Synthesis and X-ray Crystal Structures of Chiral, Nonracemic 5,6-Dihydro-4*H*-1,3,4-oxadiazines

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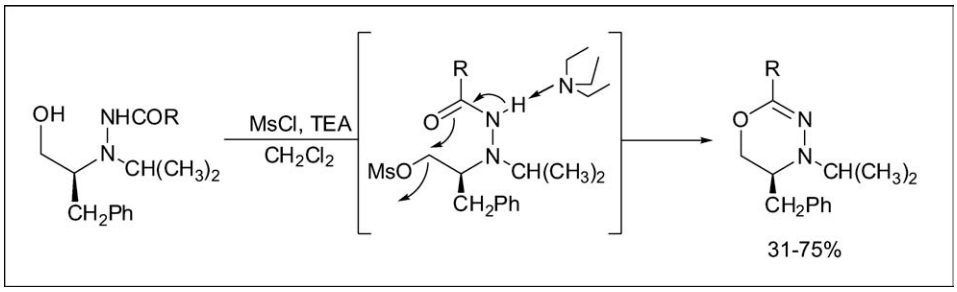

A series of chiral, nonracemic oxadiazines have been prepared from (1*R*,2*S*)-ephedrine, (1*R*,2*S*)-norephedrine, and L-phenylalaninol. The synthesis of the *Ephedra*-based oxadiazines was accomplished by a process of *N*-nitrosation, reduction, acylation, and acid-catalyzed cyclization. The *trans*- and *cis*-diastereomeric oxadiazines derived from (1*R*,2*S*)-ephedrine were analyzed by ^{1}H NMR spectroscopy and by single crystal X-ray crystallographic analysis. The stereochemistry of the (1*R*,2*S*)-norephedrine–derived oxadiazines was assigned based on ^{1}H NMR spectroscopy and by analogy with the X-ray crystal structure of the (1*R*,2*S*)-ephedrine–based oxadiazines. In addition, L-phenylalaninol was used as a template to prepare a series of oxadiazines substituted at the N_4-nitrogen with an isopropyl group. This was accomplished by a reductive alkylation of L-phenylalaninol with acetone and subsequent hydrazide formation. These hydrazides were reacted with methanesulfonyl chloride to yield the corresponding oxadiazines by a base-mediated cyclization.

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INTRODUCTION

Many heterocyclic systems such as oxazolidinones [1] and oxazolines [2] have been well-developed in terms of their synthetic [3,4] and medicinal applications [5,6]. In contrast, the heterocycles known as 5,6-dihydro-4*H*-1,3,4-oxadiazines (oxadiazines, **1**) have not been the subject of much interest (Fig. 1). The first report concerning this ring system was described by Ishidate *et al.* and the oxadiazine that was formed only considered to be a contaminant [7]. Research that was directly focused on oxadiazines, as synthetic targets of medicinal worth was launched by the Pitman-Moore division of Dow chemical in the early 1960s [8a]. Consequently, chiral, nonracemic oxadiazines derived from *Ephedra* alkaloids were first prepared by Dow chemists Trepanier *et al.* [8a–f]. The synthetic pathway that was developed involved the preparation of β-hydrazido-alcohols, which were converted into their corresponding oxadiazines by acid-catalyzed cyclization (Scheme 1) [8a–f]. Specifically, ephedrine was converted to *N*-aminoephedrine by *N*-nitrosation and $LiAlH_4$ reduction. The resultant β-hydrazido-alcohol was treated with two equivalents of benzoyl chloride to generate the bis(benzoylated) derivative **4**. Hydrolysis of the ester yielded the required β-hydrazido-alcohol **5**. Trepanier *et al.* used this sequence of steps because of the competitive nucleophilicity between the hydrazine and alcohol. The β-hydrazido-alcohol **5** was then treated with acid [8a–e] to induce cyclization to afford a diasteroemeric mixture of oxadiazines **6** and **7**. The dominant oxadiazine was dependent on the acid that was used. Oxadiazine **6** was the dominant diastereomer [8a–c] when sulfuric acid was used, and oxadiazine **7** was dominant when an acetic acid/HBr mixture was used [8d]. On the basis of seminal efforts of Trepanier *et al.* [8] and the later research efforts of others [9–11] who have investigated the preparation of oxadiazines, we became interested in the synthesis of these compounds as potential tools for conducting asymmetric syntheses via intramolecular chiral relay [12–14,15a].

RESULTS AND DISCUSSION

The first course of action that was taken involved the preparation of the (1*R*,2*S*)-ephedrine–derived oxadiazines **6** and **7** for the sake of evaluating the literature

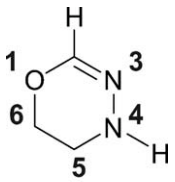

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Figure 1. 5,6-Dihydro-4*H*-1,3,4-oxadiazine.

method for preparing these compounds. The (1*R*,2*S*)-ephedrine hydrazine was prepared in the same manner as in Trepanier's work using an experimental procedure (*N*-nitrosation/reduction) developed in the our laboratories (Scheme 2) [15]. In contrast to the earlier work involving the use of excess benzoyl chloride (Scheme 1), the hydrazine was treated with one equivalent of benzoic anhydride via dropwise addition at 0°C to afford the corresponding hydrazide **5** in 66% yield without the need for the bis(acylation).

The H_2SO_4-catalyzed cyclization of **5** gave a 7:1 ratio of the *trans*-oxadiazine **6** to the *cis*-oxadiazine **7**. This mixture of diastereomers, which presumably arose from stereochemical inversion/retention at the benzylic position, was purified by multiple recrystallizations to afford the diastereomerically enriched **6** in 22%. The low yield was attributed to the competitive process of hydrolysis of the hydrazide to hydrazine **3**. Despite numerous attempts, we were not able to reproduce the yields for this compound that Trepanier *et al*. obtained in his early work perhaps due to the purification [8a].

