Synthesis, Asymmetric Aldol Reactions, and X-ray Crystallography of some Oxadiazinanone Derivatives

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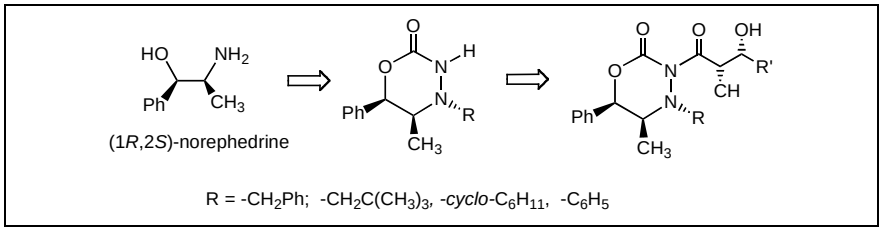

A series of N_4-substituted oxadiazinanones have been synthesized from (1*R*,2*S*)-norephedrine by a process of either reductive alkylation or arylation, *N*-nitrosation, reduction and cyclization. These derivatives (R = -CH_2Ph, -$CH_2C(CH_3)_3$, -*cyclo*-C_6H_{11}, -C_6H_5) have been acylated with propanoyl chloride and employed in the asymmetric Aldol reaction. The observed diastereoselectivities for the formation of the "non-Evans" syn-adduct ranged from 88:12 to 99:1. The hydrolysis of the Aldol adducts varied with the nature of the nitrogen substituent.

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INTRODUCTION

Oxadiazinanones derived from enantiomerically enriched *Ephedra* alkaloids have been used as chiral auxiliaries for the asymmetric aldol reaction (Figure 1) [1,2]. Research with these systems [2,3] suggested that the N_4-position of the oxadiazinanone ring was responsible for the observed stereochemical outcome of the aldol addition reaction *via* a chiral relay tandem [4] involving the N_4-C_5-C_6 positions. In fact, the N_4-methyl group present in the (1*R*,2*S*)-ephedrine based oxadiazinanone generated very good diastereoselectivities in the asymmetric Aldol reaction. In this context we sought to increase the diastereoselectivities beyond the capacity

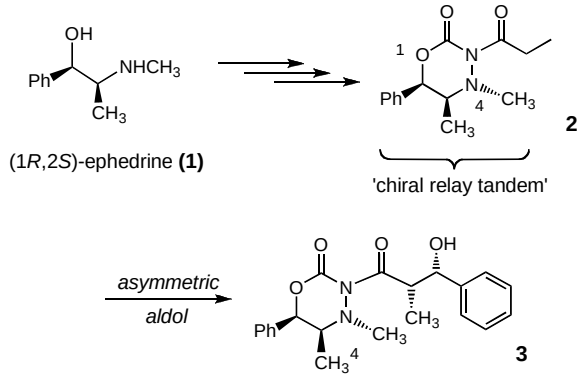


Figure 1. Oxadiazinanones in the aldol reaction.

of N_4-methyl substituent by introducing substituents that were more sterically demanding. Thus, the N_4-isopropyl-oxadiazinanone gave superior diastereoselectivity results in the asymmetric aldol reaction. Unfortunately, the Aldol adducts proved to be more difficult to hydrolyze than the corresponding N_4-methyloxadiazinanones (Figure 2) [5].

The next stage of development of the oxadiazinanones involved the introduction of a bornyl group at the N_4-position [6]. The N_4-bornyloxadiazinanone **(6)** also gave very good asymmetric induction but the hydrolysis isopropyl system. This led to the conclusion that the oxadiazinanone-mediated Aldol reaction was very sensitive to the steric demands of the N_4-substituent.

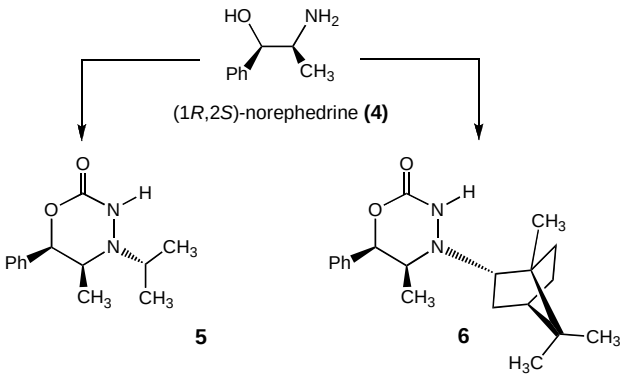


Figure 2. Oxadiazinanone modifications.

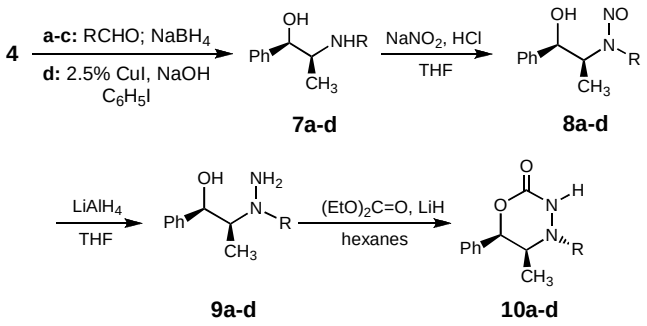
We became interested in determining if there might be an optimal substituent that would allow for high diastereoselection and an effective hydrolysis of the resultant Aldol adducts. Herein, we report on our efforts to prepare both N_4-alkyl and N_4-aryloxadiazinanones and

to investigate the stereoselectivities in the Aldol reaction and the effectiveness of the hydrolysis process with their Aldol products.

RESULTS AND DISCUSSION

(1*R*,2*S*)-Norephedrine was reductively alkylated with a variety of aldehydes and sodium borohydride to afford the *N*-alkyl derivatives **7a-c** (Scheme 1). As there was an interest in expanding the scope of substituents that would be ultimately introduced at the N_4-position, a copper catalyzed *N*-arylation method was also employed [7]. This process afforded the *N*-phenylnorephedrine as a crystalline solid after column chromatography and recrystallization. The norephedrine derivatives **7a-d** were subsequently *N*-nitrosated by treatment with sodium nitrite and HCl [8,9].

Scheme 1



a: R = -$CH_2C_6H_5$ (benzaldehyde); **b:** R =-$CH_2C(CH_3)_3$ (pivaldehyde); **c:** R = -*cyclo*-C_6H_{11}(cyclohexanone); **d:** R = -C_6H_5 (iodobenzene)

The *N*-nitrosamines **8a-d** were then reduced with $LiAlH_4$ to the corresponding β-amino hydrazines **9a-d** [10]. Cyclization of these derivatives to afford oxadiazinanones **10a-d** was achieved with diethyl carbonate and lithium hydride. These compounds were acylated with propanoyl chloride and lithium hydride to afford N_3-propanoyloxadiazinanones **11a-d**. The isolated chemical yields for these processes are listed in Table 1 and Table 2. In order to prepare the Aldol adducts of interest, oxadiazinanones **11a-d** were each reacted with two equivalents of titanium tetrachloride at 25 °C for 25 minutes. The reaction mixture was cooled to 0 °C and triethylamine was added to effect enolate formation over a period of 45 minutes. The selected aldehyde was then added and the reaction stirred for 18 hours. This process yielded Aldol adducts **12a-m** in good yield and diastereoselectivity (Table 2).

Table 1

Isolated chemical yields from oxadiazinanone synthesis.

entry	substrate	R-	%yield[a]
1	**7a**	-$CH_2C_6H_5$	99[b]
2	**7b**	-$CH_2C(CH_3)_3$	89[b]
3	**7c**	-*cyclo*-C_6H_{11}	85[b]
4	**7d**	-C_6H_5	34[b,c]
5	**8a**	-$CH_2C_6H_5$	67[b]
6	**8b**	-$CH_2C(CH_3)_3$	99[b]
7	**8c**	-*cyclo*-C_6H_{11}	86[b]
8	**8d**	-C_6H_5	81[c]
9	**9a**	-$CH_2C_6H_5$	80[d]
10	**9b**	-$CH_2C(CH_3)_3$	90[d]
11	**9c**	-*cyclo*-C_6H_{11}	69[b]
12	**9d**	-C_6H_5	56[c]
13	**10a**	-$CH_2C_6H_5$	65[b]
14	**10b**	-$CH_2C(CH_3)_3$	67[b]
15	**10c**	-*cyclo*-C_6H_{11}	64[b]
16	**10d**	-C_6H_5	94[c]
17	**11a**	-$CH_2C_6H_5$	65[b]
18	**11b**	-$CH_2C(CH_3)_3$	59[b]
19	**11c**	-*cyclo*-C_6H_{11}	54[b]
20	**11d**	-C_6H_5	78[c]

[a]All reported yields are reported after purification. [b]Purification by recrystallization. [c]Purification by column chromatography. [d]Percent recovery for the formation of the hydrazine. The hydrazines underwent decomposition when attempts to purify them by chromatography and were made and were not characterized.

The stereochemical outcome of the asymmetric Aldol reaction was unambiguously determined by single crystal X-ray diffraction (Figure 3, Table 3). There are two molecules of similar bond distances and angles in the asymmetric unit cell; only one is pictured (see experimental section. This X-ray crystal structure suggested that the stereochemistry of the addition process followed the same mechanistic pathway as in the case of the N_4-methyl and N_4-isopropyl systems, *i.e.* that a Zimmerman-Traxler chair-like transition state [11], wherein the N_4-substituent influenced the direction of approach of the electrophile (Figure 4).

