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Synthesis, reactivity and conformational stability of an L-phenylalanine derived oxadiazinanone

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Abstract—An L-phenylalanine derived oxadiazinanone bearing an isopropyl group at the N_4-position was prepared and acylated with either hydrocinnamoyl or propanoyl chloride. These oxadiazinanones were utilized in titanium-mediated asymmetric aldol reactions with aromatic and aliphatic aldehydes. The diastereoselectivities observed from these reactions ranged from fair to very good and suggested that the N_4-isopropyl-L-phenylalanine based oxadiazinanones are conformationally and configurationally stable at the N_4-nitrogen.

1. Introduction

3,4,5,6-Tetrahydro-2*H*-1,3,4-oxadiazin-2-ones (oxadiazinanones) are structurally unique chiral auxiliaries that have been employed in asymmetric aldol reactions.[1–6] The oxadiazinanones that have been synthesized have been derived from the *Ephedra* alkaloids, namely (1*R*,2*S*)-ephedrine,[1–4] (1*R*,2*S*)-norephedrine,[5,6] and (1*S*,2*S*)-pseudoephedrine[7] (Chart 1). We have demonstrated the utility of (1*R*,2*S*)-ephedrine and (1*R*,2*S*)-norephedrine derived oxadiazinanones as chiral auxiliaries in the asymmetric aldol addition.[1–6] Based on the observed diastereoselectivities from these studies, as well as computational studies and ^{1}H NMR studies, the ephedrine and norephedrine derived oxadiazinanones are considered to be conformationally and, consequently, configurationally stable at the N_4-nitrogen.

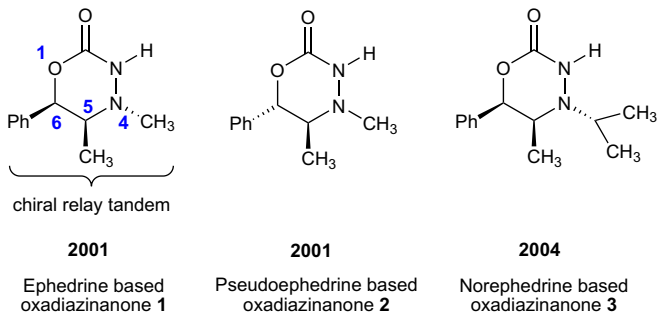

Chart 1. *Ephedra* based oxadiazinanones.

In contrast, the pseudoephedrine based oxadiazinanones are conformationally flexible at the N_4-nitrogen and have not been used as chiral auxiliaries in the asymmetric aldol reaction.[7] The success of the (1*R*,2*S*)-ephedrine and (1*R*,2*S*)-norephedrine based oxadiazinanone mediated aldol reactions is believed to be dependent upon the positional stability of the stereogenic N_4-nitrogen. Our previous studies of these systems have shown that the C_5- and C_6-positions of these oxadiazinanones directly influence the stereochemical orientation of the N_4 position by means of an intramolecular chiral relay.[8–10] The stereochemical tandem of the C_6–C_5–N_4-positions then influences the approach of the aldehyde to the oxadiazinanone enolate in asymmetric aldol additions.[1–6] Based on this argument, the stereochemical position of the C_6-phenyl ring is largely responsible for the conformational stability of the N_4-nitrogen because of its 'anchoring' position in the relay tandem (cf. oxadiazinanones **1** and **2** in Chart 1). We became interested in determining the impact of the absence of a substituent at the C_6-position of the oxadiazinanone ring system. α-Amino acids serve as excellent chiral, non-racemic starting materials that can yield oxadiazinanones that are unsubstituted at the C_6-position. Herein, we report on our use of L-phenylalanine to synthesize such an oxadiazinanone and we report on its application in the aldol reaction. Finally, an argument is made for the conformational and configurational stability of

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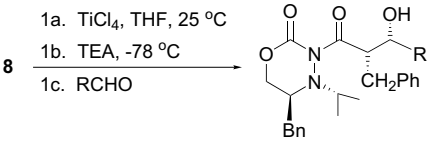
the L-phenylalanine derived oxadiazinanone as compared to the *Ephedra* based oxadiazinanones.

2. Results and discussion

L-Phenylalanine **4** was reduced to L-phenylalaninol by reduction with sodium borohydride and iodine using a method developed by Kanth and Periasamy[11] and later optimized for α-amino acids by Meyers et al. (Scheme 1).[12] The resultant β-aminoalcohol was reductively alkylated[13] with acetone and sodium borohydride to afford the *N*-isopropyl derivative **5**, which was converted to its corresponding β-hydrazino-alcohol **6**. The β-hydrazino alcohol was then cyclized by treatment with lithium hydride and diethyl carbonate to afford oxadiazinanone **7** in 58% yield after column chromatography. The oxadiazinanone was acylated with hydrocinnamoyl chloride to afford the N_3-hydrocinnamoyl derivative **8** in 79% isolated yield. This particular side chain was selected as there was an interest in employing **8** in the synthesis of a key intermediate of the HIV protease inhibitor saquinavir.[14] With oxadiazinanone **8** in hand, we attempted the asymmetric aldol reaction with a variety of aromatic and aliphatic aldehydes.

The aldol reactions were conducted by dissolving oxadiazinanone **8** in THF followed by the addition of 2 equiv of titanium tetrachloride at 25 °C for 25 min (Table 1). The solution was cooled to −78 °C and 2 equiv of triethylamine was added. The solution was allowed to warm up to 0 °C over 45 min, then re-cooled to −78 °C, and the appropriate aldehyde was added. The aldol adducts were obtained in 49–79% isolated yield with diastereoselectivities ranging from 7:1 to greater than 19:1, as determined by either ^{1}H NMR spectroscopy or HPLC. The stereochemistry of the aldol side chain in adducts **9a–e** was tentatively assigned as the non-Evans *syn*-stereochemistry based on earlier studies concerning N_4-isopropyloxadiazinanones.[5] In order to determine the relative stereochemistry of the aldol adducts (i.e., *syn*- vs *anti*-), oxadiazinone **9e** was hydrolyzed with 6 M H_2SO_4 (Scheme 2). This process afforded the expected β-hydroxycarboxylic acid **10** in 68% yield.[15] The carboxylic acid was treated with diphenylphosphoryl azide and triethylamine to effect the Curtius rearrangement[14,16] in toluene to yield the known *syn*-oxazolidinone **11**, an intermediate in the synthesis of a key fragment of saquinavir developed by Ghosh et al. The oxazolidinone was obtained in 63% isolated yield and was spectroscopically identical with the reported literature data.[14] There was no reported specific rotation for the oxazolidinone and efforts to evaluate the enantiomeric purity by chiral stationary phase HPLC were not pursued.