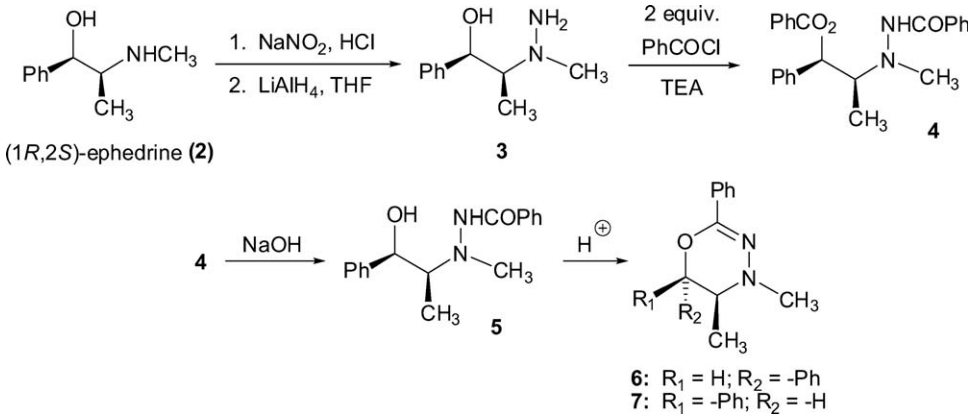
Nonetheless, we were also interested in conducting the hydrobromic acid/propanoic acid cyclization pathway. Under these conditions, treatment of **5** afforded a 6:1 diastereomeric mixture of oxadiazines favoring the *cis*-isomer **7**. Purification by flash chromatography yielded the diastereomerically enriched **7** in 36% isolated yield.

Base-induced cyclization was of interest as there was the possibility that such a pathway might afford improved diastereoselectivities in the oxadiazine products. Trepanier had demonstrated that the base-mediated cyclization (Scheme 1) was limited due to the failure of the intramolecular nucleophilic substitution. The cyclization pathway was investigated through a different synthetic route involving the generation of the mesylate of hydrazide **5**. To pursue this idea, **5** was reacted with methanesulfonyl chloride in the presence of excess triethylamine (TEA) to generate benzylic mesylate intermediate **10**, which presumably underwent further cyclization to **6** (Scheme 2). This process yielded oxadiazine **6** in only 9% yield after flash chromatography from a complex mixture, suggesting that the base-mediated cyclization for the *Ephedra* series was not viable.

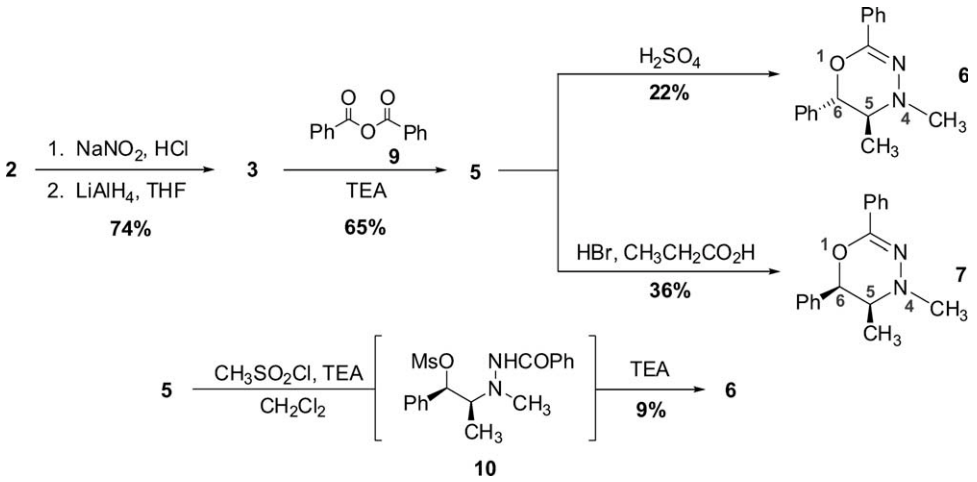
Trepanier originally assigned the configurations of the *trans*- and *cis*-oxadiazines based on the observed coupling constants for the C_5 and C_6 methine protons (Scheme 2). The $J_{H5–H6}$ coupling constant of the proposed *trans*-isomer **6** was calculated to be 7.4 Hz, whereas the $J_{H5–H6}$ coupling constant of the *cis*-isomer was determined to be 2.9 Hz. The calculated coupling constants were in agreement with the expected values based on the Karplus relation [16], but we were still interested in determining the relative and absolute stereochemistry of these compounds beyond the ^{1}H NMR analysis. Thus, the stereochemical structures of **6** and **7** were unambiguously determined by single crystal X-ray crystallography (Figs. 2 and 3) [17].

The oxadiazines **6** and **7** were determined to have relatively planar structures as compared with the twist boat conformations that the related oxadiazinanones possess [18]. In addition to this observation, it was determined that there was a difference in terms of conformational

Scheme 1. Trepanier's synthesis of oxadiazines **6** and **7**.



Scheme 2. Synthesis of oxadiazines **6** and **7**.



behavior of the N_4-nitrogen with regard to the *cis*-oxadiazine **7** as compared with the related oxadiazinanones. Oxadiazine **7** possesses an equatorial N_4-methyl group, whereas the corresponding oxadiazinanone possesses an axial N_4-methyl group.