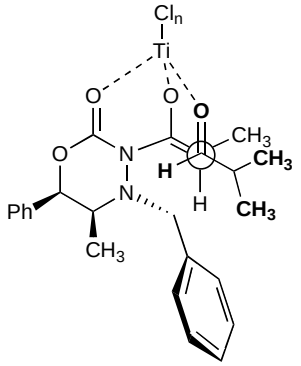
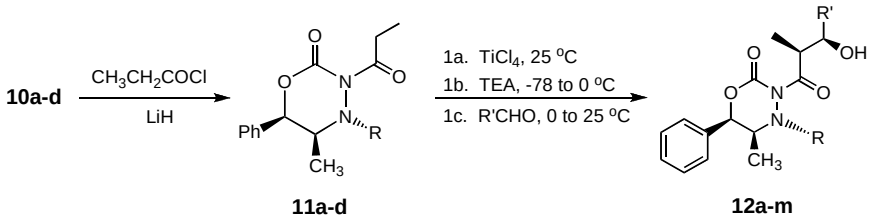


Figure 4. Proposed transition state for the oxadiazinone mediated asymmetric aldol addition reaction.

Table 2

Isolated yields and diastereoselectivities for the oxadiazinanone based asymmetric aldol addition reaction.



entry	Substrate	R'	adduct	crude d.r.[a,b]	% yield[c]
1	**11a** (R = - $CH_2C_6H_5$-)	C_6H_5-	**12a**	88:12	99
2	**11a**	$C_{10}H_7$-	**12b**	99:1	95
3	**11a**	$(CH_3)_2CH$-	**12c**	95:5	70
4	**11a**	$(CH_3)_3C$-	**12d**	96:4	99
5	**11b** (R = - $CH_2C(CH_3)_3$)	C_6H_5-	**12e**	91:9	98
6	**11b**	*p*-ClC_6H_4-	**12f**	99:1	91
7	**11b**	$C_{10}H_7CHO$	**12g**	99:1	99
8	**11b**	$(CH_3)_2CH$-	**12h**	97:3	95
9	**11b**	$(CH_3)_3C$-	**12i**	95:5	99
10	**11c** (R = -cyclo-C_6H_{11})	*p*-ClC_6H_4-	**12j**	95:5	67
11	**11c**	$(CH_3)_3C$-	**12k**	92:8	99
12	**11d** (R = -C_6H_5)	C_6H_5-	**12l**	91:9	88
13	**11d**	*p*-ClC_6H_4-	**12m**	93:7	62

[a]Diastereomer ratios reported as major isomer: Σ other isomers. [b]Diastereomer ratio determined by either 400 MHz NMR spectroscopy or HPLC. [c]Chemical yield of the purified product after chromatography or recrystallization.

The X-ray crystal structure further suggested that the N_4-substituent was being held in a pseudo-axial position. The measured dihedral angle between the C_5-methyl group and the N_4-methyl group (C50a-C5a-N4a-C40a) was 172.7° (3) in molecule *a*, and 173.9° (3) in molecule *b* (C50b-C5b-N4b-C40b). This value is close to the idealized 180° dihedral angle that would be expected from the optimized chiral relay tandem of the C_6-C_5-N_4-positions.

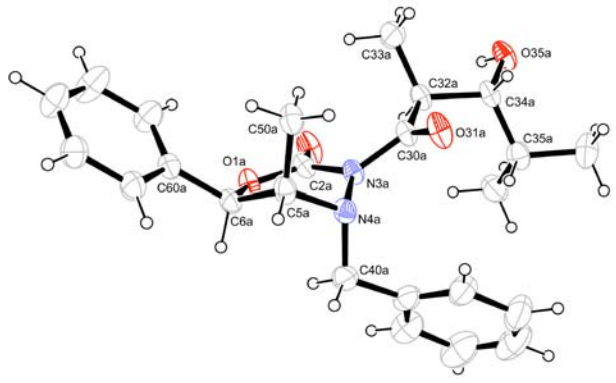


Figure 3. ORTEP diagram of one of the two independent molecules of oxadiazinanone **12c** showing the partial atom-numbering scheme with 30% probablility ellipsoids. Hydrogen atoms have been drawn arbitrarily small.

The diastereoselectivities of the Aldol reactions for oxadiazinanones **11a-c** (N_4- = -benzyl, -neopentyl, and -cyclohexyl) were all very good. The N_3-propanoyl-N_4-phenyloxadiazinanone **11d** also gave comparable diastereoselectivities even though the N_4-phenyl is more sterically demanding. It is proposed that there is a resonance interaction between the N_4-nitrogen and the phenyl ring would lead to the N_4-position not having the nearly idealized 180° dihedral angle with the C_5-position and its substituent (Figure 5). Effectively, the impact of the intramolecular chiral relay would not be transmitted as effectively and this would potentially lead to the observed diastereoselectivities.

At this stage we turned our attention to the hydrolysis process. The reaction involving the acid catalyzed hydrolytic cleavage of the N_3-amide bond has been a consistent problem with the oxadiazinanone family of chiral auxiliaries. Our previous efforts suggested that the success of the hydrolysis reaction was coupled with the steric demands of the N_4-substituent [2,3,5]. In order to evaluate the hydrolysis reaction for the oxadiazinanones **10a-d** (R = -benzyl, -neopentyl, -cyclohexyl, and -phenyl) in this work, Aldol adducts **12a**, **12e**, **12j**, and **12l** were subjected to the hydrolysis conditions (Table 4).

Table 3

X-ray crystallographic data.

Formula	$C_{24}H_{30}N_2O_4$
Formula weight	410.5
Crystal dimensions (mm)	0.45 × 0.36 × 0.36
Space group	Monoclinic, $P2_1$ (No. 4)
a (Å)	10.032(2)
b (Å)	10.860(5)
c (Å)	20.964(5)
β (°)	93.09(2)
V (Å^3)	2280.8(12)
Z	4
ρ_{calc} (g cm^{-1})	1.195
μ (mm^{-1})	0.081
Radiation	Mo Kα (λ = 0.71069Å)
Temperature (K)	297
Reflections Collected	11612
Independent reflections	5499
Reflections observed [$I > 2\sigma(I)$]	3465
R indices (all data)	0.058 (0.100)
wR_2 indices (all data)	0.149 (0.174)
Goodness-of-fit	0.9940

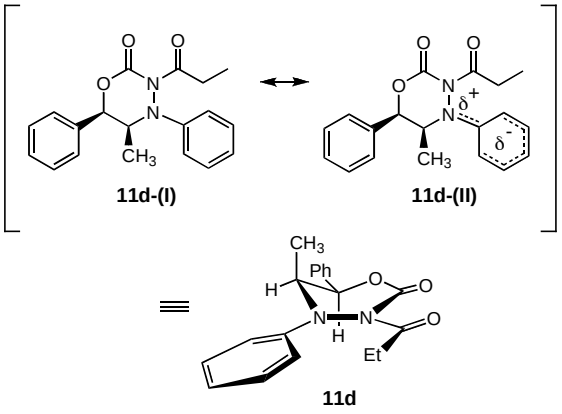
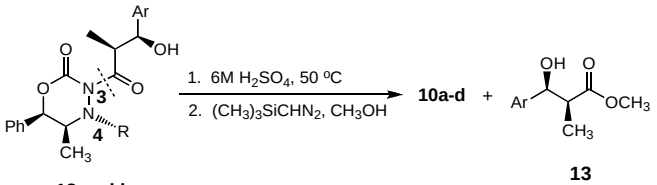


Figure 5

The isolated yields were poor to fair and the enantiomeric excesses were in line with the diastereomeric excess of the samples that were used (*i.e.*, there was no significant compromise of the stereochemical integrity of the Aldol adduct) [12]. Unfortunately, all attempts at the hydrolysis of the N_4-phenyloxadiazinanone derivative **12l** gave complicated mixtures (retro-Aldol products, ring opening of the oxadiazinanone, dehydration of the Aldol adduct, *etc*). Attempts at reductive cleavage of the Aldol adducts also met with problems that appeared to be primarily connected with the decomposition of the oxadiazinanone, *e.g.* ring opening events. It is proposed that the N_4-phenyl substituent was detrimental to the hydrolysis process by virtue of its steric volume in combination with an electronic effect.

Table 4

Hydrolysis of selected oxadiazinanone Aldol adducts.



entry	substrate	% yield[a]	er[b]	isomer[c]
1	**12a**	43	91:9	(2*S*,3*S*)
2	**12e**	21	93.5:6.5	(2*S*,3*S*)
3	**12j**	18	97.5:2.5	(2*S*,3*S*)
4	**12l**	-	-	-

[a]Isolated yield after column chromatography. [b]Enantiomeric ratio determined by chiral stationary phase HPLC: OD column, 95:5 hexanes, iPrOH, 1 mL/min, t_r (2*R*,3*R*)-ester = 8.7 min.; t_r (2*S*,3*S*)-ester = 10.0 min. [c]The absolute stereochemistry was determined by polarimetry.[12]

CONCLUSION

Oxadiazinanones can be used successfully in the asymmetric Aldol reaction to good effect with regard to isolated yield and the diastereoselectivity of the Aldol adducts obtained. However, there is an intrinsic problem associated with the hydrolysis of the Aldol adducts. Simple modifications of the N_4-position with either alkyl or aryl substituents are not enough to allow for both good diastereoselectivity in the Aldol addition reaction and for a clean hydrolysis process. The primary substituted N_4-benzyl and N_4-neopentyl systems did not offer superior hydrolyses over the secondary N_4-isopropyl oxadiazinanone previously described [5]. The hydrolysis of the N_4-cyclohexyloxadiazinanone **12j** afforded the desired product but with a compromised yield. Finally, the hydrolysis of the N_4-phenyl oxadiazinanone proved to be ineffective, perhaps due to the electronic contribution of the aromatic ring. Research is underway to investigate the introduction of substituents that carry a greater possibility for influencing the final outcome of the oxadiazinanone mediated Aldol reaction and the associated hydrolysis.

