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Towards the development of oxadiazinanones as chiral auxiliaries: synthesis and application of N_3-haloacetyloxadiazinanones

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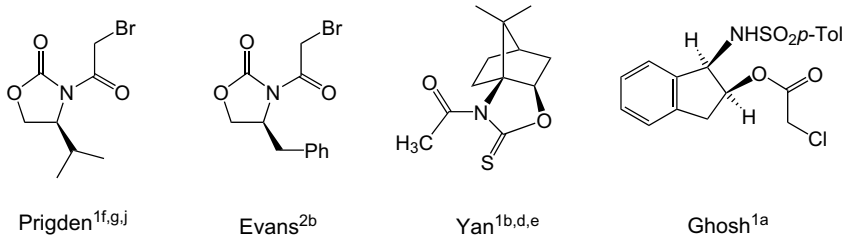
Abstract—Oxadiazinanones derived from (1*R*,2*S*)-ephedrine and (1*R*,2*S*)-norephedrine were employed in the asymmetric α-halo aldol reaction. The optimized yields and diastereoselectivities for the ephedrine based oxadiazinanone aldol reaction ranged from fair to good. The ephedrine based aldol adducts were hydrolyzed to afford the α-bromo-β-hydroxycarboxylic acids. The absolute stereochemistry and enantiomeric purity of these products were determined by chiral HPLC and specific rotation measurements.

1. Introduction

There has been considerable interest in the synthesis of enantiomerically enriched substrates, which contain the α-halo-β-hydroxycarboxyl functional group.[1] This is primarily due to their utility as versatile intermediates (e.g., conversion to optically active α,β-epoxy carboxyl systems)[2] in the synthesis of a wide variety of natural products.[3–7] In 1984, Pridgen et al.[1f,g,j] conducted seminal studies in this area by using *N*-haloacetyloxazolidinones as templates for conducting asymmetric aldol reactions (Chart 1). Later in 1999 and 2000, Yan et al. successfully employed a camphor based oxazolidine-2-thione in a related bromination–aldolization process.[1b,d,e] More recently in 2004, Ghosh and Kim[1a] applied the α-chloroacetate ester of *cis*-1-tosylamido-2-indanol in the synthesis of α-halo-β-hydroxy esters.

We previously demonstrated that (1*R*,2*S*)-ephedrine and (1*R*,2*S*)-norephedrine based oxadiazinanones[8] could be employed as 'chiral relay' auxiliaries in the asymmetric aldol addition reaction. It has been determined that stereochemical induction in the oxadiazinanone mediated aldol reaction is not the direct result of the asymmetry of the *Ephedra* component. Rather, the asymmetric induction is transmitted via an intramolecular 'chiral relay' from the ephedrine based substituents at the C_5 and C_6 positions of the ring system to the stereogenic N_4-nitrogen



Prigden[1f,g,j] Evans[2b] Yan[1b,d,e] Ghosh[1a]

Chart 1.

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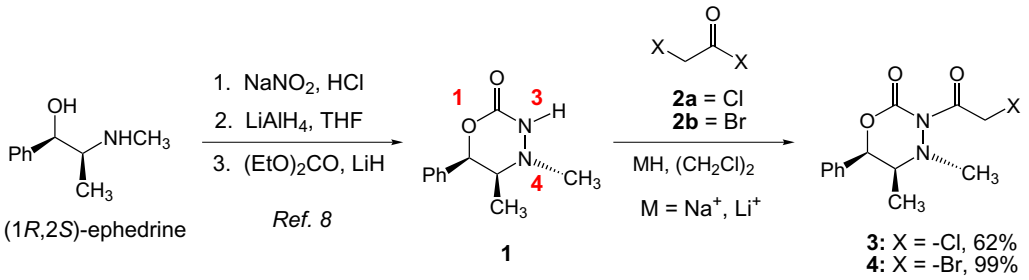


Scheme 1. Synthesis of oxadiazinanones **3** and **4**.

(Scheme 1).[9] Based on this work, we became interested in investigating the potential of oxadiazinanones in the α-haloaldol addition reaction. Herein, we report on our efforts to employ α-haloacetyl derivatives (chloro- and bromo-) of an ephedrine based oxadiazinanone in the aldol reaction.

2. Results and discussion

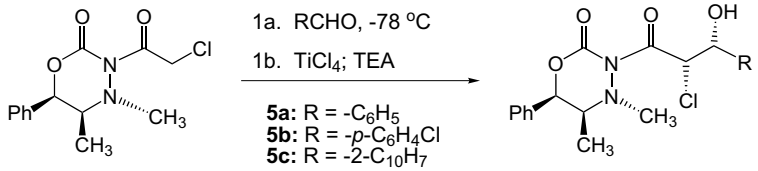
The (1*R*,2*S*)-ephedrine based oxadiazinanone **1** was prepared as previously described by a process of N-nitrosation, reduction to the corresponding β-hydroxyhydrazine, and cyclization with lithium hydride and diethylcarbonate (Scheme 1).[8b,d] The oxadiazinanone was acylated with either chloroacetyl chloride or bromoacetyl bromide to afford oxadiazinanones **3** and **4** in 62% and 99% yield, respectively. These substrates were then evaluated in the asymmetric aldol reaction with a variety of aromatic and aliphatic aldehydes.

We initiated our asymmetric aldol addition studies by first conducting the reactions with N_3-chloroacetyloxadiazinanone **3**. These reaction conditions involved the addition of $TiCl_4$ to a THF solution of oxadiazinanone (~0.33 M), followed by cooling to −78 °C and addition of triethylamine along with the selected aldehyde. These conditions were not satisfactory as the solution would freeze and there was very little product formation and poor stereoselectivity. The reaction conditions were changed so that **3** was dissolved in THF along with an aldehyde and the reaction mixture cooled to −78 °C (Table 1). This mixture was then treated with 2 equiv of titanium tetrachloride followed by triethylamine. The reaction was quenched after 4 h and the product mixtures then analyzed by ^{1}H NMR spectroscopy and HPLC. The observed diastereoselectivities were low and the purified yields ranged from low to fair (Table 1).

The major diastereomer was tentatively assigned as the *syn*-stereoisomer based on our previous studies of the asymmetric aldol reactions of oxadiazinanones, wherein the absolute stereochemistry of the aldol fragment was unambiguously established by X-ray crystallography.[8a,c] In addition, the measured coupling constants for the vicinal protons of the aldol fragment were found to be 5.5 Hz. These values suggested that the stereochemical relationship between the two protons was *syn* as the values were in the accepted range ($J_{syn} \approx 3$–6 Hz) for *syn*-aldol products.[10]

Aromatic aldehydes were reactive in this process while aliphatic aldehydes gave complex reaction mixtures that included significant deacylation of the oxadiazinanone auxiliary. The formation of a discrete enolate came into question and so a deuterium incorporation test was performed (Scheme 2).[11] Oxadiazinanone **3** was dissolved in THF and treated with $TiCl_4$ at 0 °C and allowed to stir for 15 min (Scheme 2). Triethylamine was then added and after 15 min D_2O. Oxadiazinanone **7** was obtained in 92% yield after column chromatography and deuterium incorporation (ca. 90%) at the α-position of the chloroacetyl group was confirmed by both ^{1}H and ^{13}C NMR spectroscopy.

Table 1. Asymmetric aldol reaction of oxadiazinanone **3**

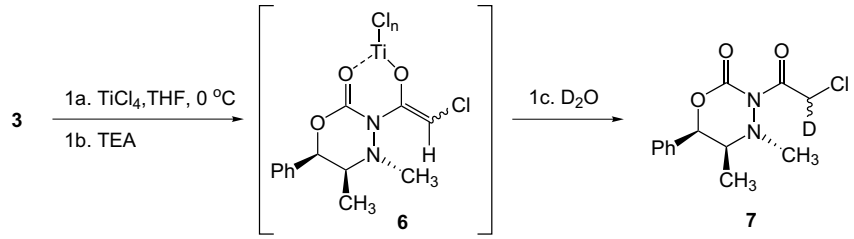


3 **5a-c**

Entry	RCHO	Adduct	Yield (%)[a]	dr[b]
1	C_6H_5CHO	**5a**	54	62:38
2	*p*-ClC_6H_4CHO	**5b**	49	74:26
3	2-$C_{10}H_7CHO$	**5c**	26	59:41

[a] Purified yield after column chromatography.

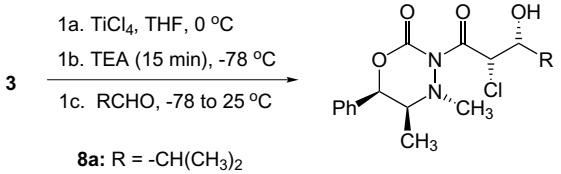
[b] All crude diastereomeric ratios were measured by HPLC using a Shimadzu SCL-10AVP system with a Dynamax Si-100 Å column (3:2, hexanes–ethyl acetate, flow rate = 1.0 mL/min). Diastereoselectivities are represented as major diastereomer: ∑ all other diastereomers.