Once the stereochemistry of the oxadiazines was unambiguously determined, the synthesis of related oxadiazines derived from (1*R*,2*S*)-norephedrine was pursued (Scheme 3). The (1*R*,2*S*)-ephedrine hydrazine **3** was treated with either 1-naphthoyl chloride or propanoic anhydride to afford the corresponding hydrazides **12** (68%) and **13** (71%), respectively. Hydrazide **12** was reacted with either H_2SO_4 or HBr in propanoic acid to afford *trans*-oxadiazine **15** (28%) and *cis*-oxadiazine **16** (21%), respectively. The relative stereochemistry for the oxadiazines **15** and **16** were assigned based on the coupling constants [$J_{H5–H6}$(*trans*) = 7.4 Hz and $J_{H5–H6}$(*cis*) = 3.0 Hz] and correlation with the collected X-ray crystallographic data for **6** and **7**. Interestingly, cyclization of the propanoyl hydrazide **13** with sulfuric acid gave *trans*-oxadiazine **17** in 64% after flash chromatography. With regard to the higher yield of oxadiazine **17**, it is proposed that the 1-naphthoyl group of hydrazide **12** undergoes acid-catalyzed hydrolysis at a rate that is competitive with the cyclization; whereas the propanoyl group of hydrazide **13** does not.

The modifications that were made to prepare oxadiazines **15–17** varied the C_2-position. The N_4-position was also of interest as this position has been proposed to be the primary means of asymmetric induction in the related oxadiazinanone family of chiral auxiliaries [19]. To examine the impact of altering the N_4-position of the oxadiazine core, hydrazine **11** [19] was benzoylated by reaction with benzoic anhydride to yield hydrazide **14** in 31% after chromatography. The lower yield for the acylation process was attributed to the competitive nucleophilicity between the amino group of the hydrazine and the β-hydroxy group due to the presence of the *N*-

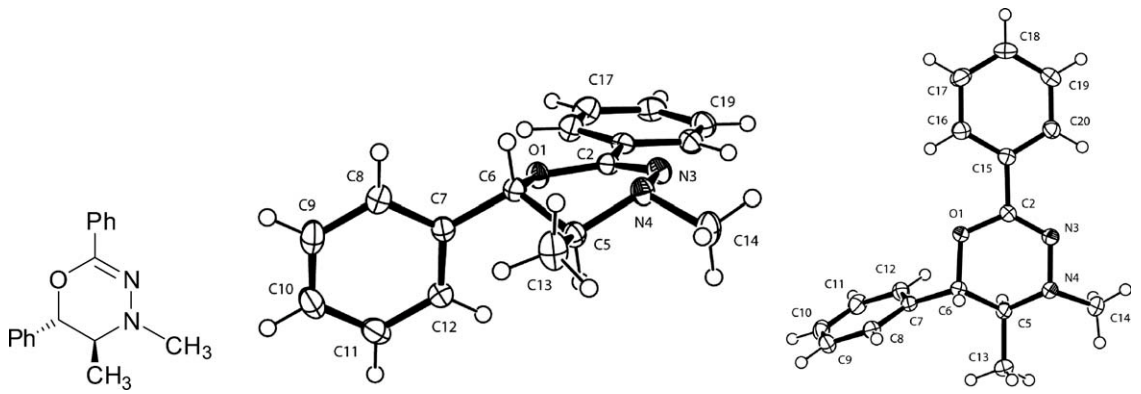


Figure 2. ORTEP-3 diagram of **6** with 50% probability ellipsoids shown. Hydrogen atoms are drawn arbitrarily small for clarity. ORTEP of *trans*-oxadiazine **6**.

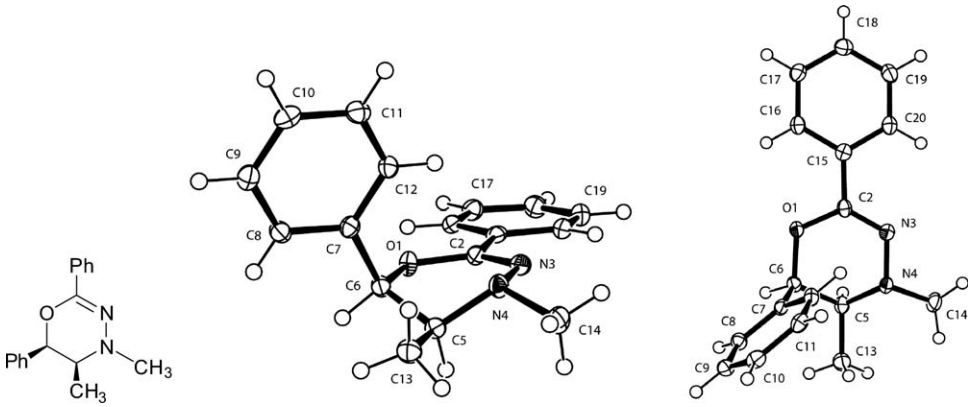


Figure 3. ORTEP-3 diagram of **7** with 50% probability ellipsoids shown. Hydrogen atoms are drawn arbitrarily small for clarity.

isopropyl group. The hydrazide **14** was cyclized with H_2SO_4 to yield the *trans*-oxadiazine **18** in 40% yield.