Table 1. Asymmetric aldol reactions of oxadiazinanone **8**

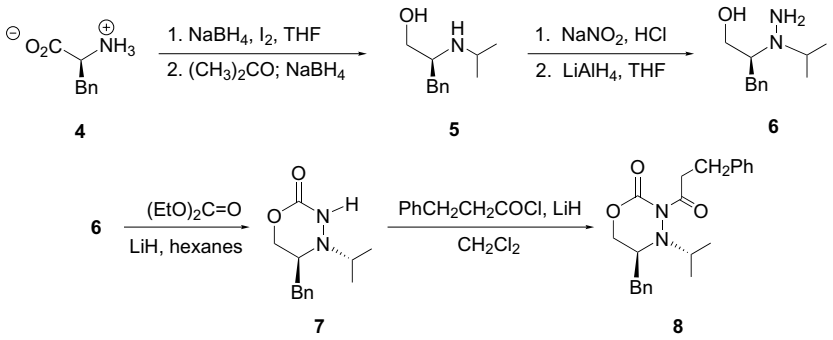


9a-e

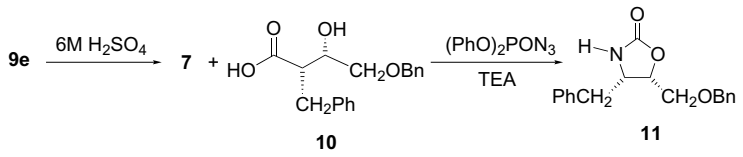
Entry	RCHO	Product	% Yield[a]	dr (crude)[c]
1	C_6H_5CHO	**9a**	55	⩾19:1[d]
2	*p*-Cl-C_6H_4CHO	**9b**	51	19:1[d]
3	2-$C_{10}H_7CHO$	**9c**	70	⩾19:1[d]
4	$(CH_3)_3CCHO$	**9d**	79	7:1[d]
5	$C_6H_5CH_2OCH_2CHO$	**9e**	49[b]	21:1[e]

[a] Purified yield after column chromatography.
[b] Purified yield after chromatography and recrystallization.
[c] Diastereoselectivities are represented as major diastereomer:∑ all other diastereomers.
[d] Crude diastereomeric ratios were determined from 400 MHz ^{1}H NMR spectroscopy.
[e] Crude diastereomeric ratio was determined by HPLC using a Shimadzu SCL-10AVP system with a Dynamax Si-100 Å column (7:3, hexanes/EtOAc, flow rate = 1.0 mL/min).

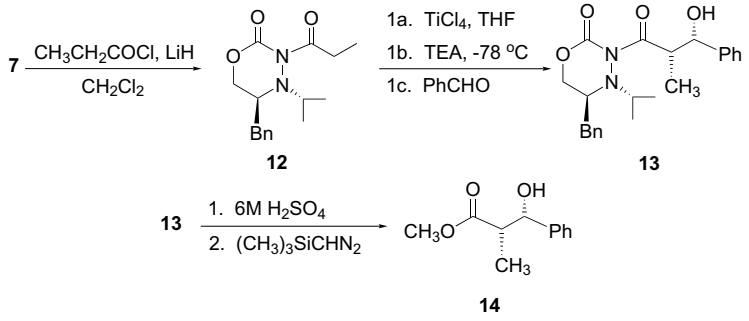
The determination of the absolute stereochemistry of the aldol addition reaction with L-phenylalanine derived oxadiazinanone was carried out by using an alternate substrate. Thus, oxadiazinanone **7** was acylated with propanoyl chloride and lithium hydride to yield **12** in 30% yield (Scheme 3). This material was dissolved in THF and treated with titanium tetrachloride, triethylamaine at −78 °C, and benzaldehyde. This process gave aldol adduct **13** in 47% yield in greater than 19:1 diastereomeric ratio favoring the proposed *syn*-diastereomer, as determined by ^{1}H NMR spectroscopy. This adduct was hydrolyzed with 6 M H_2SO_4 and the resultant β-hydroxycarboxylic acid **13** was esterified with trimethylsilyldiazomethane to afford ester **14** in 59% yield after chromatography. The specific rotation was determined to be $[\alpha]_D^{29} = -11.6$ (*c* 0.74, $CHCl_3$) and the literature value[17a] for the (2*R*,3*R*)-ester was reported as $[\alpha]_D^{25} = +23.5$ (*c* 3.23, $CHCl_3$). The abso-



Scheme 1. Synthesis of L-phenylalanine derived oxadiazine **8**.



Scheme 2. Synthesis of oxazolidinone **11**.



Scheme 3. The formation of β-hydroxyester **14**.

lute stereochemistry of the recovered ester was assigned as the (2*S*,3*S*)-enantiomer. We were uncertain of the enantiomeric purity and so used chiral stationary phase HPLC to determine that the enantiomeric ratio was 96:4 (92% e.e.) [Chiralcel OD column, hexanes/*i*-PrOH, 95:5, 1 mL/min: t_R (2*R*,3*R*)-ester[17b] = 8.58 min; t_R (2*S*,3*S*)-ester = 10.0 min].