Scheme 2. Deuterium incorporation of oxadiazinanone **3**.

Unfortunately, the deuteration conditions were not optimal for use of the aliphatic aldehydes in the aldol addition reaction. The final optimized conditions involved dissolving oxadiazinanone **3** in THF, followed by the addition of $TiCl_4$ at 0 °C, with a 15 min induction period. Triethylamine was then added, and after 15 min the reaction mixture was cooled to −78 °C. After 10 min, the appropriate aliphatic aldehyde was added. We were gratified to learn that these reaction conditions led to the formation of aldol adducts **8a** and **8b** in 34% and 82% yields, respectively (Table 2). The superior yield of **8b** [R = –C(CH$_3$)$_3$] can be attributed to the absence of an α-proton in the aldehyde. The diastereoselectivities observed for these two reactions were slightly improved as compared to the diastereoselectivities associated with aldol adducts **5a**–**c**. Again, the stereochemistry was tentatively assigned as the *syn*-stereochemistry.

Table 2. Asymmetric aldol reaction of oxadiazinanone **3** with aliphatic aldehydes



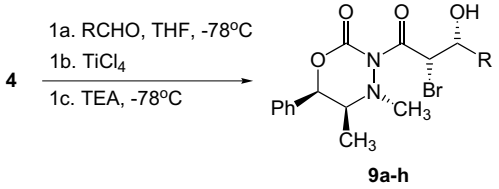
Entry	RCHO	Adduct	Yield (%)[a]	dr[b]
1	$(CH_3)_2CHCHO$	**8a**	34	83:17
2	$(CH_3)_3CCHO$	**8b**	82	82:18

[a] Purified yield after column chromatography.

[b] All crude diastereomeric ratios were measured by HPLC using a Shimadzu SCL-10AVP system with a Dynamax Si-100 Å column (3:2, hexanes–ethyl acetate, flow rate = 1.0 mL/min). Diastereoselectivities are represented as major diastereomer: ∑ all other diastereomers.

The asymmetric aldol reactions of the N_3-chloroacetyloxadiazinanone **3** ultimately yielded results that were not satisfactory for synthetic purposes. Thus, efforts were made to investigate the usefulness of the N_3-bromoacetyloxadiazinanone **4**. The acylated heterocycle was combined with an aromatic aldehyde in THF, cooled to −78 °C, treated with titanium tetrachloride (1.05 equiv) and after 15 min, was finally treated with triethylamine. This process afforded aldol adducts **9a**–**h** (Table 3). The diastereomeric ratios obtained for these aldol adducts were superior to those for the α-chloroaldol reactions, but were still not optimal. Increasing the number of equivalents of $TiCl_4$ to 2 equiv afforded significantly improved chemical yields and a slight improvement in the diastereoselectivities. The origin of the increased diastereoselectivity is unknown. Interestingly, entry 11 had a very low diastereoselectivity. The *syn*-diastereomer was presumed to be the major diastereomer; however, the sum of the other diastereomers was greater. This anomalous result was attributed to the steric environment of the aldehyde.

Table 3. Asymmetric aldol reactions of oxadiazinanone **4**

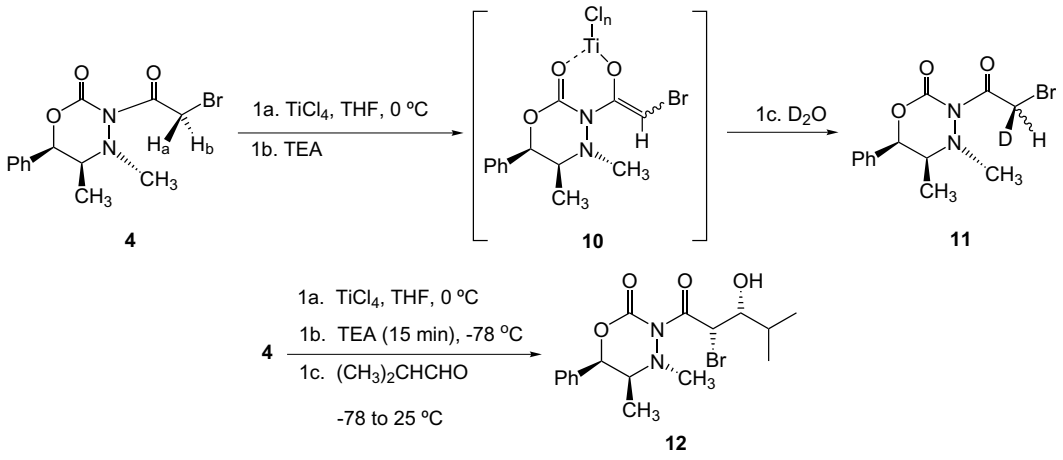


Entry	RCHO	$TiCl_4$ (equiv)	Adduct	Yield (%)[a]	dr[b]
1	C_6H_5CHO	1	**9a**	44	86:14
2	C_6H_5CHO	2	**9a**	72	91:9
3	*p*-$CH_3OC_6H_4CHO$	1	**9b**	49	85:15
4	*p*-ClC_6H_4CHO	1	**9c**	72	77:23
5	*p*-ClC_6H_4CHO	2	**9c**	83	83:17
6	2-$C_{10}H_7CHO$	1	**9d**	36	87:13
7	2-$C_{10}H_7CHO$	2	**9d**	36	77:23
8	*m*-$CH_3C_6H_4CHO$	1	**9e**	30	89:11
9	*p*-$O_2NC_6H_4CHO$	2	**9f**	85	86:14
10	*p*-NCC_6H_4CHO	2	**9g**	90	82:18
11	*p*-$C_6H_5CH_2OC_6H_4CHO$	2	**9h**	28	42:58

[a] Purified yield after column chromatography on silica gel or recrystallization.

[b] All crude diastereomeric ratios were measured by HPLC using a Shimadzu SCL-10AVP system with a Dynamax Si-100 Å column (60:40, hexanes–ethyl acetate, flow rate = 1.0 mL/min). Diastereoselectivities are represented as major diastereomer: ∑ all other diastereomers.

Even though there was an improvement in the yield and diastereoselectivity of the aldol addition reactions of the N_3-bromoacetyloxadiazinanone **4** with the aromatic aldehydes when compared to the N_3-chloroacetyloxadiazinanones **3**, aliphatic aldehydes still gave little carbon–carbon bond formation and poor diastereoselectivity. A deuteration study was conducted to determine if the formation of a discrete enolate might lead to a superior result (Scheme 3).[8] The reaction conditions involved dissolving oxadiazinanone **4** in THF and treating with $TiCl_4$ at 0 °C for 15 min. The reaction mixture was then treated with triethylamine and after 15 min, the reaction mixture was cooled to −78 °C. Finally, D_2O was added and the solution warmed to 25 °C. Deuterium incorporation (ca. 90%) was



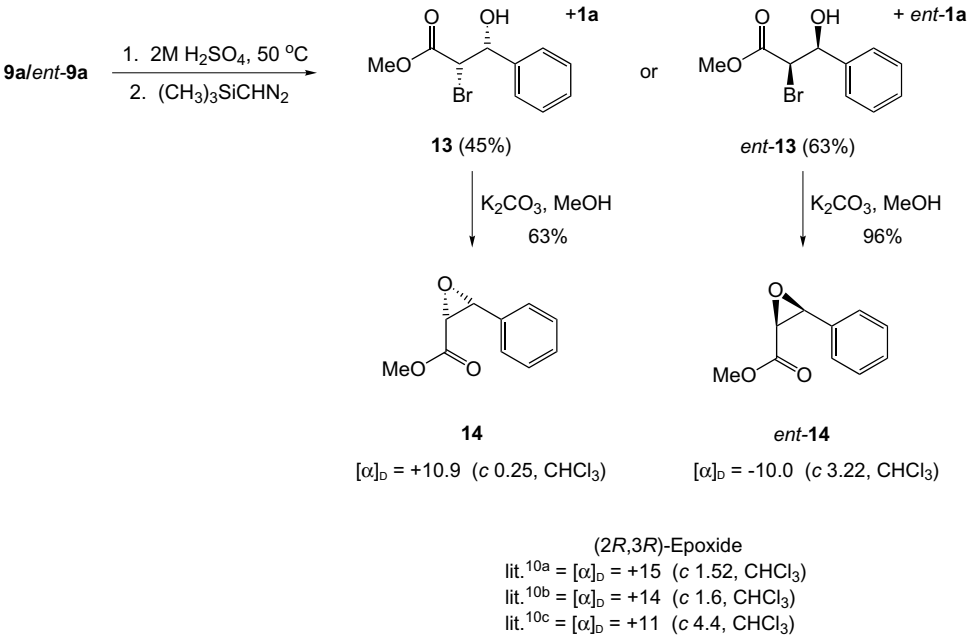
Scheme 3. Deuteration and aliphatic aldol reaction of oxadiazinanone **4**.

confirmed by NMR spectroscopy and the product was isolated by chromatography in 82% yield.