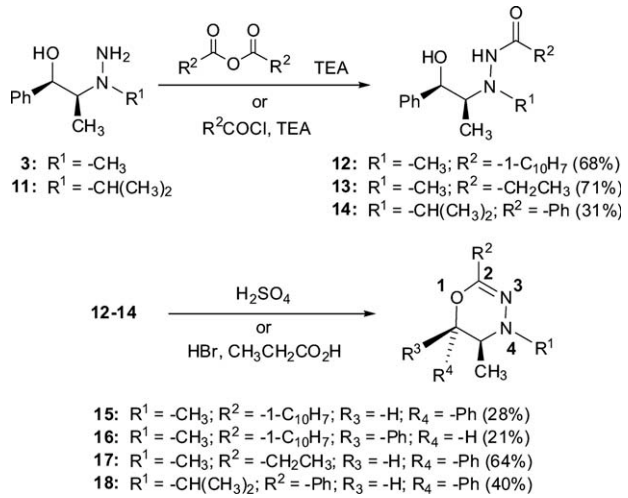
We became interested in determining if it would be possible to prepare chiral oxadiazines from a variety of α-amino acids. We had previously prepared hydrazine **19** from L-phenylalaninol [20] and sought to use this material to prepare a series of oxadiazines (Scheme 4). Thus, hydrazine **19** was acylated at nitrogen using either propanoyl chloride, benzoyl chloride, or 1-naphthoyl chloride to afford the corresponding hydrazides **20a–c**, respectively. The use of acyl chlorides proved to be as effective as the use of anhydrides when the reactions were conducted in 0.1*M* solutions of dichloromethane. The hydrazide **20c** was not directly isolated due to difficulties associated with the crystallinity of the hydrazide and the byproduct naphthoic acid.

The use of an acid-catalyzed process to induce the cyclization of these hydrazides was not pursued as these systems contained primary alcohols that might be susceptible to degradation. Ultimately, a base-mediated process for the cyclization of compounds **20a–c** was used. Thus, the hydrazides were treated with methanesulfonyl chloride and an excess of TEA to afford the desired oxadiazines **22a–c** through putative intermediates **21a–c**. The isolated yields for the oxadiazines were significantly better than the acid-catalyzed pathway perhaps due to the circumvention of the hydrolysis of the hydrazide.

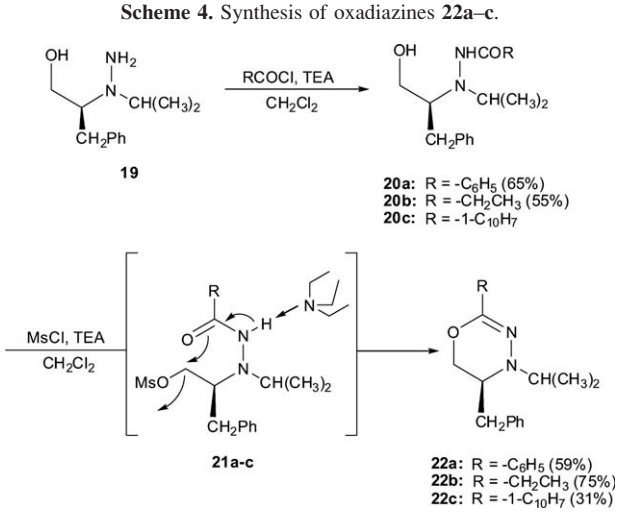
CONCLUSIONS

We have synthesized a series of *Ephedra*-based oxadiazines using a modified method based on the earlier works of Trepanier *et al*. The stereochemistry of the *Ephedra*-based oxadiazines were evaluated by ^{1}H NMR spectroscopy and by X-ray crystallography. The preparation of the oxadiazines from L-phenylaninol was accomplished using a hydrazide pathway with formation on a labile mesylate intermediate.

Scheme 3. Synthesis of oxadiazines **15–18**.



Scheme 4. Synthesis of oxadiazines **22a–c**.



EXPERIMENTAL

General remarks. Methylene chloride (CH_2Cl_2) was purchased as an anhydrous reagent. Unless otherwise stated, all reactions were run under anhydrous conditions and a nitrogen atmosphere. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ operating at 400 and 100 MHz, respectively, or at 300 and 75 MHz as specified. 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. Mass spectral analyses were conducted using a quadrupole time of flight mass spectrometer hybrid with MS/MS capability. Optical activities were measured at 589 nm using a digital polarimeter purchased with NSF grant.

(5*S*,6*R*)-*N*′-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*′-methyl) benzoic acid hydrazide (5). To a flame dried, nitrogen purged round bottom, the (1*R*,2*S*)-ephedrine–derived hydrazine **4** (2.50 g, 13.9 mmol), dichloromethane (70 mL), and TEA (2.13 mL, 15.3 mmol) was added. The reaction mixture was then cooled to 0°C. The reaction stirred for 5 min and benzoic anhydride (3.30 g, 14.6 mmol) was added by means of a dropping funnel. After 24 h, the reaction was quenched by the addition of a saturated aqueous solution of ammonium chloride (100 mL) and diluted with $CHCl_3$ (100 mL). The organic layer was washed with brine (100 mL) and then dried ($MgSO_4$). The solvent was removed via rotary evaporation to afford the title compound: white solid (66%), Mp = 163–165°C, $[\alpha]_D^{24} = -61.9$ (*c* 0.59, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.94 (d, *J* = 6.6 Hz, 3H), 2.83 (s, 3H), 2.99 (qd, *J* = 6.6, 2.2 Hz, 1H), 5.16 (d, *J* = 2.2 Hz, 1H), 7.20–7.52 (m, 8H), 7.76 (d, *J* = 7.4 Hz, 2H), 8.01 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 9.9, 42.3, 65.8, 71.5, 125.6, 126.3, 127.2, 127.7, 128.3, 131.3, 133.4, 142.7, and 165.7 ppm. IR (nujol mull): 3205 and 1641 cm^{-1}. ESI-HRMS calcd. for $C_{17}H_{21}N_2O_2$ ($M + H^+$): 285.1603. Found: 285.1604.

