.02 (d, 1H, $J = 4.0$ Hz), 6.90 (d, 4H, $J = 8.8$ Hz), 7.29–7.45 (m, 5H). ^{13}C NMR ($CDCl_3$): 11.9, 42.8, 55.0, 56.3, 58.5, 73.3, 77.6, 85.1, 113.3, 124.6, 127.4, 128.1, 128.5, 132.4, 135.1, 148.6, 158.8, 171.0. IR (neat): 3310, 2938, 1720, 751, 700 cm^{-1}. HRMS calcd for $C_{22}H_{27}N_2O_6$: 415.1869. Found: 415.1867.

4.8.4. (2′*S*,3′*R*,4*R*,5*S*,6*R*)-3,4,5,6-Tetrahydro-3-(3-hydroxy-2-methoxy-3-naphthalen-2-yl-propionyl)-4,5-dimethyl-6-phenyl-2*H*-1,3,4-oxadiazin-2-one 14d

Yellow oil purified by column chromatography on silica gel (20:80 hexanes:EtOAc, $R_f = 0.22$, column dimensions = 3×40 cm) to yield **14d** (99%) as a yellow powder. This material was recrystallized from EtOAc to afford **14d** (31%). Mp: 150–152°C. Crude product contained 11.8% ephedrine heterocycle, and the purified product contained 15.9% ephedrine heterocycle. The contaminant could not be efficiently separated by column chromatography or HPLC. $[\alpha]_D^{25} = -56.9$ (*c* 1.77, methanol). ^{1}H NMR ($CDCl_3$): δ 0.88 (d, 3H, $J = 6.6$ Hz), 2.91 (s, 3H), 3.29 (s, 3H), 3.41–3.47 (m, 1H), 5.31 (d, 1H, $J = 2.6$ Hz), 5.36 (s, 1H), 6.02 (d, 1H, $J = 4.0$ Hz), 7.27–7.96 (m, 12H). ^{13}C NMR ($CDCl_3$): 11.7, 42.6, 56.0, 58.5, 73.4, 77.4, 85.0, 124.0, 124.5,

124.8, 125.4, 125.6, 127.2, 127.5, 127.7, 127.9, 128.3, 132.5, 132.7, 134.9, 138.0, 148.6, 170.7. IR (CCl_4): 3450, 1720, 754, 700 cm^{-1}. HRMS calcd for $C_{25}H_{27}N_2O_5$: 435.1920. Found: 435.1921.

4.8.5. (2′*S*,3′*R*,4*R*,5*S*,6*R*)-3,4,5,6-Tetrahydro-3-(3-hydroxy-2-methoxy-3-*m*-tolylpropionyl)-4,5-dimethyl-6-phenyl-2*H*-1,3,4-oxadiazin-2-one 14e. Yellow oil purified by column chromatography on silica gel (30:70, hexanes:EtOAc, $R_f = 0.21$, column dimensions = 3×40 cm) to yield **14e** (64%) as an oil. Crude product contained 7.0% ephedrine heterocycle, and the purified product contained 8.6% ephedrine heterocycle. The contaminant could not be efficiently separated by column chromatography or HPLC. $[\alpha]_D^{25} = -28.6$ (*c* 2.28, methanol). ^1H NMR ($CDCl_3$): δ 0.87 (d, 3H, $J = 6.9$ Hz), 2.37 (s, 3H), 2.90 (s, 3H), 3.32 (s, 3H), 3.41–3.47 (m, 1H), 5.13 (d, 1H, $J = 2.6$ Hz), 5.23 (d, 1H, $J = 2.6$ Hz), 6.03 (d, 1H, $J = 4.0$ Hz), 7.10–7.44 (m, 10H). ^{13}C NMR ($CDCl_3$): 11.8, 21.2, 42.7, 56.2, 58.4, 73.5, 77.5, 84.9, 123.1, 124.5, 125.0, 126.7, 127.8, 128.0, 128.4, 135.0, 137.3, 140.2, 148.5, 170.8. IR (neat): 3466, 2938, 1728, 1720, 1260, 1132, 750, 700 cm^{-1}. HRMS calcd for $C_{22}H_{27}N_2O_5$: 399.1920. Found: 399.1921.

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9. Oxadiazinone **1** is prepared on multigram scale (10–75 g) in a three-step reaction sequence of *N*-nitrosation, reduction, and cyclization. There is no need for chromatography as the products are all crystalline. See Ref. 4b.
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12. Successful reaction of oxadiazinone **6** required that the enolate was formed over a period of 1 h rather than 15 min. The temperature was allowed to warm from −78 to 0°C. This process was optimal for complete enolate formation. This is believed to be the source of the lower diastereoselectivities, i.e. formation of (*Z*)- and (*E*)-configured enolates.
13. Attempts to remove the auxiliary using lithium hydroperoxide were not successful, possibly due to competitive side reactions.

14. Acid hydrolysis (6*M* H_2SO_4, THF) of adduct **8a** under reflux conditions afforded β-hydroxy acid **9a** (74%) yield, but the heterocycle was also hydrolyzed to the corresponding β-hydroxyhydrazine. See: Vicario, J. L.; Baida, D.; Dominguez, E.; Rodriguez, M.; Carrillo, L. *J. Org. Chem.* **2000**, *65*, 3754–3760.
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