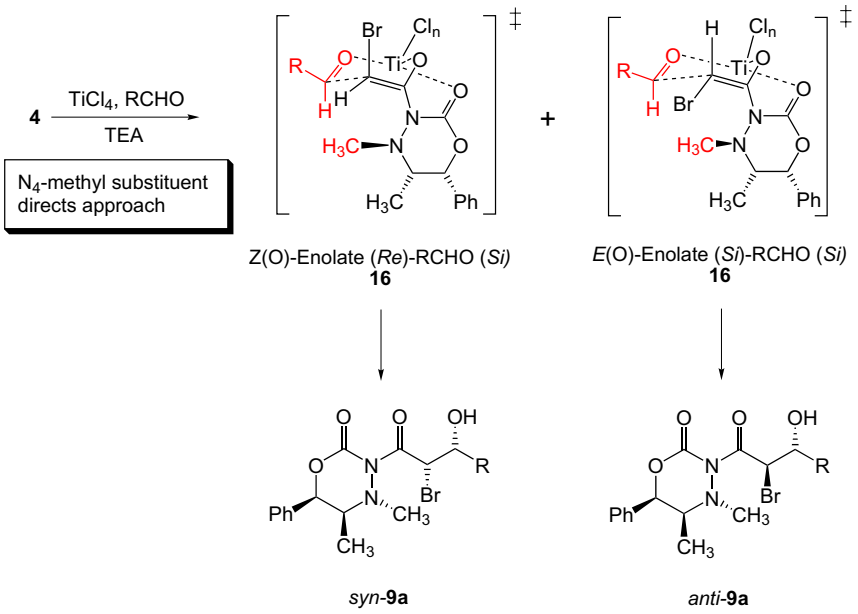
Following the conditions established for the deuterium incorporation, a series of aldol addition reactions with various aliphatic aldehydes was conducted. The N_4-bromoacetyloxadiazinanone **4** was dissolved in THF and treated with $TiCl_4$ at 0 °C for 15 min. Triethylamine was then added, and after 15 min, the reaction mixture was cooled to −78 °C. After 10 min, isobutyraldehyde was added. This process led to the formation and isolation of aldol adduct **12** in 84% yield and a diastereoselectivity of 78:22 favoring the presumed major diastereomer, tentatively assigned as the *syn*-diastereomer.

We became interested in determining the absolute stereochemistry of the aldol fragment and its corresponding enantiomeric purity once cleaved from the oxadiazinone auxiliary. Oxadiazinanone aldol adduct **9a** was used for the determination of the stereochemical outcome of the asymmetric aldol reaction and success of the subsequent hydrolysis to obtain the aldol component. The enantiomer of **9a** (*ent*-**9a**) was also prepared for this study by using (1*S*,2*R*)-ephedrine as the starting material and following the synthetic pathway outlined in Scheme 1 and Table 1.

The enantiomeric aldol adducts **9a** and *ent*-**9a** were both recrystallized to a diastereomeric purity of 19:1 as determined by ^1H NMR spectroscopy. The adducts were then hydrolyzed with 2 M H_2SO_4 and the resultant α-bromo-β-hydroxyacids[12a] were subsequently esterified with trimethylsilyldiazomethane[12b,c] to afford the expected methyl esters **13** and *ent*-**13** in 45% and 63% overall yield, respectively (Scheme 4). The corresponding oxadiazinanones, **1a**



Scheme 4. Stereospecific formation of epoxides **14** and *ent*-**14**.



Scheme 5. Proposed transition states for the aldol addition reaction of **4**.

and *ent*-**1a** could be recovered in ca. 80% crude yield but were not reused. Chiral stationary phase (CSP) HPLC analysis revealed that methyl ester **13** was obtained in ⩾98% ee and *ent*-**13** was obtained in ⩾98% ee.[13] Methyl ester **13** had a specific rotation of $[\alpha]_D = -27.7$ (*c* 082, $CHCl_3$) while methyl ester *ent*-**13** had a specific rotation of $[\alpha]_D = +29.1$ (*c* 0.42, $CHCl_3$).[14] Methyl esters **13** and *ent*-**13** were converted into the corresponding epoxides **14** and *ent*-**14** by treatment with potassium carbonate in methanol. Each of the epoxides **14** and *ent*-**14** were determined to be present in greater than 98% ee by CSP HPLC analysis. Correlation with known literature values[15,16] for the specific rotation of (+)-methyl (2*R*,3*R*)-phenylglycidate confirmed the earlier tentative assignment of aldol adducts **9a**–**h**.

With regard to the observed diastereoselectivity, a Zimmerman–Traxler transition state involving a chair like intermediate (Scheme 5) was proposed.[8a,b,17,18] The presence of the two enolates would lead to the formation of both *syn*- and *anti*-aldol adducts that are observed.

3. Conclusion

In conclusion, we have demonstrated that N_3-haloacetyl-N_4-methyloxadiazinanones may be employed in the asymmetric α-haloaldol reaction, although to limited effect. The stereochemistry of the aldol fragment was unambiguously determined and it was established that the major product was the *syn*-diastereomer. The low to fair diastereoselectivities that were observed were primarily attributed to the formation of *Z*(O)- and *E*(O)-enolates of the acylated oxadiazinanones. These results observed were not as successful as those generated by Yan et al. whose camphor based oxazolidine-2-thione (Chart 1) gave reported diastereoselectivities greater than 99:1 favoring the *syn*-diastereomer.[1d,e] Thus, efforts are currently underway to improve the diastereoselectivity of the α-haloaldol reaction of oxadiazinanones by conducting investigations directed toward the stereoelectronic tuning of the oxadiazinanone chiral auxiliary.

4. Experimental

4.1. General remarks

Tetrahydrofuran (THF) was distilled from a potassium/sodium alloy with benzophenone ketyl. Methylene chloride and 1,2-dichloroethane were distilled from calcium hydride. All reactions were run under a nitrogen atmosphere. Unless otherwise noted, all ^1H and ^{13}C $\{^1H\}$ NMR spectra were recorded in $CDCl_3$ using an NMR spectrometer 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 the internal standard ($\delta = 0$ ppm). Infrared spectra are reported in reciprocal centimeters (cm^{-1}) and are measured as either a neat liquid or as a KBr window. Melting points were recorded on a Mel-Temp apparatus and are uncorrected.

4.2. General procedure for the preparation of acylated oxadiazinanones 3 and 4

In a flame-dried, nitrogen purged 250 mL round-bottomed flask equipped with a condenser were placed the (1*R*,2*S*)-ephedrine based oxadiazinanone (7.0 g, 34 mmol), freshly distilled dichloroethane (34 mL), and the appropriate acyl halide (41 mmol; chloroacetyl chloride for **3** and bromoacetyl bromide for **4**). The reaction mixture was heated at reflux and lithium hydride (0.28 g, 36 mmol) was added. The reaction was allowed to stir overnight and 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 brine solution, dried over $MgSO_4$, and the solvent was removed via rotary evaporation.

4.2.1. (4*R*,5*S*,6*R*)-3-(2-Chloroacetyl)-4,5-dimethyl-6-phenyl-2*H*-1,3,4-oxadiazinan-2-one 3. The isolated product was purified by column chromatography (hexanes–EtOAc, 60:40, $R_f = 0.28$) to yield **3** (62%) as a yellow oil $[\alpha]_D^{25} = -28.3$ (*c* 0.53, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.89 (d, 3H, $J = 7.0$ Hz), 3.00 (s, 3H), 3.41–3.47 (m, 1H), 4.79 (d, 2H, $J = 1.8$ Hz), 6.07 (d, 1H, $J = 4.4$ Hz), 7.29–7.44 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 12.2, 43.1, 46.0, 56.8, 77.9, 124.7, 128.3, 128.7, 134.9, 148.2, 166.7. IR (neat): 2978, 1783, 1731, 738, 700 cm^{-1}. HRMS calcd for $C_{13}H_{15}ClN_2O_3$: 282.0771. Found: 282.0772.

4.2.2. (4*R*,5*S*,6*R*)-3-(2-Bromoacetyl)-4,5-dimethyl-6-phenyl-2*H*-1,3,4-oxadiazinan-2-one 4. The isolated product was purified by column chromatography (hexanes–EtOAc, 60:40, $R_f = 0.28$) to yield **4** (99%) as a yellow oil $[\alpha]_D^{25} = -19.6$ (*c* 0.58, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.90 (d, 3H, $J = 7.0$ Hz), 3.00 (s, 3H), 3.41–3.48 (m, 1H), 4.51 (d, 1H, $J = 12.8$ Hz), 4.71 (d, 1H, $J = 12.5$ Hz), 6.08 (d, 1H, $J = 4.39$ Hz), 7.29–7.44 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 12.2, 31.9, 42.9, 56.7, 77.9, 124.6, 128.1, 128.5, 134.9, 147.7, 166.3. IR (neat): 2978, 1779, 1728, 738, 700 cm^{-1}. HRMS calcd for $C_{13}H_{15}BrN_2O_3$: 326.0266. Found: 326.0262.