***trans*-(5*S*,6*S*)-4,5-Dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (6).** Hydrazide **5** (1.00 g, 3.40 mmol) and concentrated sulfuric acid (18*M*, 10 mL) were combined and stirred at room temperature. After 2 h, the solution was diluted with water (100 mL) and treated with a saturated solution of sodium bicarbonate until the solution was neutralized as determined by the use of pH paper. The organic layer was extracted with EtOAc (100 mL), treated with $NaHCO_3$ (50 mL), and washed with brine (50 mL). The organic layer was dried ($MgSO_4$), and the solvent was removed by rotary evaporation to afford the title compound as a 7:1 mixture of the *trans*- and *cis*-isomers of the oxadiazine. The title compound was recrystallized thrice with hexanes and ethyl acetate to afford the isomerically pure *trans*-isomer as a white solid (22%). Mp = 139–141°C, $[\alpha]_D^{24} = +160.8$ (*c* 0.91, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.06 (d, *J* = 6.6 Hz, 3H), 2.69 (dq, *J* = 7.4, 6.6 Hz, 1H), 2.88 (s, 3H), 5.05 (d, *J* = 7.4 Hz, 1H), 7.30–7.40 (m, 8H), 7.82–7.85 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 43.6, 57.5, 82.3, 125.3, 127.4, 128.0, 128.5, 128.6, 128.9, 132.5, 138.1, and 146.0 ppm. IR (nujol mull): 1622 and 1448 cm^{-1}. ESI-HRMS calcd. for $C_{17}H_{19}N_2O$ $(M + H)^+$: 267.1497. Found: 267.1487.

***cis*-(5*S*,6*R*)-4,5-Dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (7).** Hydrazide **5** (1.00 g, 3.40 mmol) and HBr in propanoic acid (15 mL, 30% by weight) were combined in 100 mL flask and stirred for 24 h. The solution was diluted with H_2O (100 mL) and neutralized with $NaHCO_3$. The organic layer was diluted with EtOAc (100 mL), washed with brine (50 mL), and dried with $MgSO_4$. Solvents were removed via rotary evaporator. The title product was isolated by flash column chromatography (hexanes:EtOAc, 98:2). White solid (36%), Mp = 94–97°C. $[\alpha]_D^{24} = -176.2$ (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 0.81 (d, *J* = 6.5 Hz, 3H), 2.88 (s, 3H), 3.35 (dq, *J* = 6.5, 2.9 Hz, 1H), 5.52 (d, *J* = 2.9 Hz, 1H), 7.24–7.91 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 7.9, 42.9, 54.8, 79.1, 125.2, 126.2, 127.9, 128.0, 128.3, 128.8, 132.5, 138.2, and 144.3. IR (diamond): 1621, 1003, 772, and 647 cm^{-1}. ESI-HRMS calcd. for $C_{17}H_{19}N_2O$ ($M + H^+$): 267.1497. Found: 267.1496.

***N*′-[(1*R*,2*S*)-1-Hydroxy-1-phenyl-2-propyl]-*N*′-methyl naphthoic hydrazide (12).** In a 250-mL nitrogen purged round-bottom flask was placed hydrazine **3** (3.00 g, 16.6 mmol), dichloromethane (208 mL), TEA (4.60 mL, 33.3 mmol), and 1-naphthoyl chloride (2.50 mL, 16.6 mmol). After 24 h, the reaction was diluted by the addition of CH_2Cl_2 (100 mL) and NH_4Cl (100 mL). The organic layer was washed with brine (100 mL) and then dried with $MgSO_4$. The solvents were removed via rotary evaporation. The title product was isolated by flash column chromatography (hexanes:EtOAc, 60:40). Yellow solid (68%), Mp = 75–77°C. $[\alpha]_D^{25} = -23.5$ (*c* 1.01, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.91 (d, *J* = 6.1 Hz, 3H), 2.79 (s, 3H), 2.89 (dq, *J* = 6.1, 3.7, 1H), 4.33 (s, 1H), 5.13 (s, 1H), 7.20–7.63 (m, 8H), 7.80–7.86 (m, 3H), 8.19–8.22 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 10.2, 43.5, 66.7, 72.4, 124.5, 125.1, 125.2, 125.7, 126.5, 126.8, 127.3, 128.0, 128.1, 128.2, 130.3, 130.9, 132.3, 133.5, and 168.5. IR (nujol): 3291, 1658, 1511, 735, and 701 cm^{-1}. ESI-HRMS calcd. for $C_{21}H_{23}N_2O_2$ ($M + H^+$): 335.1760. Found: 335.1761.

***N*′-[(1*R*,2*S*)-1-Hydroxy-1-phenyl-2-propyl]-*N*′-methyl propanoic hydrazide (13).** In a 250-mL nitrogen purged round-bottom flask was placed hydrazine **3** (2.00 g, 11.1 mmol), dichloromethane (35 mL), and TEA (1.70 mL, 12.2 mmol). The solution was cooled to 0°C and propanoic acid anhydride (1.50 mL, 11.7 mmol) dissolved in dichloromethane (20 mL) was added slowly via a dropping funnel. After 24 h, the reaction was diluted by the addition of CH_2Cl_2 (100 mL) and NH_4Cl (100 mL). The organic layer was washed with brine (100 mL) and then dried with $MgSO_4$. The solvents were removed via rotary evaporation. The title compound was isolated as a 7:1 mixture of diasteromers after recrystallization with hexanes:EtOAc and only the major rotomeric diasteromers have been characterized. White solid (71%), Mp = 81–83°C. $[\alpha]_D^{24} = -32.3$ (*c* .04, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.85 (d, *J* = 6.6 Hz, 3H), 1.15 (t, *J* = 7.6 Hz, 3H), 2.17 (q, *J* = 7.6 Hz, 2H), 2.69 (s, 3H), 2.86 (dq, *J* = 6.6, 2.3 Hz, 1H), 5.01 (d, *J* = 2.3 Hz, 1H), 7.20–7.54 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 10.1, 27.8, 43.2, 66.5, 72.2, 125.7, 126.7, 128.0, 141.4, 173.5, and 178.4 ppm. IR (diamond): 3256, 1655, and 1451 cm^{-1}. ESI-HRMS calcd. for $C_{13}H_{21}N_2O_2$ ($M + H^+$): 237.1603. Found: 237.1598.