From the collected spectroscopic data and optical activity data, a chair like Zimmerman–Traxler transition state was proposed (Fig. 1).[18] This is in accordance with our earlier work regarding a norephedrine derived N_4-isopropyloxadiazinanone.[5,6]

Regarding the conformational stability of the L-phenylalanine derived oxadiazinanones in this work, the diastereomeric ratios obtained from the aldol reaction are most likely a reflection of the conformational and configurational stability of the N_4-isopropyl substituents in oxadiazinanones **8** and **12**. Indeed, the presence of multiple conformers would have given rise to diminished diastereoselectivities, but these values were comparable to those obtained in prior work.[1–6] These results seem to suggest that the C_6-position need not be substituted in order to obtain high stereoselectivities in the aldol reaction. Rather, it is the C_5-position that is dominant in establishing the conformational behavior of the N_4-nitrogen in this α-amino acid derived system. Interestingly, Rodrigues et al.[19,20] have also prepared an α-amino acid derived oxadiazinanone **15** derived from (*R*)-phenylglycine and noted that they observed two conformers in the unit cell of the X-ray crystal structure (Fig. 2). The reason for this conformational flexibility in their oxadiazinanones is most likely attributed to the relative sizes of the N_4-methyl and C_5-phenyl substituents. In contrast, the stereochemical orientation of the N_4-isopropyl and C_5-benzyl substituents of the L-phenylalanine oxadiazinanone **7** is probably more rigid and retains a dominant conformation and configuration at the stereocontrol element, the N_4-position.

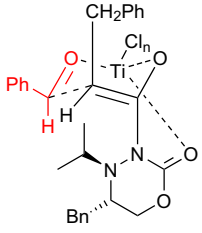


Figure 1. Proposed transition state **15**.

3. Conclusion

An L-phenylalanine derived oxadiazinanone has been synthesized and utilized in aldol addition reactions with fair to very good diastereoselectivities being obtained. An intermediate in the synthesis of a key fragment of saquinavir was prepared using the Curtius rearrangement. The absolute stereochemistry and enantiomeric purity of the aldol adducts were determined by correlation with the specific rotation and chiral stationary phase HPLC of the ester derived from oxadiazinanone **13**. The observed diastereoselectivities suggest that the C_6-unsubstituted oxadiazinanones are configurationally stable at the N_4-nitrogen. However, the work of Rodrigues et al. offers a compelling argument for selecting C_5 and C_6 substituents that are of a

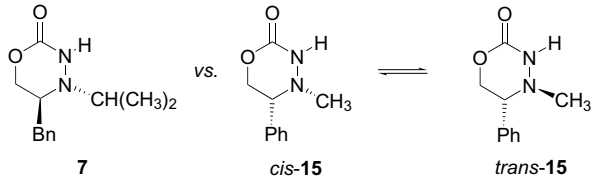


Figure 2. Conformational stability in oxadiazinanones **7** and **15**.

proper steric size to stabilize the conformational dynamics of the stereodirecting N_4-position.

4. Experimental

4.1. General remarks

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). 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 with carbon tetrachloride (CCl_4) or chloroform ($CHCl_3$). 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. HPLC chromatographic data were collected using a Shimadzu HPLC and dynamax column (silica, 10 μ, 4.6 mm × 25 cm). Elemental analyses were conducted by the Microanalytical Laboratory, School of Chemical Sciences, University of Illinois, Urbana-Champaign. Optical Rotation data were collected at the University of Illinois, Urbana-Champaign on a JASCO P-1010 digital polarimeter operating at 589 nm.

4.2. (*S*)-2-*N*-Isopropylamino-3-phenyl-1-propanol 5

In a flame-dried, nitrogen-purged 5 L three-neck round-bottomed flask fitted with a condenser and an addition funnel were placed sodium borohydride (27.5 g, 726 mmol), THF (1 L), and L-phenylalanine **4** (50.0 g, 303 mmol). This mixture was cooled to 0 °C utilizing an ice bath. A solution of iodine (76.8 g, 303 mmol dissolved in 250 mL of THF) was poured into the addition funnel and added dropwise over a period of 45 min resulting in a vigorous evolution of hydrogen gas. Once the gas evolution had ceased, the contents of the flask were heated at reflux for 18 h and then cooled to room temperature, after which methanol (200 mL) was added until the mixture became clear. After stirring for 30 min, the solvent was removed in vacuo leaving a white paste, which was dissolved with 3 M KOH (500 mL). The mixture was extracted with methylene chloride. The organic extracts were washed with a saturated brine solution, dried with $MgSO_4$, and the solvents were removed in vacuo. The crude material was recrystallized with ethyl acetate and hexanes to yield 27.37 g (60%) of (*S*)-phenylalaninol as a white solid. Mp: 85–87 °C. ^1H NMR ($CDCl_3$): δ, 2.40–2.65 (m, 2H), 2.79 (dd, $J = 5.1$, 5.5 Hz, 1H), 3.09–3.15 (m, 1H), 3.37–3.42 (m, 1H), 3.64 (dd, $J = 3.7$, 3.7 Hz, 1H), 7.18–7.33 (m, 5H). ^{13}C NMR ($CDCl_3$): δ, 40.7, 54.2, 66.1, 126.4, 128.6, 129.2, 138.5. In a flame-dried, nitrogen-purged 2 L round-bottomed flask were placed (*S*)-phenylalaninol (25.0 g, 165 mmol) and 100% ethanol (200 mL). To this stirred mixture were added 2 g of $MgSO_4$ and the reagent grade acetone (24.3 mL, 331 mmol). The resulting mixture was allowed to stir at room temperature for 5 h and then 100% ethanol (200 mL) was added. To the stirred mixture was slowly added sodium borohydride (18.3 g, 484 mmol). The mixture was allowed to stir at room temperature for 18 h and then quenched with 1 M NaOH (300 mL). Once the solvents were removed in vacuo, the mixture was extracted with EtOAc. The organic extracts were washed with brine, dried with $MgSO_4$, and solvents were removed in vacuo. The crude material was recrystallized with ethyl acetate and hexanes to yield 23.33 g (73%) of **5** as a white solid: Mp = 52–54 °C; $[\alpha]_D^{25} = +6.6$ (c 0.38, $CHCl_3$); $R_f = 0.53$ (hexanes/EtAOc, 1:1). ^1H NMR ($CDCl_3$): δ, 0.98 (d, $J = 6.2$ Hz, 3H), 1.03 (d, $J = 6.2$ Hz, 3H), 2.14 (broad singlet, –OH), 2.68–2.81 (m, 2H), 2.87 (septet, $J = 6.2$ Hz, 1H), 2.95–3.00 (m, 1H), 3.22–3.26 (m, 1H), 3.55 (dd, $J = 4.0$, 10.6 Hz, 1H), 7.16–7.33 (m, 5H). ^{13}C NMR ($CDCl_3$): δ, 23.3, 38.5, 45.8, 57.2, 62.9, 126.3, 128.5, 129.2, 138.4. IR (CCl_4): 2964, 1479, 1039 cm^{-1}. Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 73.88; H, 9.84; N, 7.50.