4.3. General procedure for the preparation of aldol adducts 5a–c

In a nitrogen purged 100 mL round-bottomed flask were placed oxadiazinanone **3** (3.54 mmol), freshly distilled THF (10.6 mL, 0.33 M), and the appropriate aldehyde (7.08 mmol). The reaction mixture was then cooled to −78 °C. After stirring for 10 min, titanium tetrachloride (0.86 mL, 7.79 mmol) was added. The titanium tetrachloride was allowed to coordinate for 15 min and then triethylamine (0.98 mL, 7.08 mmol) was added. The reaction was allowed to run for 4 h and then quenched upon the addition of a saturated solution of sodium bicarbonate. The resulting mixture was then extracted with EtOAc (3 × 50 mL), and the extract then washed with a saturated solution of NaCl, dried over $MgSO_4$, and the solvent was removed via rotary evaporation.

4.3.1. (2′*S*,3′*R*,4*R*,5*S*,6*R*)-3-(2-Chloro-3-hydroxy-3-phenylpropanoyl)-4,5-dimethyl-6-phenyl-2*H*-1,3,4-oxadiazinan-2-one 5a. The residual light brown oil was purified by column chromatography on silica gel (hexanes–EtOAc, 60:40, $R_f = 0.22$) to yield **5a** in 54% yield as an oil. Analytical data are reported only for the major diastereomer. $[\alpha]_D^{25} = -20.3$ (*c* 0.48, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.68 (d, 3H, $J = 7.0$ Hz), 2.88 (s, 3H), 3.34–3.38 (m, 1H), 5.34 (d, 1H, $J = 5.5$ Hz), 5.85 (d, 1H, $J = 5.5$ Hz), 6.02 (d, 1H, $J = 4.0$ Hz), 7.20–7.48 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 12.0, 43.3, 56.8, 61.5, 73.5, 78.2, 124.7, 127.0, 127.1, 128.2, 128.3, 128.7, 135.0, 138.4, 147.0, 169.0. IR (neat): 3450, 3016, 1774, 1728, 1214, 1009, 746, 699 cm^{-1}. FAB-HRMS calcd for $C_{20}H_{21}N_2O_4NaCl$ (M^++H): 411.1088. Found: 411.1092.

4.3.2. (2′*S*,3′*R*,4*R*,5*S*,6*R*)-3-[2-Chloro-3-(4-chlorophenyl)-3-hydroxypropanoyl]-4,5-dimethyl-6-phenyl-2*H*-1,3,4-oxadiazinan-2-one 5b. The yellow oil was purified by column chromatography on silica gel (50:50, hexanes–EtOAc, $R_f = 0.20$) to yield **5b** in 49% yield as a yellow oil. $[\alpha]_D^{25} = -17.2$ (*c* 0.31, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.75 (d, 3H, $J = 7.0$ Hz), 2.94 (s, 3H), 3.27 (br s, 1H), 3.37–3.43 (m, 1H), 5.34 (d, 1H, $J = 4.8$ Hz), 5.80 (d, 1H, $J = 4.8$ Hz), 6.05 (d, 1H, $J = 4.8$ Hz), 7.33–7.44 (m, 9H). ^{13}C NMR ($CDCl_3$): δ 12.0, 43.3, 56.8, 61.5, 72.6, 78.3, 124.7, 128.27, 128.3, 128.4, 128.6, 134.0, 134.8, 137.1, 147.2, 168.9. IR (CCl_4): 3436, 2980, 1738, 1723, 1214, 1015, 792, 760 cm^{-1}. FAB-HRMS calcd for $C_{20}H_{21}N_2O_4Cl_2$ (M^++1): 423.0878. Found: 423.0880.

4.3.3. (2′*S*,3′*R*,4*R*,5*S*,6*R*)-3-(2-Chloro-3-hydroxy-3-naphthalen-2-yl-propanoyl)-4,5-dimethyl-6-phenyl-2*H*-1,3,4-oxadiazinan-2-one 5c. The white powder was purified by recrystallization from ethyl acetate and hexanes to yield **5c** in 26% yield as a white powder (hexanes–EtOAc, 60:40, $R_f = 0.23$). Mp = 174–176 °C. $[\alpha]_D^{25} = -30.0$ (*c* 0.33, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.68 (d, 3H, $J = 7.0$ Hz), 2.85 (s, 3H), 3.32–3.38 (m, 2H), 5.52 (d, 1H, $J = 5.5$ Hz), 5.99 (d, 1H, $J = 4.8$ Hz), 5.99 (d, 1H, $J = 3.3$ Hz), 7.21–7.96 (m, 12H). ^{13}C NMR ($CDCl_3$): 12.2, 43.3, 57.2, 61.9, 73.6, 78.4, 124.3, 124.8, 126.27, 126.3, 126.4, 127.6, 128.2, 128.3, 128.4, 128.8, 133.0, 133.2, 135.0, 135.8, 147.3, 169.3. IR (CCl_4): 3489, 3035, 1766, 1690, 1283, 1226, 770 cm^{-1}. FAB-HRMS calcd for $C_{24}H_{23}N_2O_4NaCl$: 461.1244. Found: 461.1246.

4.4. (4*R*,5*S*,6*R*)-3-(2-Chloro-2-deuterioacetyl)-4,5-dimethyl-6-phenyl-2*H*-1,3,4-oxadiazinan-2-one 7

In a 100 mL round-bottomed flask were placed oxadiazinanone **3** (3.54 mmol), THF (10.6 mL, 0.33 M), and titanium tetrachloride (3.72 mmol) at 0 °C and the mixture was allowed to react for 15 min. Triethylamine (7.08 mmol) was then added, and after 15 min the reaction mixture was cooled to −78 °C. The reaction mixture had cooled for 10 min, D_2O was added. The reaction mixture was stirred for 30 min and then quenched by the addition of a saturated solution of sodium bicarbonate. The resulting mixture was then extracted with EtOAc (3 × 50 mL), washed with a saturated aqueous solution of NaCl, dried over $MgSO_4$, and the solvent removed via rotary evaporation. The isolated product was purified by column chromatography (hexanes–EtOAc, 60:40, $R_f = 0.28$) to yield **7** (92%) as a yellow oil. ^1H NMR ($CDCl_3$): δ 0.90 (d, 3H, $J = 5.9$ Hz), 3.02 (s, 3H), 3.45 (br s, 1H), 4.78 (d, 1H, $J = 7.7$ Hz), 6.08 (s, 1H), 7.30–7.44 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 12.3, 43.3, 45.9 (t, 1:1:1, ^{13}C–^2H, $J = 80$ Hz), 57.0, 78.0, 124.8, 128.4, 128.7, 135.0, 148.3, 166.8. IR (neat): 2979, 1785, 1728, 1261, 736, 700 cm^{-1}. FAB-HRMS calcd for $C_{13}H_{14}DN_2O_3NaCl$: 306.0732. Found: 306.0736.

4.5. General procedure for the preparation of aldol adducts 8a,b

In a 100 mL round-bottomed flask were placed oxadiazinanone **3** (3.54 mmol), THF (10.6 mL, 0.33 M), and titanium tetrachloride (3.72 mmol). The reaction mixture was kept at 0 °C for 15 min. Triethylamine (7.08 mmol) was then added, and after 15 min, the reaction mixture was cooled to −78 °C. After the reaction mixture was cooled for 10 min, after which the appropriate aliphatic aldehyde (7.08 mmol) was added. The reaction was allowed to run for 4 h and then quenched upon the addition of a saturated solution of sodium bicarbonate. The resulting mixture was then extracted with EtOAc (3 × 50 mL), washed with a brine solution, dried over $MgSO_4$, and the solvent was removed via rotary evaporation.

4.5.1. (2′*S*,3′*R*,4*R*,5*S*,6*R*)-3-(2-Chloro-3-hydroxy-4-methylpentanoyl)-4,5-dimethyl-6-phenyl-2*H*-1,3,4-oxadiazinan-2-one 8a. The yellow oil was purified by column chromatography on silica gel (hexanes–EtOAc, 55:45, $R_f = 0.16$) to yield **8a** in 34% yield as a yellow oil. $[\alpha]_D^{25} = -31.9$ (*c* 0.25, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.91 (d, 3H, $J = 6.6$ Hz), 1.00 (d, 3H, $J = 6.6$ Hz), 1.10 (d, 3H, $J = 6.6$ Hz), 1.88–1.97 (m, 1H), 2.87 (br s, 1H), 3.02 (s, 3H), 3.44–3.48 (m, 1H), 3.79 (d, 1H, $J = 7.3$ Hz), 5.91 (d, 1H, $J = 1.8$ Hz), 6.10 (d, 1H, $J = 3.3$ Hz), 7.29–7.44 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 12.4, 18.5, 18.7, 31.2, 43.3, 56.9, 60.9, 76.2, 78.3, 124.8, 128.3, 128.7, 135.0, 147.8, 170.0. IR (neat): 3467, 2964, 1775, 1716, 1255, 1139 cm^{-1}. FAB-HRMS calcd for $C_{17}H_{23}N_2O_4NaCl$: 377.1244. Found: 377.1248.