***N*′-[(1*R*,2*S*)-1-Hydroxy-1-phenyl-2-propyl]-*N*′-isopropyl benzoic hydrazide (14).** In a 250-mL nitrogen purged round-bottom flask was placed hydrazine **11** (2.00 g, 9.60 mmol), dichloromethane (30 mL), and TEA (1.50 mL, 10.6 mmol). The solution was cooled to 0°C and benzoic anhydride (2.28 g, 10.1 mmol) dissolved in dichloromethane (18 mL) was slowly added via a dropping funnel. After 24 h, the reaction was diluted by the addition of CH_2Cl_2 (100 mL) and NH_4Cl (100 mL). The

title compound was isolated by recrystallization (EtOAc:hexanes). White solid (31%), Mp = 119–120°C. $[\alpha]_D^{24} = -58.6$ (*c* 0.58, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.86 (d, *J* = 6.6 Hz, 3H), 1.14 (d, *J* = 6.6 Hz, 3H), 1.20 (d, *J* = 6.6 Hz, 3H), 3.09–3.11 (m, 1H), 3.43–3.50 (m, 1H), 5.00 (d, *J* = 2.0 Hz, 1H), 7.19–7.78 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.9, 17.0, 18.9, 52.3, 63.3, 73.2125.7, 127.7, 127.1, 128.0, 128.7, 131.9, 133.2, 141.3, and 168.9. IR (diamond): 3264, 1653, 748, and 680 cm^{-1}. ESI-HRMS calcd. for $C_{19}H_{25}N_2O_2$ ($M + H^+$): 313.1916. Found: 313.1913.

***trans*-(5*S*,6*S*)-4,5-Dimethyl-2-(1-naphthyl)-6-phenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (15).** Hydrazide **12** (0.50 g, 1.50 mmol) was combined with H_2SO_4 (5 mL, 12*M*) was stirred for 2 h. The solution was diluted with H_2O (100 mL) and neutralized with $NaHCO_3$. The organic layer was diluted with EtOAc (100 mL), washed with brine (50 mL), and dried ($MgSO_4$). The title compound was isolated by trituration with pentane. This process afforded the title compound as a ~7:1 mixture of the *trans*- and *cis*-isomers of the title oxadiazine. Yellow solid (28%), Mp = 140–142°C. $[\alpha]_D^{25} = +56.9$ (*c* 0.70, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.13 (d, *J* = 6.4 Hz, 3H), 2.88 (dq, *J* = 7.4, 6.4 Hz, 1H), 2.95 (s, 3H), 5.19 (d, *J* = 7.4 Hz, 1H), 7.36–7.85 (m, 8H), 7.81–7.84 (m, 3H), 8.79 (d, *J* = 8.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.4, 43.7, 57.4, 82.8, 124.9, 125.7, 126.1, 126.8, 127.5, 128.3, 128.6, 128.7, 129.7, 130.7, 133.9, 137.9, and 147.1. IR (nujol): 1614, 1020, 759, and 706 cm^{-1}. ESI-HRMS calcd. for $C_{21}H_{21}N_2O$ ($M + H^+$): 317.1654. Found: 317.1643.

***cis*-(5*S*,6*S*)-4,5-Dimethyl-2-(1-naphthyl)-6-phenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (16).** Hydrazide **13** (1.00 g, 3.40 mmol) and a 30% solution of HBr in propanoic acid (15 mL) were combined in a 100-mL round-bottom flask and this reaction mixture stirred. After 24 h, the reaction was diluted with H_2O (100 mL) and neutralized with $NaHCO_3$. The organic layer was diluted with EtOAc (100 mL), washed with brine (50 mL), dried with $MgSO_4$, and the solvents were removed via rotary evaporation. The title compound was isolated by flash chromatography (95:5, hexanes:EtOAc). Yellow solid (21%), Mp = 125–128°C. $[\alpha]_D^{23} = -86.4$ (*c* 0.53, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.94, (d, *J* = 6.6 Hz, 3H), 2.95 (s, 3H), 3.46 (dq, *J* = 6.6, 3.0 Hz, 1H), 5.65 (d, *J* = 3.0 Hz, 1H), 7.39–7.53 (m, 8H), 7.84–7.89 (m, 3H), 8.74 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 8.2, 43.0, 54.8, 79.6, 124.9, 125.7, 126.1, 126.3, 126.5, 126.8, 127.9, 128.3, 129.7, 130.0, 130.8, 133.9, 138.1, and 145.5. IR (nujol): 1613, 995, 746, and 709 cm^{-1}. ESI-HRMS calcd. for $C_{21}H_{21}N_2O$ ($M + H^+$): 317.1654. Found: 317.1642.

***trans*-(5*S*,6*S*)-2-Ethyl-4,4-dimethyl-6-phenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (17).** Hydrazide **13** (0.25 g, 1.06 mmol) and H_2SO_4 (3 mL, 12*M*) were combined in 100-mL round-bottom flask and stirred for 24 h. The solution was diluted with H_2O (100 mL) and neutralized with $NaHCO_3$. The organic layer was diluted with EtOAc (100 mL), washed with brine (50 mL), dried with $MgSO_4$, and the solvents were removed via rotary evaporation. The title product was isolated by flash column chromatography (hexanes:EtOAc, 9:1). Yellow oil (64%). $[\alpha]_D^{23} = +288.8$ (*c* 0.10, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90 (d, *J* = 6.3 Hz, 3H), 1.1 (t, *J* = 7.5 Hz, 3H), 2.17 (q, *J* = 7.5 Hz, 2H), 2.37–2.43 (m, 6.3 Hz, 1H), 2.63, (s, 3H), 4.79 (d, *J* = 7.8 Hz, 1H), 7.19–7.30 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 11.1, 14.3, 26.6, 43.5, 57.8, 82.3, 127.4, 128.5, 128.6, 138.0, and 151.9. IR (neat): 1656, 1066, 756, and 700 cm^{-1}. ESI-HRMS calcd. for $C_{13}H_{19}N_2O$ ($M + H^+$): 219.1497. Found: 219.1489.