EXPERIMENTAL

General Remarks. All reactions were run under a nitrogen atmosphere. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from a potassium/sodium alloy with benzophenone ketyl. Unless otherwise noted, all ^{1}H and ^{13}C NMR spectra were recorded at 25 °C in $CDCl_3$ operating at 400 MHz and 100 MHz, respectively. Chemical shifts are reported in parts per million (δ scale), and coupling constants (*J* values) are listed in hertz (Hz). Infrared spectra are reported in reciprocal centimeters (cm^{-1}) and are measured either as a neat

liquid or as a KBr window. Melting points were recorded on a Mel-Temp apparatus and are uncorrected. High Resolution ESI Mass spectral analyses were conducted by the mass spectrometry analytical laboratories of the University of Illinois at Urbana-Champaign (UIUC) using a quadrapole time of flight mass spectrometer hybrid with MS/MS capability. A 50/50 mixture of water and acetonitrile was used as the flow phase for the ESI measurements. High Resolution EI mass spectral analyses were conducted using a micromass 70 VSE 8kV mass spectrometer with extended geometry and gas chromatographic capacity (UIUC). High resolution FAB mass spectral data (xenon gas matrix) were collected on a four-sector 8 kV 70-SE-4F mass spectrometer with extended geometry and gas chromatographic capacity (UIUC). Optical activities were measured using at 589 nm using a Jasco digital polarimeter purchased with NSF grant #CHE 644950.

X-ray crystallography. Crystallographic data (excluding structure factors) for structure **12c** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre. The atomic coordinates and equivalent isotropic displacement coefficients are included in the deposited material (CCDC 617657) as are a complete list of bond distances and angles. Copies of available material can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2, 1EZ, UK (Fax: + 44-1223-336033 or email: deposit@ccdc.am.ac.uk).

Colorless crystals of $C_{24}H_{30}N_2O_4$ suitable for crystallography were isolated by layering a solution of $C_{24}H_{30}N_2O_4$ in CH_2Cl_2 with hexanes. Data were collected on a Bruker-Nonius CAD4/Mach3 diffractometer at 297 K. Data collection and cell refinement was performed using CAD4 express [13]. Data reduction was carried out using XCAD4 [14]. Unit cell parameters were obtained from a least-squares refinement of 25 centered reflections. Solution and data analysis were performed using the WinGX software package [15]. The structures were solved using the program SHELXS-97 [16]. The refinements were completed using the program SHELXL-97 [17]. Hydrogen atoms were assigned positions based on the geometries of their attached carbons. See Table 3 for final refinement parameters. There are 2 independent molecules in the asymmetric unit cell, both with similar bond lengths and angles.

General procedure for the reductive alkylation of (1*R*,2*S*)-norephedrine (7a-c). In a flame-dried, nitrogen-purged, one liter round bottom, (1*R*,2*S*)-norephedrine (66.0 mmol) was placed with the appropriate aldehyde (69.5 mmol) and 100% ethanol (66 mL). The mixture was stirred for 24 hours and cooled to 0 °C. Sodium borohydride was added to the reaction mixture and stirred for an additional two hours. The reaction was then diluted with sodium hydroxide (1 *M*, 100 mL) and the ethanol was removed by rotary evaporation. The resultant mixture was then diluted with ethyl acetate (200 mL) and extracted. The organic layer was then washed with brine (50 mL) and the organic layer dried ($MgSO_4$) and solvent removed by rotary evaporation.

(1*R*,2*S*)-2-(Benzylamino)-1-phenyl-1-propanol (7a). Using benzaldehyde, the title compound was obtained in 99% yield as a clear oil. R_f = 0.42 (90:10 hexanes/EtOAc). $[\alpha]_D^{25}$ = -30.0 (*c* 0.86, $CHCl_3$). IR ($CHCl_3$): 3406, 3028, 1603, 1028, 910, 732, 700cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.86 (d, *J* = 6.6 Hz, 3H), 3.01 (dq, *J* = 6.6, 3.9 Hz, 1H), 3.89 (s, 2H), 4.80 (d, *J* = 3.18 Hz, 1H), 7.26-7.35 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 14.7, 51.4, 58.1, 73.9, 126.6, 127.4, 127.5, 128.4, 128.5, 128.9, 140.3, 142.2. HRMS (ESI) calcd for $C_{16}H_{20}NO$ (M + H)$^+$: 242.1535 Found: 242.1545.

(1*R*,2*S*)-2-(2,2-Dimethylpropylamino)-1-phenyl-1-propanol (7b). The ^{1}H and ^{13}C NMR spectra matched the previously prepared material.

(1*R*,2*S*)-2-Cyclohexylamino-1-phenyl-1-propanol (7c). The purified product was isolated *via* recrystallization, affording 19.73 g of a white solid in 85% yield. Mp: 89-91 °C (hexanes/EtOAc). $[\alpha]_D^{25}$ = +11.2 (*c* 1.66, CH_2Cl_2). IR (nujol mull): 3278, 1102, 738, 701 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ, 0.78 (d, *J* = 6.8 Hz, 3H), 1.00-1.34 (m, 7H), 1.59-1.64 (m, 1H), 1.71-1.75 (m, 1H), 1.85-1.96 (m, 1H), 2.52-2.59 (m, 1H), 3.05-3.11 (m, 1H), 4.66 (d, *J* = 4.0 Hz, 1H), 7.21-7.34 (m, 5H). ^{13}C NMR ($CDCl_3$): δ, 12.7, 24.8, 24.9, 25.5, 31.8, 32.5, 54.3, 55.8, 72.4, 126.0, 127.0, 128.0, 140.9. HRMS (ESI) calcd for $C_{15}H_{23}NO$ (M + H)$^+$: 234.1858. Found: 234.1858.

(1*R*,2*S*)-2-(*N*-Phenylamino)-1-phenyl-1-propanol (7d). In a flame-dried, nitrogen-purged 1 L round bottom flask fitted with a condenser, was placed (1*R*,2*S*)-norephedrine (20.0 g, 132 mmol), sodium hydroxide (10.6 g, 265 mmol), iodobenzene (18 mL, 158 mmol), and 2-propanol (132 mL). A catalytic amount of copper(I) iodide (2.5 mol %, 0.630 g, 3.3 mmol) was then added and the reaction was heated at reflux for a period of 18 hours. At the end of this time, the reaction was cooled to room temperature and the reaction solvent was removed by rotary evaporation. The solid residue was treated with EtOAc and a saturated solution of NH_4Cl. The organic layer was subsequently washed with a saturated solution of brine, dried ($MgSO_4$), and the solvent was removed by rotary evaporation. The resultant dark brown oil was purified on silica gel with a yield of 34% as white crystals. Mp: 78-80 °C. IR ($CHCl_3$): 3180, 1601, 1073, 757, 704 cm^{-1}. $[\alpha]_D^{25}$ = +84.9 (*c* 0.85, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 1.03 (d, *J* = 6.6 Hz, 3H), 2.38 (s, -OH), 3.77-3.82 (dq, *J* = 6.6, 3.1 Hz, 1H), 5.01 (d, *J* = 3.1 Hz, 1H), 6.69-6.78 (m, 3H), 7.18-7.24 (m, 2H), 7.27-7.32 (m, 1H), 7.37-7.41 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 13.6, 54.1, 74.0, 113.9, 117.8, 125.7, 127.1, 128.1, 129.2, 141.4, 146.9. HRMS (EI) calcd for $C_{15}H_{17}NO$ (M + H)$^+$: 228.1388. Found: 228.1392.

General procedure for the *N*-nitrosation of the *N*-alkylated norephedrine derivatives (8a-d). In a 1 L round bottom flask equipped with a stir bar was placed the (1*R*,2*S*)-2-(benzylamino)-1-phenyl-1-propanol (66.0 mmol) along with 2.74 *M* hydrochloric acid (75.9 mmol) and THF (66 mL). Sodium nitrite (79.0 mmol) was added in small portions. The reaction was diluted with a saturated solution of sodium bicarbonate (50 mL) and THF was removed by rotary evaporation. The resulting mixture was then extracted with ethyl acetate (2 x 20 mL). The organic layer was washed with brine solution (20 mL) and the resultant organic layer was dried ($MgSO_4$). The remaining solvent was removed by rotary evaporation to afford the desired product.