4.5.2. (2′*S*,3′*R*,4*R*,5*S*,6*R*)-3-(2-Chloro-3-hydroxy-4,4-dimethylpentanoyl)-4,5-dimethyl-6-phenyl-2*H*-1,3,4-oxadiazinan-2-one 8b. The yellow oil was purified by column chromatography on silica gel (hexanes–EtOAc, 50:50, $R_f = 0.31$) to yield **8b** as a colorless oil in 82% yield as a mixture of diastereomers and an unknown contaminant that could not be resolved. Only experimental data for the major diastereomer are reported. $[\alpha]_D^{25} = -20.5$ (*c* 0.48, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.90 (d, 3H, $J = 6.6$ Hz), 1.05 (s, 9H), 3.04 (s, 3H), 3.43–3.50 (m, 1H), 3.78–3.84 (m, 1H), 3.89 (br s, 1H), 5.86 (d, 1H, $J = 2.6$ Hz), 5.98 (d, 1H, $J = 2.6$ Hz), 7.28–7.42 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 12.5, 26.6, 35.7, 43.2, 56.9, 57.9, 76.4, 78.5, 124.7, 128.2, 128.6, 135.0, 147.6, 171.1. IR (neat): 3459, 2962, 1760, 1680, 1216, 753 cm^{-1}. FAB-HRMS calcd for $C_{18}H_{25}N_2O_4NaCl$: 391.1401. Found: 391.1397.

4.6. General procedure for the preparation of aldol adducts 9a–h

In a nitrogen purged 100 mL round-bottomed flask were placed oxadiazinanone **4** (0.750 g, 2.31 mmol), freshly distilled THF (6.92 mL, 0.33 M), and the appropriate aldehyde (4.6 mmol). The reaction mixture was then cooled to −78 °C. After stirring for 10 min, titanium tetrachloride (0.56 mL, 5.1 mmol) was added and the reaction mixture stirred for 15 min before the addition of triethylamine (0.64 mL, 4.6 mmol). The reaction was allowed to run for 4 h and then quenched upon the addition of a saturated solution of sodium bicarbonate. The resulting mixture was then extracted with EtOAc (3 × 50 mL), washed with a saturated aqueous solution of NaCl, dried over $MgSO_4$, and the solvent was removed via rotary evaporation.

4.6.1. (2′*S*,3′*R*,4*R*,5*S*,6*R*)-3-(2-Bromo-3-hydroxy-3-phenylpropanoyl)-4,5-dimethyl-6-phenyl-2*H*-1,3,4-oxadiazinan-2-one 9a. The residual off-white powder was purified by recrystallization from ethyl acetate and hexanes (hexanes–EtOAc, 60:40, $R_f = 0.29$) to yield **9a** in 72% yield as an off-white powder. Mp = 152–154 °C. $[\alpha]_D^{25} = -22.7$ (*c* 0.29, CH_3OH). ^1H NMR ($CDCl_3$): δ 0.68 (d, 3H, $J = 7.0$ Hz), 2.88 (s, 3H), 3.34–3.38 (m, 1H), 3.41 (br s, 1H), 5.24 (d, 1H, $J = 5.9$ Hz), 5.92 (d, 1H, $J = 5.9$ Hz), 6.01 (d, 1H, $J = 4.8$ Hz), 7.22–7.47 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 12.2, 43.2, 52.3, 57.1, 73.0, 78.4, 124.8, 127.0, 127.2, 128.3, 128.4, 128.7, 135.0, 138.5, 147.0, 170.0. IR (CCl_4): 3503, 3039, 1766, 1690, 1277, 1086, 768, 701 cm^{-1}. FAB-HRMS calcd for $C_{20}H_{21}N_2O_4NaBr$: 455.0582. Found: 455.0588.

4.6.2. (2′*S*,3′*R*,4*R*,5*S*,6*R*)-3-[2-Bromo-3-hydroxy-3-(4-methoxyphenyl)propanoyl]-4,5-dimethyl-6-phenyl-2*H*-1,3,4-oxadiazinan-2-one 9b. The yellow oil was purified by column chromatography on silica gel (hexanes–EtOAc, 50:50, $R_f = 0.35$) to yield **9b** in 49% yield as a yellow oil. $[\alpha]_D^{25} = -16.5$ (*c* 0.53, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.67 (d, 3H, $J = 7.0$ Hz), 2.87 (s, 3H), 3.34–3.38 (m, 1H), 3.79 (s, 3H), 5.20 (d, 1H, $J = 6.6$ Hz), 5.89 (d, 1H, $J = 6.2$ Hz), 6.01 (d, 1H, $J = 4.4$ Hz), 6.86 (d, 4H, $J = 8.8$ Hz), 7.22–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 12.2, 43.2, 52.2, 55.2, 57.0, 72.8, 78.3, 113.7, 124.8, 128.3, 128.34, 128.7, 130.5, 135.0, 147.0, 159.6, 170.0. IR (neat): 3464, 2936, 1770, 1732, 1251 cm^{-1}. FAB-HRMS calcd for $C_{21}H_{23}N_2O_5NaBr$: 485.0688. Found: 485.0685.

4.6.3. (2′*S*,3′*R*,4*R*,5*S*,6*R*)-3-[2-Bromo-3-hydroxy-3-(4-chlorophenyl)propanoyl]-4,5-dimethyl-6-phenyl-2*H*-1,3,4-oxadiazinan-2-one 9c. The yellow oil was purified by column chromatography on silica gel (hexanes–EtOAc, 50:50, $R_f = 0.28$) to yield **9c** in 83% yield as a white powder. Mp = 141–143 °C. $[\alpha]_D^{25} = -27.4$ (*c* 0.49, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.75 (d, 3H, $J = 7.0$ Hz), 2.93 (s, 3H), 3.37–3.43 (m, 1H), 3.57 (br s, 1H), 5.22 (d, 1H, $J = 5.1$ Hz), 5.88 (d, 1H, $J = 5.1$ Hz), 6.04 (d, 1H, $J = 4.4$ Hz), 7.23–7.42 (m, 9H). ^{13}C NMR ($CDCl_3$): δ 12.4, 43.3, 52.3, 57.1, 72.2, 78.5, 124.8, 128.36, 128.4, 128.5, 128.8, 134.1, 134.9, 137.1, 147.1, 169.9. IR (CCl_4): 3488, 3033, 1756, 1685, 1216, 1080, 762, 699 cm^{-1}. FAB-HRMS calcd for $C_{20}H_{20}N_2O_4NaBrCl$: 489.0193. Found: 489.0196.

4.6.4. (2′*S*,3′*R*,4*R*,5*S*,6*R*)-3-(2-Bromo-3-hydroxy-3-naphthalen-2-yl-propanoyl)-4,5-dimethyl-6-phenyl-2*H*-1,3,4-oxadiazinan-2-one 9d. The white powder was purified by recrystallization from ethyl acetate and hexanes to yield the title compound in 36% yield as a white powder. Mp = 176–177 °C. $[\alpha]_D^{25} = -27.4$ (*c* 0.32, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.68 (d, 3H, $J = 7.0$ Hz), 2.85 (s, 3H), 3.32–3.38 (m, 1H), 3.53 (br s, 1H), 5.41 (d, 1H, $J = 5.5$ Hz), 5.98 (d, 1H, $J = 4.4$ Hz), 6.06 (d, 1H,

$J = 5.5$ Hz), 7.20–7.96 (m, 12H). ^{13}C NMR ($CDCl_3$): δ 12.3, 43.3, 52.5, 57.2, 73.1, 78.4, 124.3, 124.8, 126.2, 126.3, 126.5, 127.6, 128.2, 128.3, 128.4, 128.8, 133.1, 133.2, 135.0, 136.0, 147.2, 170.0. IR (CCl_4): 3492, 3036, 1761, 1688, 1278, 1226, 861, 786 cm^{-1}. Anal. Calcd for $C_{24}H_{23}BrN_2O_4$: C, 59.64; H, 4.80; N, 5.80. Found: C, 59.47; H, 4.75; N, 5.76. FAB-HRMS calcd for $C_{24}H_{23}N_2O_4NaBr$: 505.0739. Found: 505.0740.