(5*S*,6*S*)-4-Isopropyl-5-methyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (18). Hydrazide **14** (0.50 g, 1.60 mmol) was combined with H_2SO_4 (5 mL, 12*M*) and stirred for 2 h. The solution was diluted with H_2O (100 mL) and neutralized with $NaHCO_3$. The organic layer was diluted with EtOAc (100 mL), washed with brine (50 mL), dried with $MgSO_4$, and the solvents were removed via rotary evaporation. The title product was isolated by flash column chromatography (hexanes:-TEA, 97.5:2.5). White solid (40%), Mp = 160–162°C. $[\alpha]_D^{24} = +175.0$ (*c* 0.25, $CHCl_3$). IR (diamond): 1625, 1027, 756, and 686 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.00 (d, *J* = 6.2 Hz, 3H), 1.04 (d, *J* = 6.2 Hz, 3H), 1.40 (d, *J* = 6.6 Hz, 3H), 2.92 (dq, *J* = 12.9, 6.6 Hz, 1H), 3.52 (septet, *J* = 6.6 Hz, 1H), 5.04 (d, *J* = 6.6 Hz, 1H), 7.25–7.86 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.9, 15.6, 21.4, 50.2, 53.4, 82.4, 125.1, 127.6, 127.9, 128.5, 128.6, 133.2, 138.6, and 145.3. ESI-HRMS calcd. for $C_{19}H_{23}N_2O$ ($M + H^+$): 295.1810. Found: 295.1798.

General procedure for the formation of hydrazides 20a and 20b. Hydrazine **19** (0.700 g, 3.36 mmol) was combined with dichloromethane (17 mL) and TEA (0.515 g, 3.70 mmol) and this mixture was cooled to 0°C. The anhydride (0.798 g, 3.53 mmol) was then added. After 24 h, the reaction was diluted by the addition of a saturated solution of ammonium chloride (100 mL) and diluted with CH_2Cl_2 (100 mL). The organic layer was washed with brine (100 mL), dried ($MgSO_4$), and the solvent was removed by rotary evaporation.

***N′*-(1-Benzyl-2-hydroxyethyl)-*N′*-isopropyl benzoic acid hydrazide (20a)** The use of benzoic acid afforded the title compound as a yellow solid (55%) contaminated with <5% of benzoic acid: Mp = 126–128°C, $[\alpha]_D^{22} = +27.4$ (*c* 1.24, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.16 (d, *J* = 6.6 Hz, 3H) 1.22 (d, *J* = 6.6 Hz, 3H), 2.53 (m, 1H), 2.91 (d, *J* = 13.3, 3.9 Hz, 1H), 3.23–3.33 (m, 1H), 3.44–3.50 (m, 1H), 7.05 (s, 1H), 7.13–7.74 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.6, 32.4, 53.5, 61.3, 63.3, 126.3, 127.1, 128.6, 128.6, 128.9, 131.7, 138.5, and 168.9 ppm. IR (nujol mull): 3203 and 1648 cm^{-1}. ESI-HRMS calcd. for $C_{19}H_{25}N_2O_2$ ($M + H^+$): 313.1916. Found: 313.1909.

***N′*-(1-Benzyl-2-hydroxyethyl)-*N′*-isopropyl propanoic acid hydrazide (20b)** The use of propanoic anhydride afforded a white solid (65%). Mp = 118–120°C, $[\alpha]_D^{24} = -7.28$ (*c* 0.82, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.08 (d, *J* = 6.3 Hz, 3H), 1.14 (d, *J* = 6.3 Hz, 3H), 1.21 (t, *J* = 7.4 Hz, 3H), 2.20 (q, *J* = 7.4 Hz, 2H), 2.38–2.50 (m, 1H), 2.83 (d, *J* = 13.2, 4.1 Hz, 1H), 3.11–3.23 (m, 2H), 3.33–3.45 (m, 2H), 4.52 (broad singlet, 1H) 6.26 (s), 7.12–7.32 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.1, 20.5, 27.3, 31.7, 52.7, 61.1, 62.8, 126.1, 128.4, 128.7, 138.5, and 175.5 ppm. IR (nujol mull): 3225 and 1666 cm^{-1}. ESI-HRMS calcd. for $C_{15}H_{25}N_2O_2$ ($M + H^+$): 265.1916. Found: 265.1921.

***N′*-(1-Benzyl-2-hydroxyethyl)-*N′*-isopropyl 1-naphthoic acid hydrazide (20c)** Hydrazine **19** (1.00 g, 4.80 mmol) was combined with dichloromethane (24 mL) and TEA (0.736 mL, 5.28 mmol) and the solution was cooled to 0°C. The reaction was stirred for 5 min and 1-naphthoyl chloride (0.76 mL, 5.0 mmol) was added by syringe. After 24 h, the reaction was quenched by the addition of a saturated solution of ammonium chloride (100 mL) and diluted with CH_2Cl_2 (100 mL). The aqueous layer was drawn off and the organic layer was washed with brine (100 mL), dried ($MgSO_4$), and the solvent was

removed by rotary evaporation to afford hydrazide **20c**. This product proved to be difficult to handle due to its poor solubility and was directly converted to oxadiazine **21c**.