(1*R*,2*S*)-*N*-Benzyl-*N*-nitroso-2-amino-1-phenyl-1-propanol (8a). This process yielded a yellow oil, which, after recrystallization from ethyl acetate and hexanes, gave white crystals in a 67% yield (12.0 g, 44.4 mmol); wherein the rotameric ratio was determined by ^{1}H NMR to be *ca*. 95:5 (*E*:*Z*). The ^{1}H NMR and ^{13}C NMR spectral values reported are of the major diastereomer only. Mp: 90-91°C (hexanes/EtOAc). $[\alpha]_D^{25}$ = +115.7 (*c* 3.02, $CHCl_3$). IR ($CHCl_3$): 3329, 1634, 1024, 730, 700 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.47 (d, *J* = 6.6 Hz, 3H), 4.30 (dq, *J* = 7.0, 5.1 Hz, 1H), 4.45 (d, *J* = 14.8 Hz, 1H), 5.82 (d, *J* = 14.8 Hz, 1H), 5.11 (d, *J* = 5.1 Hz, 1H), 7.01-7.03 (m, 1H),

7.25-7.33 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 9.7, 15.0, 48.1, 64.3, 126.5, 128.0, 128.3, 128.4, 128.8, 129.1, 134.5, 140.9. HRMS (EI) calcd for $C_{16}H_{18}N_2O_2$ ($M^{+\bullet}$): 270.1369. Found: 270.1368. *Anal*. calcd for $C_{16}H_{18}N_2O_2$: %C, 70.82, %H, 6.68, %N, 10.33. Found: %C, 71.01, %H, 6.66, %N, 10.36.

(1*R*,2*S*)-*N*-Nitroso-*N*-2-amino-(2,2-dimethylpropyl)-1-phenyl-1-propanol (8b). The ^{1}H and ^{13}C NMR spectra matched the previously prepared material.

(1*R*,2*S*)-*N*-Cyclohexyl-*N*-nitroso-2-amino-1-phenyl-1-propanol (8c). Recrystallization of the product afforded the title compound as a white solid in 86% yield. Mp: 96-98 °C (hexanes/EtOAc). $[\alpha]_D^{25}$ = +48.3 (*c* 1.02, CH_2Cl_2). Only the major *N*-nitrosamine diastereomer is reported. IR (nujol): 3448, 1030, 700, 671 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.17-1.22 (m, 1H), 1.26 (d, *J* = 7.0, 3H), 1.28-1.42 (m, 2H), 1.58-1.78 (m, 3H), 1.82-1.94 (m, 4H), 3.17 (broad singlet, 1H), 3.95-4.01 (m, 1H), 4.35 (broad singlet, -OH), 4.92 (d, *J* = 3.6 Hz, 1H), 7.25-7.37 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 10.1, 24.9, 25.5, 25.6, 32.5, 33.4, 61.9, 73.6, 125.6, 127.4, 127.9, 141.7. HRMS (ESI) calcd for $C_{15}H_{22}N_2O_2$ (M + H)$^+$: 263.1760. Found: 263.1761.

(1*R*,2*S*)-2-(*N*-Nitroso-*N*-phenylamino)-1-phenyl-1-propanol (8d): The dark brown oil was purified on silica gel to yield the title compound as a light brown oil in 81% yield. Only the major *N*-nitrosamine diastereomer is reported**.** This compound decomposes upon standing at room temperature for more than one hour. $[\alpha]_D^{25}$ = +31.9 (*c* 0.88, CH_2Cl_2). IR ($CHCl_3$): 3408, 1167, 758, 700 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.19 (d, *J* = 7.6 Hz, 3H), 2.76 (broad singlet, 1H), 4.88-4.94 (m, 1H), 5.13 (d, *J* = 4.4 Hz, 1H), 7.27-7.41 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 11.0, 60.1, 73.4, 125.0, 125.9, 127.9, 128.4, 128.9, 129.3, 140.8, 141.3. HRMS (EI) Calcd for $C_{15}H_{16}N_2O_2$ (M + H)$^+$: 257.1290. Found: 257.1300.

General Procedure for the formation of the hydrazine and resultant oxadiazinanone (10a-c). In a flame-dried, nitrogen-purged 3-necked 2 L round bottom flask fitted with an addition funnel with a pressure equalizing arm, and a condenser were placed lithium aluminum hydride (132 mmol) and anhydrous THF (270 mL). The mixture was then heated to reflux. The *N*-nitrosamine (44.4 mmol) was dissolved in anhydrous THF (100 mL) and placed into the addition funnel, where it was added dropwise into the lithium aluminum hydride solution at reflux. After the last drop of dissolved nitrosamine had been added, the reaction mixture was stirred at reflux for two and a half hours and then was cooled to room temperature. Once at room temperature the 3-necked 2 L round bottom flask was placed into an ice bath and the reaction was quenched with water (100 mL), which was added dropwise through the addition funnel. Then 3 *M* sodium hydroxide (40 mL) was added dropwise to finalize the quenching process. The reaction mixture was then transferred to a 2 L round bottom flask where the THF was removed by rotary evaporation. The resulting mixture, free of most of the THF was then extracted with ethyl acetate (2 x 20 mL). The combined organic layer was then washed in Rochelle's solution (20 mL) and then in brine (20 mL). The final organic layer is dried using magnesium sulfate and the ethyl acetate removed by rotary evaporation to afford the hydrazine, which was directly converted into the corresponding oxadiazinone heterocycle derivatives, due to facile decomposition.

In a flame-dried, nitrogen purged 1 L round bottom flask was placed the hydrazine (44.4 mmol) and hexanes (270 mL). To this solution was added diethyl carbonate (48.8 mmol) and the solution was heated to reflux. Once at reflux, lithium hydride (LiH, 88.8 mmol) was added to the reaction mixture, which was allowed to stir overnight. The mixture was then cooled to room temperature and the solvent was removed by rotary evaporation. The reaction mixture was dissolved in ethyl acetate and washed with 1 *M* HCl (3 x 25 mL), a saturated solution of sodium bicarbonate (100 mL), and then a saturated solution of brine (100 mL). The organic layer was then dried ($MgSO_4$) and the solvent was removed by rotary evaporation.

(5*S*,6*R*)-4-Benzyl-5-methyl-6-phenyl-3-propanoyl-2*H*-1,3,4-oxadiazinan-2-one (10a). The *N*-nitrosamine reduction was carried out at room temperature. The hydrazine was obtained in 80% recovered yield. The cyclization of the hydrazine afforded a solid product that was recrystallized from ethyl acetate and hexanes to yield a white solid in a 65% yield. Mp: 98-99 °C. R_f = 0.36 (80:20 hexanes/EtOAc). $[\alpha]_d^{25}$ = +16.3 (*c* 0.47, $CHCl_3$). IR ($CHCl_3$): 1776, 1695, 1218, 1014, 744, 704 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.76 (d, *J* = 7.0 Hz, 3H), 1.17 (t, *J* = 7.0 Hz, 3H), 2.83-2.93 (m, 1H), 2.96-3.07 (m, 1H), 3.35 (dq, *J* = 7.0, 4.5 Hz, 1H), 4.16 (d, *J* = 12.5 Hz, 1H), 4.34 (d, *J* = 12.5 Hz, 1H), 6.09 (d, *J* = 4.7 Hz, 1H), 7.19-7.57 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 9.2, 12.5, 31.5, 51.5, 59.5, 78.0, 125.0, 128.3, 128.6, 128.9, 129.1, 129.5, 135.5, 136.1, 148.8, 175.0. HRMS (EI) calcd for $C_{20}H_{22}N_2O_3$ ($M^{+\bullet}$): 338.1627. Found: 338.1630. *Anal*. calcd for $C_{20}H_{22}N_2O_3$: %C 70.99, %H 6.51 %N 8.28 Found: %C 70.81, %H 6.51, %N 8.42.

(5*S*,6*R*)-5-Methyl-4-(2,2-dimethylpropyl)-6-phenyl-2*H*-1,3,4-oxadiazinan-2-one (10b). The ^{1}H and ^{13}C NMR spectra matched the previously prepared material.

(5*S*,6*R*)-4-Cyclohexyl-5-methyl-6-phenyl-2*H*-1,3,4-oxadiazinanan-2-one (10c). The hydrazine product was recrystallized from hexanes and ethyl acetate to give a 69% isolated yield. The heterocycle product was isolated *via* recrystallization, affording 9.73 g of the title compound as a white solid in 64% yield. Mp: 89-91 °C (hexanes/EtOAc). $[\alpha]_D^{25}$ = +15.1 (*c* 2.01, CH_2Cl_2). IR (nujol): 1698, 1015, 727, 700 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.91 (d, *J* = 6.6 Hz, 3H), 1.20-1.41 (m, 6H), 1.62-1.72 (m, 1H), 1.80-1.85 (m, 1H), 1.91-1.98 (m, 1H), 2.16-2.25 (m, 1H), 2.86-2.94 (m, 1H), 3.51-3.57 (m, 1H), 5.67 (d, *J* = 2.9 Hz, 1H), 7.07 (s, 1H, -NH), 7.29-7.41 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 11.9, 24.2, 24.3, 25.6, 30.2, 50.6, 63.0, 75.2, 125.1, 127.7, 128.4, 136.6, 152.7. HRMS (ESI) calcd for $C_{16}H_{22}N_2O_2$ (M + H)$^+$: 275.1760. Found: 275.1760. *Anal*. calcd for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.04; H, 8.12; N, 10.21.