4.3. (*S*)-2-*N*-Isopropylhydrazino-3-phenyl-1-propanol 6

In a 1 L round-bottom flask equipped with a stirrer bar were placed (*S*)-2-*N*-isopropylamino-3-phenyl-1-propanol **5** (17.2 g, 89.0 mmol) and THF (60 mL). An aqueous solution of HCl (70 mL, 2.74 M, 192 mmol) was then added followed by the addition of sodium nitrite (6.76 g, 97.9 mmol) in small portions over a period of 10 min. The reaction mixture was stirred for 24 h, and the mixture was then diluted with a saturated aqueous solution of sodium bicarbonate (150 mL). The reaction mixture was then extracted with EtOAc and the extract was washed with brine. The resulting solution was dried over $MgSO_4$ followed by the removal of the solvent in vacuo. The crude product was isolated as a yellow oil containing a mixture of isomers in 99% yield (16.07 g). A portion was saved and purified by chromatography, which resulted in a purified mixture of isomers. The rest of the material was taken on as a mixture of isomers into the reduction: $[\alpha]_D^{25} = -29.8$ (c 0.48, $CHCl_3$); $R_f = 0.38$ (hexanes/EtOAc, 1:1). *Isomer* **1** (*major*): ^1H NMR ($CDCl_3$): δ, 0.68 (d, $J = 7.0$ Hz, 3H), 1.08 (d, $J = 7.0$ Hz, 3H), 3.05 (d, $J = 7.0$ Hz, 2H), 3.15–3.32 (m, 2H), 4.14–4.23 (m, 2H), 4.38 (broad singlet, –OH), 7.14–7.31 (m, 5H). *Isomer* **2** (*minor*): ^1H NMR ($CDCl_3$): δ, 1.24 (d, $J = 6.6$ Hz, 3H), 1.35 (d, $J = 6.6$ Hz, 3H), 2.04 (broad singlet, –OH), 3.73–3.89 (m, 2H), 3.95–4.04 (m, 3H), 4.96–5.03 (m, 1H), 7.14–7.31 (m, 5H). *Isomer* **1** (*major*): ^{13}C NMR ($CDCl_3$): δ, 18.1, 19.0, 38.9, 62.1, 65.3, 128.6, 128.6, 129.3, 137.6. *Isomer* **2** (*minor*): ^{13}C NMR ($CDCl_3$): δ, 22.2, 33.4, 45.3, 55.4, 62.2, 126.8, 126.9, 128.9, 137.4. IR (CCl_4): 3384, 2978, 1171, 732 cm^{-1}. HRMS calcd for $C_{12}H_{18}N_2O_2$: 222.1368. Found: 222.1371.

4.3.1. Reduction of the *N*-nitrosamine. In a flame-dried, nitrogen-purged 5 L, three-neck round-bottomed flask fitted with an addition funnel and a condenser were placed lithium aluminum hydride (5.47 g, 143.9 mmol) and freshly distilled THF (200 mL). The mixture was then heated at reflux and nitrosamine (16.0 g, 72.0 mmol), dissolved in freshly distilled THF (100 mL), was added slowly through the addition funnel over a period of 60 min. Once the addition was completed, the reaction mixture was maintained

under reflux for an additional 2 h. The reaction mixture was cooled to 0 °C followed by the cautious addition of NaOH (3 M) until the remaining lithium aluminum hydride was consumed. The mixture was diluted with a saturated aqueous solution of sodium potassium tartrate (*Rochelle's salt*) and stirred for 15 min. The THF was removed in vacuo. The mixture was then extracted with EtOAc and the extract washed with brine, dried over $MgSO_4$, and the solvent was removed in vacuo. This process afforded a viscous yellow oil, which was recrystallized with diethyl ether and hexanes to yield **6** as a white solid (8.6 g). Yield: 57%. Mp: 51–53 °C; $[\alpha]_D^{25} = +7.5$ (*c* 0.36, $CHCl_3$); $R_f = 0.10$ (100% EtOAc). ^1H NMR ($CDCl_3$): δ, 1.14 (d, $J = 6.2$ Hz, 3H), 1.18 (d, $J = 6.2$ Hz, 3H), 2.72–2.85 (m, 2H), 2.89–2.98 (septet, $J = 6.2$ Hz, 1H), 3.04–3.10 (m, 1H), 3.53–3.59 (m, 2H), 7.17–7.31 (m, 5H). ^{13}C NMR ($CDCl_3$): δ, 19.8, 20.9, 29.7, 55.3, 62.4, 63.1, 126.0, 128.4, 129.2, 139.4. IR (CCl_4): 3349, 2975, 796 cm^{-1}. HRMS calcd for $C_{12}H_{20}N_2O$: 208.1576. Found: 208.1570.