General procedure for the formation of oxadiazines 21a and 21b. Hydrazide **20a** (0.500 g, 1.60 mmol) was combined with dichloromethane (5 mL), TEA (0.22 mL, 1.6 mmol), and methanesulfonyl chloride (0.130 mL, 1.68 mmol). After 24 h, the reaction was quenched by the addition of a saturated solution of ammonium chloride (50 mL) and diluted with dichloromethane (50 mL). The organic layer was separated, washed with brine (50 mL), dried ($MgSO_4$), and the solvent was removed by rotary evaporation. The crude product was then purified by column chromatography using hexanes and ethyl acetate (98:2).

(S)-5-Benzyl-4-5,6-dihydro-isopropyl-2-phenyl-4H-1,3,4-oxadiazine (21a) The title compound was obtained as yellow oil (75%). $[\alpha]_D^{21} = +197.9$ (*c* 1.45, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (d, $J = 6.3$ Hz, 3H), 1.37 (d, $J = 6.3$ Hz, 3H), 2.69 (dd, $J = 13.5$, 9.9 Hz, 1H), 3.03 (dd, $J = 13.5$, 4.7 Hz, 1H), 3.32–3.53 (m, 2H), 3.98 (dd, $J = 10.3$, 2.8 Hz, 1H), 4.14 (dd, $J = 10.3$, 4.4 Hz, 1H), 7.20–7.36 (m, 8H), 7.78–7.83 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.9, 20.6, 34.5, 52.3, 53.5, 65.7, 124.8, 126.4, 127.8, 128.2, 128.4, 129.2, 133.0, 137.7, and 143.4 ppm. IR: 1628, 1176, 766, and 694 cm^{-1}. ESI-HRMS calcd. for $C_{19}H_{23}N_2O$ $(M + H^+)$: 295.1810. Found: 295.1809.

(S)-5-Benzyl-2-ethyl-5,6-dihydro-4-isopropyl-4H-1,3,4-oxadiazine (21b) Hydrazide **12b** was used in the cyclization process to yield **21b**. The product was purified by column chromatography using hexanes and ethyl acetate (97:3) and was obtained as yellow oil (59%). $[\alpha]_D^{24} = +6.12$ (*c* 0.76, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.07 (d, $J = 6.3$ Hz, 3H), 1.11 (t, $J = 7.4$ Hz, 3H), 1.28 (d, $J = 6.3$ Hz, 3H), 2.18 (q, $J = 7.4$ Hz, 2H), 2.57 (dd, $J = 13.5$, 9.9 Hz, 1H), 2.97 (dd, $J = 13.5$, 4.4 Hz, 1H), 3.18–3.3.26 (m, 1H), 3.33 (septet, $J = 6.3$ Hz, 1H), 3.91–3.93 (m, 1H), 7.16–7.33 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.7, 17.0, 20.7, 26.4, 33.1, 51.0, 52.6, 66.5, 126.3, 128.5, 129.1, 138.0, and 149.5 ppm. IR: 1662, 1176, 741, and 701 cm^{-1}. ESI-HRMS calcd. for $C_{15}H_{23}N_2O$ $(M + H^+)$: 247.1810. Found: 247.1822.

(S)-5-Benzyl-5,6-dihydro-4-isopropyl-2-naphthyl-4H-1,3,4-oxadiazine (21c) The hydrazine **20c** (1.00 g, 4.80 mmol) was combined with dichloromethane (24 mL) and TEA (0.736 mL, 5.28 mmol) and the solution was cooled to 0°C. The reaction was stirred for 5 min and 1-naphthoyl chloride (0.760 mL, 5.04 mmol) was added. After 24 h, the reaction was quenched by the addition of a saturated solution of ammonium chloride (100 mL) and diluted with CH_2Cl_2 (100 mL). The aqueous layer was drawn off and the organic layer was washed with brine (100 mL), dried ($MgSO_4$), and the solvent was removed by rotary evaporation to afford hydrazide **20c**. This product proved to be difficult to handle due to its solubility and was directly converted to oxadiazine **21c**. The hydrazide was combined with dichloromethane (15 mL), TEA (1.34 mL, 9.60 mmol), and methanesulfonyl chloride (0.39 mL, 5.04 mmol) and stirred. After 24 h, the reaction was quenched by the addition of a saturated solution of ammonium chloride (50 mL) and dichloromethane (50 mL). The layers were separated and the organic layer was washed with brine (50 mL), dried ($MgSO_4$), and the solvent was removed by rotary evaporation. The resultant oxadiazine **21c** was purified by column chromatography with hexanes. This process afforded a yellow oil (31%). $[\alpha]_D^{24} = +158.2$ (*c* 1.64, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (d, $J = 6.3$ Hz, 3H), 1.56 (d, $J = 6.3$ Hz, 3H), 2.91 (dd, $J = 13.3$, 9.8 Hz, 1H), 3.21 (dd, $J = 13.3$, 5.1 Hz, 1H), 3.64 (septet, $J = 6.3$ Hz, 1H), 4.23 (dd, $J = 10.2$, 2.7 Hz, 1H), 4.35 (dd, $J = 10.2$, 4.3 Hz, 1H), 7.38 (t, $J = 5.9$ Hz, 2H), 7.44–7.46 (m, 2H), 7.56–7.62 (m, 3H), 7.69 (m, 1H), 7.95 (t, $J = 6.6$ Hz, 2H), 8.01–8.03 (m, 1H), 9.09 (d, $J = 8.6$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.1, 20.9, 34.6, 52.5, 53.6, 66.0, 124.8, 125.5, 126.1, 126.2, 126.4, 126.5, 128.2, 128.5, 129.3, 130.0, 130.5, 133.9, 137.8, and 144.5 ppm. IR: 2970, 1627, 1131, 740, and 700 cm^{-1}. ESI-HRMS calcd. for $C_{23}H_{25}N_2O$ $(M + H)^+$: 345.1967. Found: 345.1958.

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