(5*S*,6*R*)-5-Methyl-4,6-diphenyl-2*H*-1,3,4-oxadiazinan-2-one (10d). In a flame-dried, nitrogen-purged 1 L round bottom flask fitted with a Claisen adapter, fitted with a condenser and an addition funnel, was placed $LiAlH_4$ (4.2 g, 117 mmol) and dissolved in THF (50 mL). This solution was stirred and the nitrosamine (7.2 g, 28 mmol) dissolved in THF was added drop wise *via* the addition funnel. After total incorporation of the nitrosamine, the reaction was allowed to progress for four hours. The reaction was cooled to 0 °C and quenched by the addition of 1 *M* NaOH (500 mL). The reaction mixture was extracted with EtOAc, washed with a saturated solution of brine, dried ($MgSO_4$), and the reaction solvent was removed by rotary evaporation. The remaining residue was purified by column chromatography to yield a pale yellow oil in 56%. IR ($CHCl_3$): 3404, 3057, 749, 693 cm^{-1}. **Hydrazine:** ^{1}H NMR ($CDCl_3$): δ 0.99 (d, *J* = 6.8 Hz, 3H), 3.95-4.00 (qd, *J* = 6.8, 2.0 Hz, 1H), 5.31 (d, *J* = 1.6 Hz, 1H), 6.86 (t, *J* = 7.2 Hz, 1H), 6.91 (d, *J* = 8

Hz, 2H), 7.25-7.32 (m, 3H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.45 (d, *J* = 7.2 Hz, 2H). ^{13}CNMR ($CDCl_3$): δ 5.8, 60.2, 77.4, 112.9, 119.2, 126.0, 127.1, 128.2, 129.4, 142.3, 150.9. HRMS (EI) Calcd for $C_{15}H_{18}N_2O$ $(M + H)^+$: 243.1497. Found: 243.1490.

In a flame-dried, nitrogen-purged 250 mL round bottom flask fitted with a condenser were placed the hydrazine (3.8 g, 16 mmol), and dissolved in hexanes (50 mL). Diethylcarbonate (4.7 mL, 39 mmol) was added to this stirred solution and the system was brought to reflux. Upon refluxing, lithium hydride (0.020 g, 17 mmol) was added in one portion and the reaction progressed for 18 hours. The reaction was then cooled to 25 °C and quenched with a saturated NH_4Cl solution and the hexanes removed by rotary evaporation. The solid residue obtained was extracted into EtOAc and washed with a saturated solution of sodium chloride. The organic layer was dried ($MgSO_4$) and the solvent was removed *via* rotary evaporation. The resultant brown oil was purified by chromatography, giving 2.1 g of the title compound in 94% yield as a colorless oil. $[\alpha]_D^{25}$ = +96.1 (*c* 0.38, CH_2Cl_2). IR ($CHCl_3$): 3235, 2903, 1699, 1230, 756 cm^{-1}. ^{1}HNMR ($CDCl_3$): δ 1.18 (d, *J* = 7.0 Hz, 3H), 3.96-3.99 (m, 1H), 5.38 (d, *J* = 2.9 Hz, 1H) 6.58 (broad singlet, -NH), 7.12 (t, *J* = 7.2 Hz, 1H), 7.19-7.43 (m, 9H). ^{13}C NMR ($CDCl_3$): δ, 11.1, 58.4, 76.8, 117.8, 123.2, 125.0, 128.0, 128.4, 135.6, 149.5, 152.6. HRMS (EI): calcd for $C_{16}H_{16}N_2O_2$ $(M + Na)^+$: 291.1109. Found: 291.1105.

Representative experimental for N_3-acylation of the oxadiazinanones (11a-d). In a flame dried, nitrogen purged 1 L round bottom flask was added the oxadiazinanone (44.3 mmol) and dichloromethane (45 mL). Propanoyl chloride (4.5 mL, 53 mmol) was added to this mixture and the reaction was heated to reflux. Once at reflux, lithium hydride (89 mmol) was added to the reaction vessel and the reaction was allowed to stir at reflux for 18 hours. After the 18 hour period, the reaction mixture was cooled to 0 °C and quenched with a saturated ammonium chloride solution (20 mL). The resulting mixture was extracted with dichloromethane (2 x 20 mL) and the organic layer washed with a saturated solution of sodium chloride (20 mL). The final extracted organic layer was then dried using magnesium sulfate and the solvent removed by rotary evaporation.

(5*S*,6*R*)-4-Benzyl-5-methyl-6-phenyl-3-propanoyl-2*H*-1,3,4-oxadiazinan-2-one (11a). The compound was isolated and recrystallized from ethyl acetate and hexanes to yield a white solid in a 65% yield. Mp: 98-99 °C (hexanes/EtOAc). R_f = 0.36 (80:20 hexanes/EtOAc). $[\alpha]_d^{25}$ = +16.3 (*c* 0.47, $CHCl_3$). IR ($CHCl_3$): 1776, 1695, 1652, 1218, 1014, 744, 704 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.76 (d, *J* = 7.0 Hz, 3H), 1.17 (t, *J* = 7.0 Hz, 3H), 2.83-2.93 (m, 1H), 2.96-3.07 (m, 1H), 3.35 (dq, *J* = 4.5 and 7.0 Hz, 1H), 4.16 (d, *J* = 12.5 Hz, 1H), 4.25 (d, *J* = 12.5 Hz, 1H), 6.09 (d, *J* = 4.7 Hz, 1H), 7.19-7.57 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 9.2, 12.5, 31.5, 51.5, 59.5, 78.0, 125.0, 128.3, 128.6, 128.9, 129.1, 129.5, 135.5, 136.1, 148.8, 175.0. HRMS (EI) calcd for $C_{20}H_{22}N_2O_3$ $(M^{+\bullet})$: 338.1627. Found: 338.1630 *Anal*. Calcd for $C_{20}H_{22}N_2O_3$: %C 70.99, %H 6.51 %N 8.28 Found: %C 70.81, %H 6.51, %N 8.42.

(5*S*,6*R*)-5-Methyl-4-(2,2-dimethylpropyl)-3-propanoyl-6-phenyl-2*H*-1,3,4-oxadiazinan-2-one (11b). The compound was isolated and recrystallized from ethyl acetate and hexanes to yield a transparent solid in a 59% yield (10.8 g, 33.9 mmol). Mp: 106-107 °C (hexanes/EtOAc). R_f = 0.27 (90:10 hexanes/EtOAc). $[\alpha]_d^{25}$ = -92.1 (*c* 0.60, $CHCl_3$). IR (neat): 1720, 1606, 1041, 1017, 732, 697 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.76 (d, *J* = 7.0 Hz, 3H), 1.03 (s, 9H), 1.17 (t, *J* = 7.0 Hz, 3H), 2.81 (d, *J* = 13.7 Hz, 1H), 2.85-2.98 (m, 2H), 2.98 (d, *J* = 13.7 Hz, 1H), 3.47 (dq, *J* = 7.0, 12.5 Hz, 1H), 6.07 (d, *J* = 5.5 Hz, 1H), 7.23-7.40 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 9.3, 13.2, 28.5, 31.6, 32.7, 57.3, 69.3, 80.0, 125.1, 128.3, 128.9, 136.5, 149.7, 175.0. *Anal*. Calcd for $C_{18}H_{26}N_2O_3$: %C 67.88, %H 8.26, %N 8.81. Found: %C 67.94, %H 8.35, %N 8.84.

(4*R*,5*S*,6*R*)-4-Cyclohexyl-5-methyl-6-phenyl-3-propanoyl-2*H*-1,3,4-oxadiazinan-2-one (11c). The solvent was removed *via* rotary evaporation to afford a white solid that was isolated *via* recrystallization (54% yield). Mp: 141-143 °C (hexanes/EtOAc). $[\alpha]_D^{25}$ = -93.6 (*c* 0.75, $CHCl_3$). IR (nujol): 1723, 1604, 1017, 757, 742 cm^{-1}. ^{1}HNMR ($CDCl_3$): δ, 0.77 (d, *J* = 6.8 Hz, 3H), 1.18 (t, *J* = 7.2 Hz, 3H), 1.22-2.11 (m, 10H), 2.84-3.07 (m, 3H), 3.83 (m, 1H), 5.94 (d, *J* = 5.2 Hz, 1H), 7.24-7.41 (m, 5H). ^{13}C NMR ($CDCl_3$): δ, 9.1, 12.7, 24.5, 24.7, 24.7, 25.3, 30.2, 30.3, 50.5, 61.6, 78.7, 124.6, 127.8, 128.4, 175.3. HRMS (EI): Calcd for $C_{19}H_{26}N_2O_2$ $(M^{+\bullet})$: 330.1943. Found: 330.1949. *Anal*. Calcd for $C_{19}H_{26}N_2O_2$: C, 69.06; H, 7.93; N, 8.48. Found: C, 69.25; H, 8.01; N, 8.58.

(5*S*,6*R*)-5-Methyl-4,6-diphenyl-3-propanoyl-2*H*-1,3,4-oxadiazinan-2-one (11d). The resulting light brown oil was chromatographed, yielding the title compound as a colorless oil in 78% yield. $[\alpha]_D^{25}$ = -24.7 (*c* 0.070, CH_2Cl_2). IR ($CHCl_3$): 1777, 1732, 1127, 754, 698 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.09 (d, *J* = 6.8 Hz, 3H), 1.18 (t, *J* = 7.6 Hz, 3H), 2.84 (dq, *J* = 18.0, 7.2 Hz, 1H), 3.07 (dq, *J* = 18, 7.6 Hz, 1H), 4.26-4.32 (m, 1H), 5.56 (d, *J* = 4.4 Hz, 1H), 7.03-7.10 (m, 5H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.28-7.40 (m, 5H). ^{13}C NMR ($CDCl_3$): δ, 8.7, 11.3, 30.1, 57.0, 79.8, 116.5, 123.5, 124.7, 128.2, 128.5, 128.6, 129.9, 135.0, 147.1, 147.8, 174.2. HRMS (EI): Calcd for $C_{19}H_{21}N_2O_3$ $(M + H)^+$: 325.1552. Found: 325.1553.