4.4. (4*R*,5*S*)-5-Benzyl-4-isopropyl-2*H*-1,3,4-oxadiazinan-2-one 7

In a flame-dried, nitrogen-purged 2 L round-bottomed flask equipped with a condenser were placed hydrazine **6** (26.1 g, 126 mmol) and hexanes. To this solution was added diethyl carbonate (38.0 mL, 314 mmol). After the addition was completed the resulting mixture was heated at reflux, upon which LiH (1.05 g, 132 mmol) was added. The reaction mixture was cooled to room temperature after 18 h and an aqueous saturated solution of NH_4Cl (250 mL) was added. After the solvent was removed in vacuo, the mixture was extracted with EtOAc and the extract was washed with a saturated brine solution, dried ($MgSO_4$), and the solvent was removed in vacuo. This process yielded a yellow oil that was purified by chromatography and recrystallized to yield **7** as a white solid (17.1 g). Yield: 58%. Mp = 50–52 °C; $[\alpha]_D^{25} = +24.7$ (*c* 0.36, $CHCl_3$); $R_f = 0.27$ (hexanes/EtOAc, 3:2). ^1H NMR ($CDCl_3$): δ, 1.03 (d, $J = 6.3$ Hz, 3H), 1.19 (d, $J = 6.3$ Hz, 3H), 2.82–2.89 (m, 1H), 2.93–3.07 (m, 2H), 3.30–3.49 (m, 1H), 4.05–4.15 (m, 1H), 4.46 (dd, $J = 3.4$, 11.7 Hz, 1H), 6.83 (broad singlet, –NH), 7.21–7.34 (m, 5H). ^{13}C NMR ($CDCl_3$): δ, 20.3, 20.4, 36.7, 53.0, 55.8, 64.1, 126.7, 128.6, 129.3, 137.8, 152.2. IR (CCl_4): 3514, 1702, 1093, 754 cm^{-1}. HRMS calcd for $C_{13}H_{18}N_2O_2$: 234.1368. Found: 234.1372. Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.34; H, 8.07; N, 11.39.

4.5. General procedure for acylated oxadiazinanones 8 and 12

In a flame-dried, nitrogen-purged 250 mL round-bottomed flask fitted with a Claisen adapter and a condenser was placed oxadiazinanone **7**, dissolved in methylene chloride. To this stirred mixture was added the appropriate acyl chloride via a syringe (1.1 equiv). This mixture was heated at reflux after which LiH (1.1 equiv) was added. The contents of the flask were reacted at reflux for a period of 18 h. After this time period, the mixture was cooled to room temperature and quenched with NH_4Cl and extracted with methylene chloride. The combined extracts were washed with brine and dried over $MgSO_4$. The solvents were removed in vacuo and the crude product was purified via column chromatography.

4.5.1. (4*R*,5*S*)-5-Benzyl-4-isopropyl-3-(3-phenylpropanoyl)-2*H*-1,3,4-oxadiazin-2-one 8. Hydrocinnamoyl chloride (7.6 mL, 51 mmol) was reacted with oxadiazinanone **7** (8.0 g, 34 mmol). The purified product was isolated as faint yellow crystals (9.90 g) and gave a yield of 79%. Mp = 47.5–50.0 °C; $[\alpha]_D^{25} = -61.6$ (*c* 0.30, $CHCl_3$); $R_f = 0.34$ (hexanes/EtOAc, 3:1). ^1H NMR ($CDCl_3$): δ, 0.99–1.02 (m, 6H), 2.32–2.37 (m, 2H), 2.65–2.73 (m, 1H), 2.93–3.09 (m, 2H), 3.11–3.24 (m, 1H), 3.47–3.54 (m, 1H), 3.59–3.64 (m, 1H), 4.27–4.28 (m, 2H), 7.14–7.30 (m, 10H). ^{13}C NMR ($CDCl_3$): δ, 19.5, 20.1, 30.8, 36.7, 38.8, 56.9, 57.4, 67.9, 126.1, 126.7, 128.4, 128.5, 129.1, 136.6, 140.6, 152.7, 173.0. IR ($CHCl_3$): 2977, 1790, 1220, 754 cm^{-1}. HRMS calcd for $C_{22}H_{26}N_2O_3$: 366.1943. Found: 366.1941.

4.5.2. (4*R*,5*S*)-5-Benzyl-4-isopropyl-3-propanoyl-2*H*-1,3,4-oxadiazinan-2-one 12. Propanoyl chloride (1.46 mL, 16.8 mmol) was reacted with oxadiazinanone **7**. The purified product was isolated by chromatography (hexanes/EtOAc, 1:1) to afford **12** as an oil (0.47 g). Yield: 30%. $[\alpha]_D^{29} = -167.5$ (*c* 5.5, $CHCl_3$); $R_f = 0.33$ (hexanes/EtOAc, 1:1). ^1H NMR ($CDCl_3$): δ, 1.06 (d, $J = 6.2$ Hz, 3H), 1.05 (d, $J = 6.3$ Hz, 3H), 1.20 (t, $J = 7.4$ Hz, 3H), 2.57–2.62 (dd, $J = 5.9$, 7.8 Hz, 1H), 2.65–2.74 (m, 1H), 2.87–2.97 (m, 2H), 3.04–3.11 (septet, $J = 6.3$, 1H), 3.57–3.64 (p, $J = 7.0$ Hz, 1H), 3.88–3.93 (dd, $J = 7.4$, 4.3 Hz, 1H), 4.38–4.43 (dd, $J = 6.6$, 4.7 Hz, 1H), 7.23–7.34 (m, 5H). ^{13}C NMR ($CDCl_3$): δ, 9.1, 19.8, 20.2, 28.9, 39.2, 56.9, 57.3, 68.0, 126.9, 128.7, 136.8, 152.8, 174.7; IR ($CHCl_3$): 2977, 1790, 891, 806 cm^{-1}. HRMS calcd for $C_{16}H_{22}N_2O_3$: 290.1630. Found: 290.1631.