4.6.5. (2′*S*,3′*R*,4*R*,5*S*,6*R*)-3-(2-Bromo-3-hydroxy-3-*m*-tolylpropanoyl)-4,5-dimethyl-6-phenyl-2*H*-1,3,4-oxadiazinan-2-one 9e. The yellow oil was purified by column chromatography on silica gel (hexanes–EtOAc, 60:40, $R_f = 0.28$) to yield **9e** in 30% yield as a light yellow oil. $[\alpha]_D^{25} = -19.6$ (*c* 0.30, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.70 (d, 3H, $J = 6.8$ Hz), 2.34 (s, 3H), 2.90 (s, 3H), 3.35–3.39 (m, 2H), 5.21 (d, 1H, $J = 5.9$ Hz), 5.92 (d, 1H, $J = 5.9$ Hz), 6.02 (d, 1H, $J = 4.8$ Hz), 7.10–7.41 (m, 9H). ^{13}C NMR ($CDCl_3$): δ 12.3, 21.4, 43.3, 52.5, 57.2, 73.1, 78.4, 124.1, 124.8, 127.6, 128.36, 128.38, 128.8, 129.2, 133.1, 138.1, 138.4, 147.0, 170.0. IR (CCl_4): 3465, 2978, 1774, 1720, 742, 701 cm^{-1}. FAB-HRMS calcd for $C_{21}H_{23}N_2O_4NaBr$: 469.0739. Found: 469.0744.

4.6.6. (2′*S*,3′*R*,4*R*,5*S*,6*R*)-3-[2-Bromo-3-hydroxy-3-(4-nitrophenyl)propanoyl]-4,5-dimethyl-6-phenyl-2*H*-1,3,4-oxadiazinan-2-one 9f. The yellow oil was purified by column chromatography on silica gel (hexanes–EtOAc, 50:50, $R_f = 0.22$) to yield **9f** in 85% yield as a light yellow oil. $[\alpha]_D^{25} = -23.2$ (*c* 0.38, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.79 (d, 3H, $J = 7.0$ Hz), 3.00 (s, 3H), 3.43–3.50 (m, 1H), 4.14 (br s, 1H), 5.37 (d, 1H, $J = 4.4$ Hz), 5.94 (d, 1H, $J = 4.4$ Hz), 6.09 (d, 1H, $J = 4.4$ Hz), 7.24–7.40 (m, 5H), 7.66 (d, 2H, $J = 8.8$ Hz), 8.18 (d, 2H, $J = 8.8$ Hz). ^{13}C NMR ($CDCl_3$): δ 12.4, 43.2, 51.9, 57.0, 71.6, 78.6, 123.3, 124.7, 127.7, 128.3, 128.6, 134.7, 146.1, 147.2, 147.5, 169.9. IR (CCl_4): 3479, 3026, 1738, 1732, 1216, 792, 698 cm^{-1}. FAB-HRMS calcd for $C_{20}H_{21}N_3O_6Br$ (M^++1): 478.0614. Found: 478.0623.

4.6.7. (2′*S*,3′*R*,4*R*,5*S*,6*R*)-3-[2-Bromo-3-(4-cyanophenyl)-3-hydroxypropanoyl]-4,5-dimethyl-6-phenyl-2*H*-1,3,4-oxadiazinan-2-one 9g. The yellow oil was purified by column chromatography on silica gel (hexanes–EtOAc, 40:60, $R_f = 0.22$) to yield **9g** in 90% yield as a yellow oil. $[\alpha]_D^{25} = -16.5$ (*c* 0.40, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.72 (d, 3H, $J = 6.6$ Hz), 3.00 (s, 3H), 3.43–3.45 (m, 1H), 4.17 (br s, 1H), 5.32 (d, 1H, $J = 4.0$ Hz), 5.90 (d, 1H, $J = 4.8$ Hz), 6.07 (d, 1H, $J = 6.4$ Hz), 7.23–7.40 (m, 5H), 7.60 (s, 4H). ^{13}C NMR ($CDCl_3$): δ 12.1, 43.1, 51.6, 56.7, 71.7, 78.4, 111.5, 118.4, 124.6, 127.5, 128.2, 128.5, 131.8, 134.6, 144.2, 147.0, 169.6. IR (neat): 3468, 3020, 1773, 1716, 1214, 754, 700 cm^{-1}. FAB-HRMS calcd for $C_{21}H_{21}N_3O_4Br$ (M^++1): 458.0715. Found: 458.0715.

4.6.8. (2′*S*,3′*R*,4*R*,5*S*,6*R*)-3-[2-Bromo-3-hydroxy-3-(4-benzyloxyphenyl)propanoyl]-4,5-dimethyl-6-phenyl-2*H*-1,3,4-oxadiazinan-2-one 9h. The white powder was purified by recrystallization from ethyl acetate and hexanes (hexanes–EtOAc, 50:50, $R_f = 0.33$) to yield **9h** in 28% yield as an off-white powder. Mp = 146–147 °C; $[\alpha]_D^{25} = -16.8$ (*c* 0.27, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.66 (d, 3H, $J = 7.0$ Hz), 2.86 (s, 3H), 3.22 (br s, 1H), 3.32–3.39 (m, 1H), 5.05 (s, 2H), 5.20 (d, 1H, $J = 6.2$ Hz), 5.88 (d, 1H, $J = 6.6$ Hz), 6.00 (d, 1H, $J = 4.8$ Hz), 6.92 (s, 2H), 6.95 (s, 2H), 7.23–7.42 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 12.3, 43.2, 52.3, 57.1, 69.9, 72.9, 78.4, 114.8, 124.8, 127.3, 127.9, 128.36, 128.45, 128.5, 128.8, 130.8, 135.2, 136.8, 147.0, 158.8, 169.6. IR (neat): 3517, 3047, 1768, 1694, 1277, 1218, 758, 702 cm^{-1}. Anal. Calcd for $C_{27}H_{27}BrN_2O_5$: C, 60.12; H, 5.05; N, 5.19. Found: C, 59.73; H, 5.00; N, 5.10. FAB-HRMS calcd for $C_{27}H_{28}N_2O_5Br$ (M^++1): 539.1182. Found: 539.1171.

4.7. (4*R*,5*S*,6*R*)-3-(2-Bromo-2-deuterioacetyl)-4,5-dimethyl-6-phenyl-2*H*-1,3,4-oxadiazinan-2-one 11

In a nitrogen purged 100 mL round-bottomed flask were placed oxadiazinanone **4** (3.07 mmol), THF (9.21 mL, 0.33 M), and titanium tetrachloride (3.22 mmol) and the reaction mixture was kept at 0 °C for 15 min. Triethylamine (6.14 mmol) was then added, and after 15 min the reaction mixture was cooled to −78 °C. After the reaction mixture had cooled for 10 min, D_2O was added. The reaction mixture was allowed to stir for 30 min and then a saturated solution of sodium bicarbonate was added. The resulting mixture was then extracted with EtOAc (3×50 mL), washed with brine solution, dried over $MgSO_4$, and the solvent removed via rotary evaporation. The isolated product was purified by column chromatography (hexanes–EtOAc, 60:40, $R_f = 0.28$) to yield **11** (82%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 0.90 (d, 3H, $J = 7.0$ Hz), 3.00 (s, 3H), 3.41–3.48 (m, 1H), 4.49 (br s, 1H), 4.69 (br s, 1H), 6.08 (d, 1H, $J = 4.4$ Hz), 7.29–7.44 (m, 5H). ^{13}C NMR ($CDCl_3$): 12.4, 31.1 (t, 1:1:1, ^{13}C–^{2}H, $J = 80$ Hz), 31.3, 43.3, 57.1, 78.2, 124.9, 128.3, 128.7, 135.1, 148.1, 166.6. IR (neat): 2982, 1782, 1724, 1256, 738, 700 cm^{-1}. FAB-HRMS calcd for $C_{13}H_{14}DN_2O_3NaBr$: 350.0227. Found: 350.0226.

4.8. (2′*S*,3′*R*,4*R*,5*S*,6*R*)-3-(2-Bromo-3-hydroxy-4-methylpentanoyl)-4,5-dimethyl-6-phenyl-2*H*-1,3,4-oxadiazin-2-one 12

In a nitrogen purged 100 mL round-bottomed flask were placed oxadiazinanone **4** (3.07 mmol), THF (9.21 mL, 0.33 M), and titanium tetrachloride (3.22 mmol) at 0 °C for 15 min. Triethylamine (6.14 mmol) was then added, and after 15 min the reaction mixture was cooled to −78 °C. After the reaction mixture had cooled for 10 min, isobutyraldehyde (6.14 mmol) was added. The reaction was allowed to run for 4 h and then quenched upon the addition of a saturated solution of sodium bicarbonate. The resulting mixture was then extracted with EtOAc (3×50 mL), and the extract washed with a saturated aqueous solution of NaCl, dried over $MgSO_4$, and the solvent removed via rotary evaporation. The residual yellow oil was purified by column chromatography on silica gel (hexanes–EtOAc, 60:40, $R_f = 0.20$) to yield the aldol product in 84% yield as a yellow oil. $[\alpha]_D^{25} = -25.6$ (*c* 0.30, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.96 (d, 3H, $J = 7.3$ Hz), 0.96 (d, 3H, $J = 6.6$ Hz), 1.56 (d, 3H, $J = 6.6$ Hz), 1.85–1.94 (m, 1H), 3.00 (s, 3H), 3.46 (d, 1H, $J = 3.3$ Hz), 3.50–3.55 (m, 1H), 5.98 (d, 1H, $J = 2.2$ Hz), 6.10 (d, 1H,

$J = 4.4$ Hz), 7.29–7.44 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 12.7, 18.4, 18.6, 31.4, 43.4, 50.8, 57.2, 75.4, 78.5, 124.8, 128.3, 128.7, 135.0, 147.6, 171.1. IR (neat): 3513, 2964, 1774, 1732, 1253, 1139 cm^{-1}. FAB-HRMS calcd for $C_{17}H_{23}N_2O_4NaBr$: 421.0739. Found: 421.0738.