Representative procedure for the formation of the aldol adducts (12a-m). In a flame-dried, nitrogen-purged, 100 mL round bottom flask was added the N_3-propanoyloxadiazinanone (1.47 mmol) and THF (5 mL). The solution was stirred and then $TiCl_4$ (2.96 mmol) was added and the solution was cooled to 0 °C. The reaction mixture was allowed to stir for 40 minutes before adding distilled triethylamine (2.96 mmol) by syringe. After addition of triethylamine the reaction was stirred for an hour. After the hour time period, 2-naphthaldehyde (2.96 mmol) was added at 0 °C after which the reaction mixture was allowed to gradually warm up to room temperature with stirring for 5 hours. The reaction was then quenched with saturated solution of NH_4Cl (50 mL), and the THF removed by the rotary evaporator. The solution was extracted with EtOAc (2x 50 mL) and the extracted washed with brine solution (50 mL). The final organic layer was dried ($MgSO_4$) and the solvent removed using the rotary evaporator.

(5*S*,6*R*)-4-Benzyl-3-[(2*S*,3*S*)-(3-hydroxy-2-methyl-3-phenylpropanoyl)]-5-methyl-6-phenyl-2*H*-1,3,4-oxadiazinan-2-one (12a). This reaction afforded the product which was purified by column chromatography in a gradient solvent system (90:10 hexanes/EtOAc followed by 80:20 hexanes/EtOAc), resulting in a 99% yield. R_f = 0.42 (60:40 hexanes/EtOAc). $[\alpha]_D^{25}$ = -4.7 (*c* 0.62, $CHCl_3$). IR (neat): 3582, 1718, 1252, 1007, 734 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.75 (d, *J* = 7.0 Hz, 3H), 1.13 (d, *J* = 7.0 Hz, 3H), 2.98 (d, *J* = 2.3 Hz, 1H), 3.38 (dq, *J* = 11.3, 6.6 Hz, 1H), 4.12 (d, *J* = 12.5 Hz, 1H), 4.13-416 (m, 1H), 4.20 (d, *J* = 12.5 Hz, 1H), 5.14 (s, 1H) 6.10 (d, *J* = 4.7 Hz, 1H), 7.19 (d, *J* = 7.0 Hz, 1H), 7.23-7.44 (m, 6H), 7.53 (d, *J* = 7.4 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 11.0, 12.6, 47.3, 51.7, 59.4, 73.5, 78.4, 125.0, 126.4, 127.6, 128.5, 128.8, 129.0, 129.2, 129.6, 135.3, 135.8, 141.8,

148.9, 177.9. HRMS (EI): Calcd for $C_{27}H_{28}N_2O_4$ ($M^{+\bullet}$): 444.2044. Found: 444.2049.

(5*S*,6*R*)-4-Benzyl-3-[(2*S*,3*S*)-(3-hydroxy-2-methyl-3-(2-napthyl)propanoyl)]-5-methyl-6-phenyl-2*H*-1,3,4-oxadiazinan-2-one (12b). This reaction produced clear oil (0.686 g) after performing column chromatography in a gradient solvent system (90:10 hexanes/EtOAc followed by 80:20 hexanes/EtOAc), resulting in a 95% yield. R_f = 0.80 (50:50 hexanes/EtOAc). $[\alpha]_D^{25}$ = –17.9 (*c* 0.47, $CHCl_3$). IR (neat): 3470, 1716, 1253, 749, 700 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.76 (d, *J* = 6.6 Hz, 3H), 1.15 (d, *J* = 7.0 Hz, 3H), 3.23 (d, *J* = 2.4 Hz, 3H), 3.38 (dq, *J* = 6.6, 11.3 Hz, 1H), 4.08 (d, *J* = 12.9 Hz, 1H), 4.22 (d, *J* = 12.9 Hz, 1H), 4.27 (dq, *J* = 7.0, 3.1 Hz, 1H), 5.33 (s, 1H), 6.07 (d, *J* = 4.3 Hz, 1H), 7.19 (d, *J* = 7.4 Hz, 2H), 7.26-7.57 (m, 12H), 7.82-7.86 (m, 2H), 7.94 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 10.8 12.6, 47.1, 51.8, 59.4, 73.4, 78.4, 124.5, 125.0, 125.2, 126.0, 126.3, 127.9, 128.2, 128.3, 128.5, 128.8, 129.0, 129.2, 129.6, 133.0, 133.4, 135.3, 135.8, 139.2, 149.0, 178.0. HRMS (ESI): Calcd for $C_{31}H_{31}N_2O_4$ $(M + H)^+$: 495.2293. Found: 495.2284.

(5*S*,6*R*)-4-Benzyl-3-[(2*S*,3*S*)-(3-hydroxy-2,4-dimethylpentanoyl)]-5-methyl-6-phenyl-2*H*-1,3,4-oxadiazinan-2-one (12c). This reaction product was purified using column chromatography in solvent system of 70:30 hexanes/EtOAc and then recrystallized from methylene chloride and hexanes to give transparent crystals in 99% yield. Mp. = 145-147 °C (hexanes/EtOAc). R_f = 0.64 (50:50 hexanes/EtOAc). $[\alpha]_D^{25}$ = -11.2 (*c* 0.49, $CHCl_3$). IR (nujol): 3455, 1724, 1703, 1231, 755, 696 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.78 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 1.04 (d, *J* = 6.6 Hz, 3H), 1.17 (d, *J* = 6.6 Hz, 3H), 1.69 (dq, *J* = 7.8, 14.8 Hz, 1H), 2.71 (s, 1H), 3.40 (m, 1H), 3.50 (d, 9.0 Hz, 1H), 4.09 (dq, *J* = 7.0, 14.1 Hz, 1H), 4.19 (d, *J* = 12.3 Hz, 1H), 4.35 (d, *J* = 12.3 Hz, 1H), 6.12 (d, *J* = 4.3 Hz, 1H), 7.20 (d, *J* = 7.4 Hz, 2H), 7.26-7.44 (m, 6H), 7.54 (d, *J* = 7.4 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 10.2, 12.7, 19.1, 19.8, 31.0, 42.1, 51.8, 59.5, 76.9, 78.4, 125.0, 128.4, 128.8, 128.9, 129.2, 129.6, 135.3, 135.9, 148.8, 178.9. HRMS (EI): Calcd for $C_{24}H_{30}N_2O_4$ ($M^{+\bullet}$): 410.2201. Found: 410.2205.

(5*S*,6*R*)-4-Benzyl-3-[(2*S*,3*S*)-(3-hydroxy-2,4,4-trimethylpentanoyl)]-5-methyl-6-phenyl-2*H*-1,3,4-oxadiazinan-2-one (12d). This reaction produced a clear oil that was purified by column chromatography in a gradient solvent system (90:10 hexanes/EtOAc followed by 80:20 hexanes/EtOAc), resulting in a 70% yield. R_f = 0.74 (50:50 hexanes/EtOAc). $[\alpha]_D^{25}$ = -4.5 (*c* 0.57, $CHCl_3$). IR (neat): 3525, 1716, 1249, 1137, 733, 700 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.75 (d, *J* = 6.6 Hz, 3H), 0.98 (s, 9H), 1.22 (d, *J* = 7.0 Hz, 3H), 2.60 (d, *J* = 3.9 Hz, 1H), 3.38 (dq, *J* = 11.7,7.0 Hz, 1H), 3.59 (m, 1H), 4.17 (d, *J* = 12.5 Hz, 1H), 4.23 (dq, *J* = 7.0, 2.7 Hz, 1H), 4.32 (d, *J* = 12.5 Hz, 1H), 6.09 (d, *J* = 4.7 Hz, 1H), 7.18 (d, *J* = 7.4 Hz, 2H), 7.25-7.42 (m, 6H), 7.53 (d, *J* = 6.6 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 12.8, 13.1, 27.2, 35.9, 41.3, 51.9, 59.4, 78.0, 78.4, 125.0, 128.4, 128.7, 128.9, 129.2, 129.6, 135.3, 135.9, 148.8, 179.5. HRMS (EI): Calcd for $C_{25}H_{32}N_2O_4$ ($M^{+\bullet}$): 424.2364. Found: 424.2362.