4.6. General procedures for aldol adducts 9a–e

In a nitrogen-purged 100 mL round-bottomed flask was placed oxadiazinanone **8** (1.0 g) and THF (~0.33 M). $TiCl_4$ (2 equiv) was added to this stirred solution and allowed to sit at room temperature for 25 min. After this time, the solution was cooled to −78 °C and after five min, 2 equiv of triethylamine were introduced to the flask via a syringe. Over the course of 45 min, the solution was allowed to warm up while the enolate formed. After the 45 min had elapsed, the solution was chilled to −78 °C again and the reaction allowed to run overnight after the addition of the appropriate aldehyde (1.3–2 equiv). The reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc. The combined extracts were washed with a saturated brine solution and dried ($MgSO_4$). The solvents were removed in vacuo and reaction diastereoselectivity of the crude reaction mixture was determined by ^1H NMR spectroscopy or HPLC.

4.6.1. (2′*S*,3′*S*,4*R*,5*S*)-5-Benzyl-3-[2-benzyl-3-hydroxy-3-phenylpropanoyl]-4-isopropyl-2*H*-1,3,4-oxadiazinan-2-one 9a. Benzaldehyde (0.57 mL, 5.6 mmol) was reacted with oxadiazinanone **8**. The purified product was isolated by

chromatography to afford **9a** as an oil (0.75 g). Yield: 55%. $[\alpha]_D^{29} = -130.9$ (*c* 1.39, $CHCl_3$); $R_f = 0.15$ (hexanes/EtOAc, 7:3). ^1H NMR ($CDCl_3$): δ, 0.86 (d, $J = 6.3$ Hz, 3H), 0.80 (d, $J = 5.9$ Hz, 3H), 1.89–194 (dd, $J = 7.0$, 13.3 Hz, 1H), 2.28–2.33 (m, 2H), 2.75–2.83 (m, 2H), 3.03 (t, $J = 13.3$ Hz, 1H), 3.20–3.28 (m, 1H), 3.52 (broad singlet, –OH), 3.87–3.92 (dd, $J = 7.0$, 11.3 Hz, 1H), 4.09–4.14 (dt, $J = 12.1$, 3.5 Hz, 1H), 5.27 (d, $J = 3.1$ Hz, 1H), 7.11–7.31 (m, 13H), 7.39 (t, $J = 7.4$, 1H), 7.58 (d, $J = 7.4$, 1H). ^{13}C NMR ($CDCl_3$): δ, 19.1, 20.0, 32.9, 39.1, 52.6, 57.6, 58.4, 68.0, 73.4, 126.4, 126.6, 127.6, 128.3, 128.4, 128.8, 129.3, 137.0, 139.3, 140.8, 155.2, 174.9; IR ($CHCl_3$): 3461, 2976, 1756, 1711, 1219, 753, 701 cm^{-1}. HRMS calcd for $C_{29}H_{32}N_2O_4$: 473.2440. Found: 473.2439.

4.6.2. (2′*S*,3′*S*,4*R*,5*S*)-5-Benzyl-3-[2-benzyl-3-hydroxy-3-(4-chlorophenyl)propanoyl]-4-isopropyl-2*H*-1,3,4-oxadiazinan-2-one 9b. 4-Chlorobenzaldehyde (0.79 g, 5.6 mmol) was reacted with oxadiazinanone **8**. The purified product was isolated by chromatography to afford the title compound as an oil (0.83 g). Yield: 51%. $[\alpha]_D^{29} = -125.5$ (*c* 0.58, $CHCl_3$); $R_f = 0.23$ (hexanes/EtOAc, 7:3). ^1H NMR ($CDCl_3$): δ, 0.81 (d, $J = 6.3$ Hz, 3H), 0.86 (d, $J = 6.3$ Hz, 3H), 1.88–1.93 (dd, $J = 7.0$, 6.3, 1H), 2.26–2.34 (m, 2H), 2.72–2.83 (m, 2H), 3.00 (t, $J = 12.5$ Hz, 1H), 3.21–3.29 (m, 1H), 3.60 (broad singlet, –OH), 3.89–3.94 (dd, $J = 3.1$, 5.9 Hz, 1H), 4.03–4.07 (dt, $J = 3.5$, 12.1 Hz, 1H), 5.24 (d, $J = 3.1$ Hz, 1H), 7.10–7.38 (m, 12H), 7.52 (d, $J = 8.2$, 2H); ^{13}C NMR ($CDCl_3$): δ, 19.1, 20.0, 32.7, 39.1, 52.6, 57.6, 58.4, 68.1, 72.9, 126.7, 127.8, 128.4, 128.8, 129.3, 133.3, 137.0, 139.0, 139.3, 155.2, 174.6; IR ($CHCl_3$): 3449, 2976, 1755, 1711, 1219, 754, 700 cm^{-1}. HRMS calcd for $C_{29}H_{31}N_2O_4Cl$: 507.2051. Found: 507.2043.

4.6.3. (2′*S*,3′*S*,4*R*,5*S*)-5-Benzyl-3-[2-benzyl-3-hydroxy-3-(2-naphthyl)propanoyl]-4-isopropyl-2*H*-1,3,4-oxadiazinan-2-one 9c. 2-Naphthaldehyde (0.8 g, 5.5 mmol) was reacted with oxadiazinanone **8**. The purified product was isolated by chromatography to afford the title compound as an oil (1.06 g). Yield: 70%. $[\alpha]_D^{29} = -81.9$ (*c* 0.74, $CHCl_3$); $R_f = 0.15$ (hexanes/EtOAc, 7:3). ^1H NMR ($CDCl_3$): δ, 0.78 (d, $J = 6.2$ Hz, 3H), 0.84 (d, $J = 6.6$ Hz, 3H), 1.89–1.94 (dd, $J = 7.0$, 13.7 Hz, 1H), 2.29–2.35 (m, 2H), 2.77–2.82 (m, 2H), 3.09 (t, $J = 13.3$ Hz, 1H), 3.22–3.26 (m, 1H), 3.71 (broad singlet, –OH), 3.87–3.92 (dd, $J = 7.0$, 11.3 Hz, 1H), 4.18–4.23 (dt, $J = 4.0$, 11.7 Hz, 1H), 5.44 (d, $J = 2.73$ Hz, 1H), 7.09–7.30 (m, 10H), 7.46–7.49 (m, 2H), 7.68–7.71 (d, 1H), 7.83–7.9 (m, 3H), 8.07 (s, 1H); ($CDCl_3$): δ, 19.1, 19.9, 32.7, 39.1, 52.5, 57.6, 58.4, 68.1, 73.4, 124.3, 125.3, 125.8, 126.0, 126.6, 126.7, 127.6, 128.1, 128.2, 128.4, 128.8, 129.3, 133.0, 133.2, 137.0, 138.2, 139.2, 155.4, 175.1; IR ($CHCl_3$): 3466, 2976, 1755, 1712, 1219, 754, 701 cm^{-1}. HRMS calcd for $C_{33}H_{34}N_2O_4$: 523.2597. Found: 523.2599.