4.9. Methyl (2*S*,3*R*)-2-bromo-3-hydroxy-3-phenylpropanoate 13

In a 2 L, three-neck round-bottomed flask, the aldol adduct (9.058 g, 20.90 mmol) was dissolved in THF (217 mL). To this solution was added 6.12 M sulfuric acid (6.2 equiv) and the reaction mixture stirred at 50 °C for 22 h. After the time had elapsed, heating was stopped and the reaction mixture was allowed to cool to room temperature. The solution was basified with a saturated aqueous solution of sodium bicarbonate. The THF was removed by rotary evaporation and the aqueous portion was then treated with ethyl acetate (2 × 400 mL). The water layer was then acidified with 3 M HCl to litmus. The organic layer was then washed with saturated brine and the solvent removed to give the desired α-bromo-β-hydroxyacid (4.76 g).

The α-bromo-β-hydroxyacid was then placed in a flame-dried, 250 mL round-bottomed flask, and dissolved in anhydrous THF (78 mL). To this were added methanol (39 mL) and trimethylsilydiazomethane (2 M, 30 mL) via syringe. The reaction mixture was allowed to stir for 24 h and then quenched by the addition of a saturated aqueous solution of sodium bicarbonate (75 mL). The THF was removed by rotary evaporation and the water layer was treated with ethyl acetate (3 × 75 mL). The organic layer was washed with saturated brine and the solvent was removed. The α-bromo-β-hydroxyester **13** was isolated in 45% yield after column chromatography (hexanes–EtOAc, 75:25, $R_f = 0.29$) as a yellow oil. Chiral Stationary Phase HPLC: [Daicel Chiralcel AS column, 3% *i*-PrOH in hexanes: R_T (*ent*-**13**) = 9.3 min; R_T (**13**) = 11.2 min]; Ester **13** was determined to have ⩾98% ee as compared to the racemic mixture. $[\alpha]_D = -27.7$ (*c* 0.082, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 3.07 (s, 1H), 3.67 (s, 3H), 4.45 (d, 1H, $J = 6.6$ Hz), 5.09 (d, 1H, $J = 6.6$ Hz), 7.25–7.4 (m, 5H). ^{13}C NMR ($CDCl_3$): 52.6, 53.0, 73.7, 126.6, 128.6, 128.8, 138.2, 168.9. IR (neat): 3490, 1736, 1437, 1282. ESI-HRMS calcd for $C_{10}H_{11}BrO_3$: 280.9789. Found: 280.9793.

4.10. Methyl (2*R*,3*R*)-phenylglycidate 14

The α-bromo ester 13 (1.8 g, 6.9 mmol) was dissolved in methanol (35 mL) and then potassium carbonate (1.93 g, 13.9 mmol) was added to the solution. The reaction was monitored by TLC (hexanes–EtOAc, 80:20) for 2 h and then it was quenched with a saturated aqueous solution of sodium bicarbonate (50 mL). The methanol was removed by rotary evaporation, the residue treated with ethyl acetate (50 mL), washed with a brine solution (50 mL), and then dried over $MgSO_4$. The resulting yellow oil was purified by column chromatography (hexanes–EtOAc, 75:25, $R_f = 0.23$) and the product was isolated with a yield of 63% as a clear oil. CSP HPLC: [Daicel Chiralcel AD column, 3% *i*-PrOH in hexanes: R_T (**14**) = 6.6 min; R_T (*ent*-**14**) = 7.7 min]; Ester **14** was determined to have ⩾98% ee as compared to the racemic mixture. $[\alpha]_D = +10.0$ (*c* 0.25, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 3.50 (s, 3H), 3.81 (d, 1H, $J = 4.8$ Hz), 4.23 (d, 1H, $J = 4.8$ Hz), 7.27–7.34 (m, 3H), 7.39 (d, 1H, $J = 1.6$ Hz), 7.41 (d, 1H, $J = 2.0$ Hz). ^{13}C NMR ($CDCl_3$): δ 51.7, 55.6, 57.2, 126.3, 127.8, 128.2, 132.6, 166.7. IR (neat), 1755, 1211, 751, 699 cm^{-1}. HRMS calcd for $C_{10}H_{10}O_3Na$: 201.0527. Found: 201.0528.

4.11. Synthesis of oxadiazinanone *ent*-1a: procedure for N-nitrosation of (1*S*,2*R*)-ephedrine

(1*S*,2*R*)-Ephedrine (50.30 g, 249.4 mmol), HCl (2.74 M, 109 mL), and THF (109 mL) were combined in 1 L flask. Sodium nitrite (20.7 g, 299 mmol) was added in portions and the solution was allowed to stir for 24 h. The solution was concentrated via rotary evaporation and the *N*-nitrosamine was extracted with ethyl acetate (200 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, and the excess solvent removed via rotary evaporation to yield the *N*-nitrosamine as a yellow-white solid and as a mixture of diastereomers in quantitative yield. $R_f = 0.47$ (hexanes–EtOAc, 50:50). Mp = 82–85 °C. ^{1}H NMR ($CDCl_3$): δ 1.46 (d, 3H, $J = 7.2$ Hz), 2.95 (s, 1H), 3.73 (s, 3H), 4.69 (qd, 1H, $J = 8.0$, 2.0 Hz), 5.04 (d, 1H, $J = 4.8$ Hz), 7.33 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 13.2, 31.2, 65.0, 76.5, 126.1, 128.2, 128.6, 140.7. IR (neat): 3368, 1450, 1376, 1041, 834 cm^{-1}. ESI-HRMS calcd for $C_{10}H_{14}N_2O_2$: 195.1134. Found: 195.1130.

4.11.1. Reduction of the *N*-nitrosamine. Lithium aluminum hydride (19.38 g, 510.8 mmol) and THF (1 L) were combined in a 5 L round-bottomed flask fitted with a condenser and addition funnel and the reaction mixture was heated. The *N*-nitrosamine (49.6 g, 255 mmol) was added via drop-wise addition and the solution was allowed to undergo a gentle reflux for 2 h. ***Warning***: *The addition of the nitrosamine substrate into the lithium aluminum hydride/ THF must be done drop-wise near 50 °C to prevent overheating the solution*. After 2 h, the reaction mixture was cooled to 0 °C. Sodium hydroxide (1 M, 200 mL) was added via drop-wise addition to quench the reaction and the solvent THF was removed by rotary evaporation. The product was extracted with ethyl acetate (3 × 200 mL) and Rochelle's salt (100 mL). The combined organic layers were washed with brine (200 mL), dried over $MgSO_4$, and excess solvent removed via rotary evaporation. The β-hydroxyhydrazine was recrystallized with hexanes and diethyl ether and the white crystals were collected in a 54% yield. Mp = 40–42 °C. ^{1}H NMR ($CDCl_3$): δ 0.83 (d, 3H, $J = 6.4$ Hz), 2.59 (s, 3H), 2.76 (qd, 1H $J = 8.0$, 2.0 Hz), 5.21 (s, 2H), 7.23 (m, 1H), 7.35 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 2.9, 48.7, 64.9, 77.7, 125.9, 126.7, 127.9, 142.4. IR (neat): 3310, 1618, 1449, 1045, 699 cm^{-1}. ESI-HRMS calcd for $C_{10}H_{16}N_2O$: 181.1341. Found: 181.1340.