(5*S*,6*R*)-3-[(2*S*,3*S*)-(3-Hydroxy-2-methyl-3-phenylpropanoyl)]-4-(2,2-dimethylpropyl)-5-methyl-6-phenyl-2*H*-1,3,4-oxadiazinan-2-one (12e). The resultant orange oil was chromatographed using silica gel and a gradient solvent system (90:10 hexanes/EtOAc, 80:20 hexanes/EtOAc, followed by 65:35 hexanes/EtOAc) to give clear oil in a 98%yield (0.655 g, 1.54 mmol). R_f = 0.22 (80:20, hexanes/EtOAc). $[\alpha]_D^{25}$ = -85.5 (*c* 0.74, $CHCl_3$). IR (neat): 3479, 1734, 1701, 1241, 1130, 761, 698 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.76 (d, *J* = 6.6 Hz, 3H), 1.02 (s, 9H), 1.12 (d, *J* = 7.0 Hz, 3H), 2.70 (d, *J* = 13.5 Hz, 1H), 3.01 (d, *J* = 13.5, 1 Hz), 3.12 (d, *J* = 2.7, 1H), 3.50 (p, *J* = 7.0 Hz, 1H), 4.11 (dq, *J* = 3.5, 7.0 Hz, 1H), 5.22 (m, 1H), 6.08 (d, *J* = 5.1 Hz, 1H), 7.22-7.46 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 11.0, 13.2, 28.5, 32.7, 46.7, 57.1, 68.9, 73.5, 79.2, 125.0, 126.5, 127.6, 128.4, 128.5, 129.0, 136.2, 141.7, 149.7, 177.6. HRMS (FAB): Calcd for $C_{25}H_{33}N_2O_3$ $(M + H)^+$: 425.2447. Found: 425.2440.

(5*S*,6*R*)-3-[(2*S*,3*S*)-(3-*p*-Chlorophenyl-3-hydroxy-2-methylpropanoyl)]-4-(2,2-dimethylpropyl)-5-methyl-6-phenyl-2*H*-1,3,4-oxadiazinan-2-one (12f). The resultant orange oil was chromatographed using silica gel and a gradient solvent system (90:10 hexanes/EtOAc, 80:20 hexanes/EtOAc, followed by 65:35 hexanes/EtOAc) to give clear oil in a 91% yield. R_f = 0.17 (80:20 hexanes/EtOAc). $[\alpha]_D^{25}$ = -69.7 (*c* 0.47, $CHCl_3$). IR (neat): 3502, 1719, 1240, 1014, 735 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.74 (d, *J* = 7.0 Hz, 3H), 1.01 (s, 9H), 1.08 (d, *J* = 7.0 Hz, 3H), 2.66 (d, *J* = 13.7 Hz, 1H), 3.00 (d, *J* = 13.7 Hz, 1H), 3.29 (d, *J* = 2.3, 1H), 3.49 (p, *J* = 7.0 Hz, 1H), 4.06 (dq, *J* = 7.0, 3.5 Hz, 1H), 5.17 (s, 1H), 6.07 (d, *J* = 5.1 Hz, 1H), 7.20-7.39 (m, 9H). ^{13}C NMR ($CDCl_3$): δ 11.1, 13.2, 28.5, 32.7, 46.6, 57.1, 68.9, 72.9, 79.3, 125.0, 127.9, 128.4, 128.5, 129.0, 133.2, 136.1, 140.4, 149.8, 177.4. HRMS (FAB): Calcd for $C_{25}H_{31}N_2O_4Cl$ $(M + H)^+$: 459.2048. Found: 459.2051.

(5*S*,6*R*)-3-[(2*S*,3*S*)-(3-Hydroxy-2-methyl-3-(2-naphthyl)-propanoyl)]-5-methyl-4-neopentyl-6-phenyl-2*H*-1,3,4-oxadiazinan-2-one (12g). The resultant orange oil was purified by column chromatography using silica gel and a gradient solvent system (80:20, hexanes/EtOAc followed by 75:25, hexanes/EtOAc) to give a clear oil in a 99% yield (0.737 g, 1.55 mmol). R_f = 0.29 (80:20 hexanes/EtOAc). $[\alpha]_D^{25}$ = -68.6 (*c* 1.07, $CHCl_3$). IR (neat): 3494, 1723, 1603, 1241, 1135, 753, 700 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.77 (d, *J* = 7.0 Hz, 3H), 1.00 (s, 9H), 1.13 (d, *J* = 7.0 Hz, 3H), 2.68 (d, *J* = 13.7, 1H), 2.99 (d, *J* = 13.7 Hz, 1H), 3.25 (s, 1H), 3.49 (m, 1H), 4.23 (dq, *J* = 3.5, 6.6 Hz, 1H), 5.39 (d, *J* = 2.3 Hz, 1H), 6.07 (s, 1H), 7.22-7.57 (m, 9H), 7.82-7.94 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 11.6, 13.2, 28.5, 32.6, 46.8, 56.9, 68.7, 73.9, 77.3, 77.8, 79.1, 124.8, 125.1, 125.4, 125.5, 126.0, 126.3, 127.9, 128.2, 128.4, 129.0, 133.1, 133.5, 136.2, 139.6, 149.9, 177.1. HRMS (EI): Calcd for $C_{29}H_{34}N_2O_4$ ($M^{+\bullet}$): 474.2508. Found: 474.2518.

(5*S*,6*R*)-3-[(2*S*,3*S*)-(3-hydroxy-2,4-dimethylpentanoyl)]-5-methyl-4-(2,2-dimethylpropyl)-6-phenyl-2*H*-1,3,4-oxadiazinan-2-one (12h). The resultant orange oil was chromatographed using silica gel and a gradient solvent system (90:10 hexanes/EtOAc, 80:20 hexanes/EtOAc, followed by 65:35 hexanes/EtOAc) to give clear oil in 95%yield. $[\alpha]_D^{25}$ = -55.6 (*c* 0.46, $CHCl_3$). IR (neat): 3511, 1714, 1234, 1131, 1045, 761, 698 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.78 (d, *J* = 7.0 Hz, 3H), 0.92 (d, *J* = 7.0 Hz, 3H), 0.97 (d, *J* = 6.6 Hz, 3H), 1.04 (s, 9H), 1.17 (d, *J* = 7.0 Hz, 3H), 1.58 (m, 1H), 2.78 (d, *J* = 13.7 Hz, 1H), 2.94 (s, 1H), 3.05 (d, *J* = 13.7 Hz, 1H), 3.50 (p, *J* = 7.0 Hz, 1H), 3.55-3.58 (m, 1H), 4.03 (dq, *J* = 7.0, 2.0 Hz, 1H), 6.10 (d, *J* = 5.1, 1H), 7.23-7.41 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 10.4, 13.3, 17.4, 18.8, 19.1, 19.8, 20.1, 22.0, 28.5, 30.1, 31.0, 32.7, 41.6, 57.0, 69.0, 79.1, 80.5, 125.0, 128.4, 129.0, 136.2, 149.5, 178.8, 207.0. HRMS (FAB): Calcd for $C_{22}H_{35}N_2O_4$ $(M + H)^+$: 391.2592. Found: 391.2597.

(5*S*,6*R*)-3-[(2*S*,3*S*)-(3-Hydroxy-2,4,4-trimethylpentanoyl)]-5-methyl-4-(2,2-dimethylpropyl)-6-phenyl-2*H*-1,3,4-oxadiazinan-2-one (12i). The result gave an orange oil which was chromatographed using silica gel and a solvent system of 90:10 (hexanes/EtOAc) to give a clear oil in a 99%yield (0.628 g, 1.55

mmol). R_f = 0.42 (75:25 hexanes/EtOAc). $[\alpha]_d^{25}$ = -63.0 (*c* 0.45, $CHCl_3$). IR (neat): 3521, 1726, 1713, 1229, 1130, 761, 698 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.75 (d, *J* = 7.0 Hz, 3H), 0.96 (s, 9H), 1.02 (s, 9H), 1.20 (d, *J* = 7.0 Hz, 3H), 2.73 (d, *J* = 4.3 Hz, 1H), 2.74 (d, *J* = 13.7 Hz, 1H), 3.03 (d, *J* = 13.7 Hz, 1H), 3.49 (p, *J* = 7.0, 1H), 3.64 (m, 1H), 4.16 (dq, *J* = 1.6, 7.0 Hz, 1H), 6.07 (d, *J* = 5.5 Hz, 1H), 7.19-7.37 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 13.0, 13.3, 27.2, 28.6, 32.7, 35.9, 40.9, 57.0, 68.8, 77.9, 79.1, 125.0, 128.3, 129.0, 136.3, 149.5, 179.3. HRMS (FAB): Calcd for $C_{23}H_{37}N_2O_4$ (M + H)$^+$: 405.2748. Found: 405.2753.

(5*S*,6*R*)-4-Cyclohexyl-3-[(2*S*,3*S*)-(3-*p*-chlorophenyl-3-hydroxy-2-methylpropanoyl)]-5-methyl-6-phenyl-2*H*-1,3,4-oxadiazinan-2-one (12j). The solvent was removed *via* rotary evaporation and recrystallized affording the title compound in 67% yield. Mp = 157-160 °C (hexanes/EtOAc). $[\alpha]_D^{25}$ = -915 (*c* 248, CH_2Cl_2). IR (nujol mull): 1734, 1710, 1014, 736, 718 cm^{-1}. ^1H NMR: δ 0.78 (d, *J* = 6.3 Hz, 3H), 1.11 (d, *J* = 6.3 Hz, 3H), 1.19-2.10 (m, 10H), 2.99 (broad singlet, 1H), 3.21, 3.81-3.90 (m, 1H), 4.15-4.20 (dq, *J* =7.0, 3.5 Hz, 1H), 5.21 (s, 1 H), 5.97 (s, 1H), 7.24-7.42 (m, 9H). ^{13}C NMR: δ, 11.6, 12.9, 24.6, 24.7, 25.3, 29.9, 30.6, 46.4, 51.0, 46.4, 51.0, 61.7, 73.2, 79.5, 124.7, 127.9,128.0, 128.1, 128.6, 132.9, 136.0, 140.4, 149.2, 177.4. HRMS (EI) calcd for $C_{26}H_{31}ClN_2O_4$ (M + H)$^+$: 471.2051. Found: 471.2047.