4.6.4. (2′*S*,3′*S*,4*R*,5*S*)-5-Benzyl-3-[2-benzyl-3-hydroxy-4,4-dimethylpentanoyl]-4-isopropyl-2*H*-1,3,4-oxadiazinan-2-one 9d. Pivaldehyde (0.57 mL, 5.6 mmol) was reacted with oxadiazinanone **8**. The purified product was isolated by chromatography (hexanes/EtOAc, 70:30) to afford **9d** as an oil (0.99 g). Yield: 79%. $[\alpha]_D^{29} = -180.1$ (*c* 0.67, $CHCl_3$); $R_f = 0.15$ (hexanes/EtOAc, 7:3). ^1H NMR ($CDCl_3$; values representative of major isomer only): δ, 0.85 (d, $J = 6.3$ Hz, 3H), 0.94 (d, $J = 6.6$ Hz, 3H), 1.13 (s, 9H), 1.93–1.98 (dd, $J = 7.4$, 13.7 Hz, 1H), 2.13–2.18 (t, $J = 10.5$ Hz, 1H), 2.34–2.39 (dd, $J = 7.0$, 13.7 Hz, 1H), 2.82–2.85 (m, 1H), 3.03–3.09 (t, $J = 13.3$ Hz, 1H), 3.15–3.24 (m, 3H), 3.68 (singlet, –OH), 3.79–3.83 (dd, $J = 7.0$, 4.3 Hz, 1H), 4.13–4.17 (dd, $J = 4.3$, 7.8 Hz, 2H), 7.11–7.34 (m, 10H). ^{13}C NMR ($CDCl_3$; values representative of major isomer only): δ, 19.4, 19.8, 27.4, 33.6, 39.4, 46.9, 57.8, 58.4, 67.9, 78.2, 126.9, 127.0, 128.7 129.2, 129.5, 129.6, 137.1, 139.7, 155.0, 176.5; IR ($CHCl_3$): 3507, 2957, 1756, 1697, 1226, 754, 700 cm^{-1}. HRMS calcd for $C_{27}H_{36}N_2O_4$: 453.2753. Found: 453.2746.

4.6.5. (2′*S*,3′*S*,4*R*,5*S*)-5-Benzyl-3-(2-benzyl-4-benzyloxy-3-hydroxybutanoyl)-4-isopropyl-2*H*-1,3,4-oxadiazinan-2-one 9e. Benzyloxyacetaldehyde (0.61 mL, 4.37 mmol) was reacted with oxadiazinanone **8**. The purified product was isolated by recrystallization with EtOAc and hexanes to afford the target compound as a white solid (0.73 g). Yield: 49%. Mp = 106–108 °C; $[\alpha]_D^{25} = -103.5$ (*c* 0.28, $CHCl_3$); $R_f = 0.36$ (hexanes/EtOAc, 7:3). ^1H NMR ($CDCl_3$): δ, 0.79 (d, $J = 6.2$ Hz, 3H), 0.87 (d, $J = 6.2$ Hz, 3H), 1.92–1.97 (m, 1H), 2.24–2.33 (m, 2H), 2.71–2.77 (m, 1H), 2.97 (dd, $J = 12.1$, 12.8 Hz, 1H), 3.15–3.26 (m, 2H), 3.68 (d, $J = 5.9$ Hz, 2H), 3.85–3.96 (m, 2H), 4.26–4.30 (m, 1H), 4.56 (d, $J = 11.7$ Hz, 1H), 4.67 (d, $J = 12.1$ Hz, 1H), 7.12–7.39 (m, 15H). The alcoholic proton was not observed. ^{13}C NMR ($CDCl_3$): δ, 19.3, 20.0, 35.0, 39.0, 48.8, 57.7, 58.5, 67.9, 71.4, 71.8, 73.4, 126.7, 127.7, 127.8, 128.4, 128.9, 129.3, 137.1, 137.9, 139.4, 155.2, 173.6. IR (CCl_4): 3438, 2914, 1756, 1687, 700 cm^{-1}. HRMS calcd for $C_{31}H_{37}N_2O_5$: 517.2702. Found: 517.2694. Anal. Calcd for $C_{31}H_{36}N_2O_5$: C, 72.07; H, 7.02; N, 5.42. Found: C, 72.07; H, 7.10; N, 5.57.