4.12. (5*R*,6*S*)-4,5-Dimethyl-6-phenyl-2*H*-1,3,4-oxadiazinan-2-one *ent*-1a

In a flame-dried, nitrogen purged, 2 L round-bottomed flask equipped with a condenser were placed the (1*S*,2*R*)-

ephedrine hydrazine (14.3 g, 79.4 mmol), anhydrous hexanes (398 mL), and diethyl carbonate (24.0 mL, 197 mmol). The reaction mixture was heated at reflux and lithium hydride (0.67 g, 84 mmol) was added. The reaction was allowed to stir overnight and was then cooled to 0 °C and quenched with a saturated solution of NH_4Cl (200 mL). The hexanes were removed via rotary evaporation and the resultant mixture was extracted with EtOAc (2×200 mL), washed with brine solution, dried ($MgSO_4$), and the solvent was removed via rotary evaporation. The isolated product was recrystallized from Et_2O and hexanes to yield *ent*-**1a** (71%) as a white powder. $[\alpha]_D^{25} = +24$ (*c* 0.58, $CHCl_3$); $R_f = 0.51$ (EtOAc). Mp: 117–119 °C. ^1H NMR ($CDCl_3$): δ 0.92 (d, 3H, $J = 6.6$ Hz), 2.87 (s, 3H), 3.07–3.13 (m, 1H), 5.79 (d, 1H, $J = 2.94$ Hz), 6.91 (br s, 1H), 7.30–7.42 (m, 5H). ^{13}C NMR ($CDCl_3$): 11.6, 46.5, 56.9, 74.1, 125.2, 127.9, 128.5, 136.3, 152.3. IR (CCl_4): 3224, 2943, 1688, 744, 698 cm^{-1}. Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.88; H, 6.87; N, 13.43. HRMS calcd for $C_{11}H_{14}N_2O_2$: 207.1133. Found: 207.1130.

4.13. (4*S*,5*R*,6*S*)-3-(2-Bromoacetyl)-4,5-dimethyl-6-phenyl-2*H*-1,3,4-oxadiazinan-2-one *ent*-4

The oxadiazinanone (6.00 g, 29.2 mmol) and bromoacetyl bromide (3.1 mL) were dissolved in CH_2Cl_2 (29 mL) in a 1 L round-bottomed flask. The solution was gently heated and lithium hydride (0.371 g, 46.7 mmol) added. After 24 h, the solution was cooled to room temperature and the reaction quenched with the addition of a saturated aqueous solution of NH_4Cl (100 mL). The reaction was extracted with dichloromethane (150 mL × 2). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, and the solvent removed via rotary evaporation. The product was purified via column chromatography on silica using a gradient: hexanes–EtOAc, 75:25 to 60:40. This process yielded a yellow oil in 80% yield. $R_f = 0.16$ (hexanes–EtOAc, 70:30). ^1H NMR ($CDCl_3$): δ 0.81 (d, 3H, $J = 6.8$ Hz), 2.94 (s, 3H), 3.46 (m, 1H), 4.46 (d, 1H, $J = 13.2$ Hz), 4.64 (d, 1H, $J = 13.2$ Hz), 6.07 (d, 1H, $J = 4.0$ Hz), 7.31 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 11.8, 30.9, 42.6, 56.1, 77.6, 124.4, 127.7, 128.1, 134.8, 147.2, 165.9. IR (neat): 1778, 1728, 1452, 1177, 1139, 1013, 754, 700 cm^{-1}. ESI-HRMS calcd for $C_{13}H_{15}N_2O_2Br$: 327.0344. Found: 327.0352.

4.14. (2′*R*,3′*S*,4*S*,5*R*,6*S*)-3-(2-Bromo-3-hydroxy-3-phenylpropanoyl)-4,5-dimethyl-6-phenyl-2*H*-1,3,4-oxadiazinan-2-one *ent*-9a

Oxadiazinanone *ent*-**4a** (7.98 g, 24.4 mmol), benzaldehyde (4.4 mL, 43 mmol), and THF (75 mL) were combined in a 500 mL round-bottomed flask and the solution then cooled to −60 °C. Titanium tetrachloride (5.92 mL, 53.70 mmol) was added via syringe and the solution was left to stir at −60 °C for 15 min. Triethylamine (6.80 mL, 48.8 mmol) was added via syringe and the solution left to stir for 4 h while the solution gradually warmed to room temperature. The reaction was quenched with a saturated aqueous solution of NH_4Cl (100 mL). The aldol adduct was extracted with ethyl acetate (100 mL × 3), washed with brine (100 mL), dried over $MgSO_4$, and the solvent removed via rotary evaporation. The aldol adduct was recrystallized twice from ethyl acetate and hexanes to yield a white solid in 39% yield. $R_f = 0.36$ (hexanes–EtOAc, 50:50). Mp = 154–156 °C. ^1H NMR ($CDCl_3$): δ 0.68 (d, 3H, $J = 7.2$ Hz), 2.88 (s, 3H), 3.36 (m, 1H), 5.24 (d, 1H, $J = 6.0$ Hz), 5.93 (d, 1H, $J = 6.0$ Hz), 6.01 (d, 1H, $J = 4.8$ Hz), 7.25 (m, 5H), 7.35 (m, 5H), 7.46 (d, 1H, $J = 8.0$ Hz). ^{13}C NMR ($CDCl_3$): δ 12.3, 43.3, 52.4, 57.1, 73.1, 78.4, 124.8, 127.0, 128.3, 128.4, 128.7, 135.1, 138.5, 147.0, 169.8. IR (neat): 3503, 1764, 1690, 1277, 1223, 1085, 753, 701 cm^{-1}. ESI-HRMS calcd for $C_{20}H_{21}N_2O_4Br$: 433.0763. Found: 433.0768.

4.15. Methyl (2*R*,3*S*)-2-bromo-3-hydroxy-3-phenylpropanoate *ent*-13

The aldol adduct *ent*-**9a** (2.70 g, 6.24 mmol), THF (65 mL), and H_2SO_4 (2 M, 65 mL) were combined in a round-bottomed flask. The solution was heated to an internal temperature of 50 °C for 22 h. The reaction was quenched with saturated sodium bicarbonate solution until the mixture was slightly basic. The reaction solvent was removed via rotary evaporation. The first organic layer was extracted with ethyl acetate (200 mL). The water layer was then made acidic with hydrochloric acid (3 M) and the carboxylic acid extracted with ethyl acetate (150 mL × 3). The independent organic layers were dried over $MgSO_4$, and the solvent removed via rotary evaporation. The recovered carboxylic acid (1.66 g, 6.77 mmol) was placed into a 1 L round-bottomed flask. Anhydrous tetrahydrofuran (20 mL), methanol (20 mL), and trimethylsilyldiazomethane (10.2 mL, 20.3 mmol) were sequentially added via syringe. The reaction was allowed to run for 20 h. Excess solvent was removed via rotary evaporation. The ester was purified via column chromatography on silica gel (hexanes–EtOAc, 80:20). The purified ester was a yellow oil and was collected in 63% yield from the aldol adduct. Chiral Stationary Phase HPLC: [Daicel Chiralcel AS column, 3% *i*-PrOH in hexanes: R_T (*ent*-**13**) = 9.3 min; R_T (**13**) = 11.2 min]; Ester *ent*-**13** was determined to have $\geqslant$98% ee as compared to the racemic mixture. $[\alpha]_D = +29.1$ (*c* 0.42, $CHCl_3$). $R_f = 0.31$ (hexanes–EtOAc, 80:20). ^1H NMR ($CDCl_3$): δ 3.30 (d, 1H, $J = 3.6$ Hz), 3.64 (s, 3H), 4.44 (d, 1H, $J = 6.8$ Hz), 5.06 (dd, 1H, $J = 6.4$, 3.2 Hz), 7.34 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 52.4, 52.9, 73.7, 126.5, 128.5, 128.7, 138.2, 168.8. IR (neat): 3490, 1743, 1282, 757, 700 cm^{-1}. ESI-HRMS calcd for $C_{10}H_{11}O_3Br$: 280.9789. Found: 280.9801.

4.16. Methyl (2*S*,3*S*)-phenylglycidate *ent*-14

The ester (0.860 g, 3.32 mmol) was placed in a 100 mL round-bottomed flask along with methanol (17 mL) and potassium carbonate (0.92 g, 6.64 mmol). The reaction was left to stir for 2 h. The epoxide was extracted with saturated sodium bicarbonate solution (50 mL) and ethyl acetate (100 mL × 2). The organic layers were combined, dried ($MgSO_4$), and the solvent was removed via rotary evaporation. The resultant epoxide was purified via column chromatography on silica (90:10, hexanes–EtOAc). The process yielded a colorless oil in 96% yield. $R_f = 0.45$

(80:20, hexanes–EtOAc). CSP HPLC: [Daicel Chiralcel AD column, 3% *i*-PrOH in hexanes: R_T (**14**) = 6.6 min; R_T (*ent*-**14**) = 7.7 min]; Ester *ent*-**14** was determined to have ⩾98% ee as compared to the racemic mixture. $[\alpha]_D = -10.0$ (*c* 3.22, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 3.50 (s, 3H), 3.81 (d, 1H, $J = 4.8$ Hz), 4.23 (d, 1H, $J = 4.8$ Hz), 7.34 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 51.7, 55.6, 57.2, 126.3, 127.8, 128.2, 132.6, 166.7. IR (neat): 1755, 1441, 1212, 747, 699 cm^{-1}. ESI-HRMS calcd for $C_{10}H_{10}O_3$: 179.0708. Found: 179.0708.

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16. The specific rotation measurements obtained for (2*R*,3*R*)-**14** and (2*S*,3*S*)-**14** were used only to establish the absolute stereochemistry. The use of the CSP HPLC provided more tangible evidence regarding the enantiomeric purities of the individual isomers.
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