(5*S*,6*R*)-4-Cyclohexyl-3-[(2*S*,3*S*)-(3-hydroxy-2,4,4-trimethylpentanoyl)]-4-cyclohexyl-5-methyl-6-phenyl-2*H*-1,3,4-oxadiazin-2-one (12k). This reaction produced a clear oil that was purified by column chromatography (hexanes/EtOAc, 80:20) in 99% yield. R_f = 0.19 (80:20 hexanes/EtOAc), $[\alpha]_D^{25}$ = -94.3 (*c* 0.54, $CHCl_3$). IR (nujol mull): 3528, 1732 (broad), 1604, 1237, 1132, 730, 700 cm^{-1}. ^1H NMR ($CDCl_3$): 0.73 (d, *J* = 7.0 Hz, 3H), 0.96 (s, 9H), 1.18 (d, *J* = 7.0 Hz, 3H), 1.23-1.33 (m, 4H), 1.40-1.50 (m, 1H), 1.60-1.63 (m, 1H), 1.72-1.86 (m, 2H), 1.97 (s, 1H) 2.03-2.06 (m, 1H), 2.88 (d, *J* = 3.1 Hz, 1H), 2.94-3.00 (m, 1H) 3.64-3.65 (m, 1H), 3.80 (p, *J* = 6.6 Hz, 1H), 4.20 (dq, *J* = 5.9, 7.0 Hz, 1H), 5.91 (d, *J* = 5.5 Hz, 1H), 7.18-7.35 (m, 5H). ^{13}C NMR ($CDCl_3$): 13.0, 13.5, 25.0, 25.1, 25.7, 27.3, 30.6, 30.7, 35.9, 40.7, 51.2, 62.0, 78.0, 79.6, 124.9, 128.3, 128.9, 136.1, 149.4, 180.5. HRMS (ESI): Calcd for $C_{24}H_{37}N_2O_4$ (M + H)$^+$: 417.2760. Found: 417.2753.

(5*S*,6*R*)-3-[(2*S*,3*S*)-(3-hydroxy-2-methyl-3-phenyl–propanoyl)]-5-methyl-4,6-diphenyl-2*H*-1,3,4-oxadiazinan-2-one (12l). The solvents were removed by rotary evaporation and the purified product was isolated as orange crystals in 88% yield *via* chromatography. Mp: 165-167 °C (hexanes/EtOAc). $[\alpha]_D^{25}$ = -47.9 (*c* 0.30, CH_2Cl_2). IR ($CHCl_3$): 3017, 1772, 1732, 1007, 755, 700, cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.00 (d, *J* = 7.0 Hz, 3H), 1.14 (d, *J* = 7.0 Hz, 3H), 3.00 (s, -OH, 1H), 4.19 (dq, *J* = 7.2, 4.0 Hz, 1H), 4.28 (dq, *J* = 6.8, 4.4 Hz, 1H), 5.24 (d, *J* = 4.3 Hz, 1H), 5.57 (d, *J* = 4.3 Hz, 1H), 6.95-6.97 (m, 2H), 7.09-7.13 (m, 1H), 7.20-7.46 (m, 12H). ^{13}C NMR ($CDCl_3$): δ 11.4, 11.6, 46.5, 57.5, 73.4, 80.2, 116.6, 123.8, 124.8, 126.3, 127.5, 128.3, 128.4, 128.7, 130.1, 130.2, 134.9, 141.4, 147.1, 148.1. HRMS (EI) Calcd for $C_{26}H_{26}N_2O_4$ ($M^{+\bullet}$): 431.1971 Found: 431.1967.

(4*R*,5*S*,6*R*)-3-[(2*S*,3*S*)-(3-*p*-Chlorophenyl-3-hydroxy-2-methylpropanoyl)]-5-methyl-4,6-diphenyl-2*H*-1,3,4-oxadiazinan-2-one (12m). The solvents were removed by rotary evaporation and the purified product was isolated as a colorless oil in 62% yield via chromatography (90:10, hexanes: EtOAc. $[\alpha]_D^{25}$ = -30.8 (*c* 0.70, $CHCl_3$). IR (CH_3Cl): 3482, 1772, 1734, 1012, 755, 698 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.02 (d, *J* = 6.8 Hz, 3H), 1.13 (d, *J* = 6.8 Hz, 3H), 3.07 (d, *J* = 1.6 Hz, -OH), 4.17-4.19 (dq, *J* = 7.2, 4 Hz, 1H), 4.27-4.30 (dq, *J* = 4.0, 6.8 Hz, 1H), 5.20 (s, 1H), 5.57 (d, *J* = 4.4 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 2H), 7.12 (t, *J* = 7.6 Hz, 1H), 7.21 (d, *J* = 7.6 Hz, 1H), 7.30-7.39 (m, 9H). ^{13}C NMR ($CDCl_3$): δ 11.6, 12.1, 46.9, 57.7, 73.3, 80.5, 116.8, 124.1, 125.0, 128.1, 128.6, 128.7, 129.0, 130.4, 133.4, 135.0, 140.3, 147.2, 148.6, 177.1. HRMS (EI) Calcd for $C_{26}H_{26}ClN_2O_4$ (M + H)$^+$: 465.1581. Found: 465.1577.

Methyl (2*S*,3*S*)-2-methyl-3-hydroxy-3-phenylpropanoate (13). In a 100 mL round bottom flask was placed the oxadiazinanone substrate and 6 *M* H_2SO_4 (10 mL) in THF (3 mL). This reaction mixture was then heated. The reaction mixture was allowed to stir for 18 hours at 50 °C. The resulting mixture was then quenched with a solution of saturated sodium bicarbonate (20 mL) and extracted with ethyl acetate (2 x 20 mL). The organic layer was dried with $MgSO_4$ and the solvent removed by rotary evaporation. The crude carboxylic acid was then converted to the methyl ester *via* methanol (1 mL) and trimethylsilyldiazomethane solution (1 mL in tetrahydrofuran). After addition of trimethylsilyldiazomethane to the mixture of methanol and carboxylic acid, the reaction mixture was allowed to stir for 2 hours at room temperature. The reaction was quenched with a saturated solution of sodium bicarbonate (20 mL) and extracted with ethyl acetate (2 x 20 mL). The methyl ester was then purified by column chromatography using a solvent system of 1:9 ethyl acetate and hexanes. R_f = 0.13 (95:5 hexanes/EtOAc). Hydrolysis of 12a: $[\alpha]_D^{25}$ = -15.3 (*c* 1.82, CH_2Cl_2). Hydrolysis of 12e: $[\alpha]_D^{25}$ = -13.2 (*c* 1.06, CH_2Cl_2). Hydrolysis of 12j: $[\alpha]_D^{25}$ = -15.3 (*c* 1.58, CH_2Cl_2). IR (neat): 3482, 1718, 1255, 1035, 734, 702 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.12 (d, *J* = 7.2 Hz, 3H), 2.77 (dq, *J* = 4.5, 7.2 Hz, 1H), 3.21 (s, 1H), 3.61 (s, 3H), 5.04 (d, *J* = 4.5 Hz, 1H), 7.23-7.32 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 11.1, 46.8, 52.0, 74.0, 126.2, 127.7, 128.5, 141.9, 176.3. HRMS (ESI) calcd for $C_{11}H_{15}O_3$ (M + H)$^+$: 217.0846. Found: 217.0841.

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[8] Caution: *N*-Nitrosamines should be handled with care as some *N*-nitrosamines are known to possess carcinogenic properties. Please see: Hecht, S. S. *Proceedings of the Society for Experimental Biology and Medicine* **1997**, *216*, 181-191.

[9] The *N*-phenyl-*N*-nitrosamine was susceptible to decomposition even at temperatures near -20 °C. This compound may have readily decomposed *via* a retro-Aldol type process similar to that studied by Loeppky and coworkers. Please see: (a) Loeppky, R. N.; McKinley, W. A.; Hazlitt, L. G.; Outram, J. R. *J. Org. Chem.* **1982**, *47*, 4833-4841. (b) Loeppky, R. N.; Hazlitt, L. G. *J. Org. Chem.* **1982**, *47*, 4841-4846.

[10] *N*-Nitrosamines 8b and 8c were reduced with $LiAlH_4$ in THF within 2 hours at reflux. In contrast, *N*-nitrosamines **8a** and **8d** underwent over-reduction to the corresponding amine under the same reaction conditions. We were gratified to learn that the reduction of these substrates proved to be successful when the reactions were conducted at room temperature.

[11] (a) Yan, T.-H.; Tan, C.-W.; Lee, H.-C.; Lo, H.-C.; Huang, T.-Y. *J. Am. Chem. Soc.* **1993**, *115*, 2613-2621. (b) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920-1923.

[12] The enantiomeric ratios reported in this work were determined by chiral stationary phase HPLC as this method was more reliable. The literature value for the optical activity of the (2*R*,3*R*)-methyl 2-methyl-3-phenylpropanoate is reported as $[\alpha]_D = +23.5$ (*c* 3.23, CH_2Cl_2): Oppolzer, W.; Blagg, J.; Rodriguez, I.; Walther, E. *J. Am. Chem. Soc.* **1990**, *112*, 2767-2772.

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