4.6.6. (2′*S*,3′*S*,4*R*,5*S*)-5-Benzyl-3-(3-hydroxy-2-methyl-3-phenylpropanoyl)-4-isopropyl-2*H*-1,3,4-oxadiazinan-2-one 13. Benzaldehyde (0.7 mL, 7.0 mmol) was reacted with oxadiazinanone **12**. The purified product was isolated via recrystallization with hexanes and EtOAc to afford **13** as a solid (0.65 g). Yield: 47%. Mp = 96–98.5 °C. $[\alpha]_D^{29} = -92.2$ (*c* 1.39, $CHCl_3$); $R_f = 0.15$ (hexanes/EtOAc, 7:3). ^1H NMR ($CDCl_3$): δ 1.04 (t, $J = 6.6$ Hz, 6H), 1.10 (d, $J = 7.0$ Hz, 3H), 2.52–2.57 (dd, $J = 7.8$, 5.9 Hz, 1H), 2.83–2.88 (dd, $J = 6.3$, 7.42, 1H), 3.03–3.09 (m, 1H), 3.32 (broad singlet, –OH), 3.56–3.63 (pentet, $J = 7.8$ Hz, 1H), 3.76–3.88 (m, 2H), 4.36–4.40 (dd, $J = 7.0$, 4.3 Hz, 1H), 5.25 (d, $J = 2.8$ Hz, 1H), 7.21–7.37 (m, 8H), 7.45 (d, $J = 7.8$, 2H). ^{13}C NMR ($CDCl_3$): δ, 19.1, 20.0, 32.9, 39.1, 52.6, 57.6, 58.4, 68.0, 73.4, 126.4, 126.6, 127.6, 128.3, 128.4, 128.8, 129.3, 137.0, 139.3, 140.8, 155.2, 174.9; IR ($CHCl_3$): 3492, 2978, 1786, 1754, 1223, 760, 701 cm^{-1}. HRMS calcd for $C_{23}H_{28}N_2O_4$: 397.2127. Found: 397.2124. Anal. Calcd for $C_{23}H_{28}N_2O_4$: C, 69.67; H, 7.12; N, 7.07. Found: C, 69.66; H, 6.94; N 7.10.

4.7. (4*S*,5*S*)-4-Benzyl-5-benzyloxymethyl-1,3-oxazolidin-2-one 11

In a 50 mL round-bottomed flask were placed aldol adduct **9e** (0.180 g, 0.35 mmol), THF (8 mL), and 6 M H_2SO_4

(6 mL). The mixture was heated at reflux and reacted for a period of 48 h. The mixture was cooled to 0 °C and made basic by the addition of a saturated aqueous solution of sodium bicarbonate. The solution was extracted with ethyl acetate (2 × 25 mL) and the organic portion washed with a saturated brine solution (50 mL), dried over $MgSO_4$, and the solvents were removed via rotary evaporation to yield the oxadiazinanone and its corresponding β-hydrazino-alcohol. The aqueous layer was acidified to pH 1 with ~3 M HCl and extracted with ethyl acetate (2 × 25 mL). The combined extracts were washed with a saturated brine solution, dried over $MgSO_4$ and concentrated under reduced pressure to afford 0.071 g of the β-hydroxycarboxylic acid **10** as a white solid (68% recovery). The acid was immediately taken on to the Curtius rearrangement. In a flame-dried nitrogen-purged 5 mL round-bottomed flask equipped with a condenser was placed **10** (0.135 g, 0.45 mmol) resourced from multiple hydrolysis reactions, anhydrous toluene (1.0 mL) and diphenylphosphoryl azide (0.12 mL, 0.54 mmol) followed by the addition of triethylamine (0.08 mL, 0.59 mmol). The mixture was heated at reflux for a period of 4 h. The reaction mixture was cooled to room temperature and quenched with a saturated solution of sodium bicarbonate (50 mL). The organic portion was extracted with ethyl acetate (2 × 25 mL), washed with a saturated brine solution (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/hexanes, 3:2) to afford 0.084 g as an oil representing an isolated yield of 63%. ^{1}H NMR ($CDCl_3$): δ 2.70 (m, 1H), 2.99 (dd, $J = 13.2$, 2.9 Hz, 1H), 3.81 (d, $J = 5.9$ Hz, 2H), 4.06–4.12 (m, 1H), 4.63 (*AB* spin system, benzyloxy –OCH_2–, $\Delta\nu = 26.4$ Hz, $J = 2.6$ Hz, 2H), 4.76 (s, 1H), 4.85 (q, $J = 6.8$ Hz, 1H), 7.15–7.40 (m, 10H). ^{13}C NMR ($CDCl_3$): 36.0, 56.0, 67.2, 73.8, 77.2, 127.2, 127.9, 128.0, 128.6, 128.9, 129.1, 136.7, 137.2, 158.0. HRMS calcd for $C_{18}H_{19}NO_3$: 297.1365. Found: 297.1358. These data matched the reported literature data from Ghosh et al.[14]

4.8. (2*S*,3*S*)-Methyl 3-hydroxy-2-methyl-3-phenylpropanoate 14

In a 100 mL round-bottomed flask was placed oxadiazinanone adduct **13** dissolved in 8.5 mL of THF and 6 mL of 6 M H_2SO_4. The mixture was heated at reflux for 48 h and quenched with 5 M KOH. The aqueous layer was acidified with HCl and extracted with EtOAc, washed with brine, and dried over $MgSO_4$. The solvent was evaporated in vacuo, to afford 0.326 g of the carboxylic acid. The acid was directly esterified. In a 50 mL round-bottomed flask was placed the carboxylic acid (0.326 g, 1.8 mmol) dissolved in 2 mL of THF and 2 mL of methanol. To this stirred mixture was added trimethylsilyldiazomethane (3.6 mL, 7.2 mmol). The reaction was allowed to stir overnight and was then quenched with a saturated aqueous solution of $NaHCO_3$, extracted with EtOAc, dried over $MgSO_4$, and the solvent was removed in vacuo. The purified ester product was isolated by chromatography as an oil (0.150 g). Yield: 59%. $[\alpha]_D^{29} = -11.6$ (*c* 0.74, $CHCl_3$); $R_f = 0.15$ (hexanes/EtOAc, 7:3). ^{1}H NMR ($CDCl_3$): δ, 1.13 (d, $J = 7.0$ Hz, 3H), 2.76–2.82 (m, 1H), 3.62 (s, 3H), 5.10 (d, $J = 4.3$ Hz 1H), 7.24–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$): δ, 10.7, 46.3, 51.9, 73.6, 125.9, 127.5, 128.2, 141.4, 176.2; IR ($CHCl_3$): 3477, 2949, 1732, 1198, 1172, 770, 702 cm^{-1}.

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