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Tetrahedron: *Asymmetry* 16 (2005) 1047–1053

Synthesis, X-ray crystallography and computational studies concerning an oxadiazinone derived from D-camphor: a structural limitation of oxadiazinones as chiral auxiliaries

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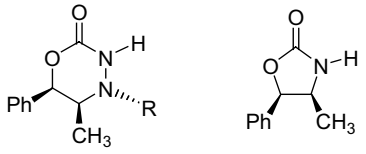
Received 10 December 2004; accepted 5 January 2005

Abstract—A camphor-based oxadiazinone was prepared by reaction of the *N*-nitroimine of D-camphor with (1*R*,2*S*)-norephedrine; the reduction of the resultant imine; *N*-nitrosation of the amine; reduction to the corresponding hydrazine and cyclization. The conformational behaviour of oxadiazinone **7** was modeled in the gas and solution phases using the semiempirical AM1 method and density functional theory. Application of the oxadiazinone in the titanium mediated asymmetric aldol reaction provided the highly diastereoselective formation of the expected *syn*-adducts **8a**–**d** as evidenced by single crystal X-ray diffraction analysis. Attempts to remove the oxadiazinone auxiliary using acidic or basic conditions failed to yield the expected β-hydroxyacid in significant yield.

1. Introduction

3,4,5,6-Tetrahydro-2*H*-1,3,4-oxadiazin-2-ones **1** (oxadiazinones) have recently been introduced as viable chiral auxiliaries for the asymmetric aldol reaction.[1] Oxadiazinones such as **1a** were first prepared by Trepanier et al. in the late 1960s for use as central nervous system stimulants.[2] Since these initial investigations, oxadiazinones have re-emerged as reagents for asymmetric synthesis.[1,3] The application of these compounds was, in part, inspired by the success of the related oxazolidinones **2** in a myriad of reactions (Figure 1).[4–6]



1a: R = -CH_3
1b: R = -$CH(CH_3)_2$

2

Figure 1. Oxadiazinones **1** and oxazolidinones **2**.

The major difference between these two heterocycle families is the transmission of stereochemical information. Oxazolidinones transmit chirality by way of direct intra ligand asymmetric induction; oxadiazinones transmit their chirality by way of intra ligand asymmetric induction via intramolecular chiral relay.[1a,7] The relay is made possible by the stereogenic N_4-nitrogen substituent of the heterocycle. In effect, the transmission of information relies on the conformational stability of the C_6-phenyl and C_5-methyl in influencing the N_4-nitrogen substituent. This N_4-nitrogen substituent can be introduced into the heterocycle by the use of reductive alkylation of substrates, such as (1*R*,2*S*)-norephedrine.[1a] In conjunction with our ongoing programme focused on the development of oxadiazinones, we have been engaged in a study of the impact of changing the nature of the N_4-substituent. In the process of developing substituents,[1e] we opted to pursue the use of D-camphor as a candidate for constructing a unique bornyl substituent. The chirality of the bornyl group derived from camphor is not expected to play a role in the asymmetric induction; it is, however, expected to only provide a sterically demanding environment at the N_4-position of the oxadiazinone core.

Herein, we report on the synthesis, X-ray crystallography, computational studies and asymmetric application

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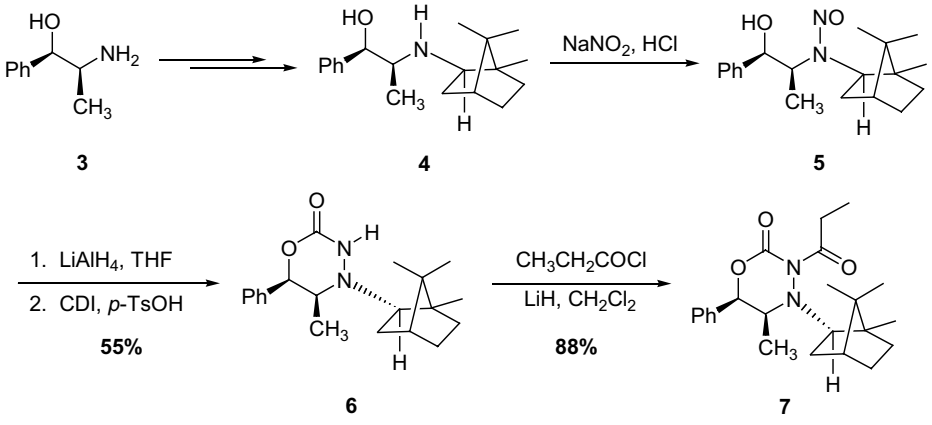
doi:10.1016/j.tetasy.2005.01.020

of the camphor-based oxadiazinone. We also report on the difficulties encountered in attempts to hydrolyze the aldol adducts of the camphor-based oxadiazinone.

2. Results and discussion

The synthesis of the N_4-bornyl heterocycle proved not to be as straightforward as other syntheses of chiral oxadiazinones (Scheme 1).[8] This difficulty was primarily due to the fact that D-camphor does not readily form imines with many amines.[9] Morris and Ryder developed a method for imine formation via the preparation of the *N*-nitroimine of camphor.[10] Using this method, we were able to condense D-camphor with (1*R*,2*S*)-norephedrine **3** to yield the corresponding β-aminoalcohol **4**.[11] This material was *N*-nitrosated[12] and subsequently reduced with $LiAlH_4$ to the corresponding β-hydrazinoalcohol. The crude β-hydrazinoalcohol was converted to the desired oxadiazinone **6** by reaction with 1,1′-carbonyldiimidazole and *p*-toluenesulfonic acid in 55% yield from the *N*-nitrosamine. In order to pursue test reactions with the asymmetric aldol reaction, oxadiazinone **6** was acylated with propionyl chloride and lithium hydride in methylene chloride to afford the N_4-bornyl-N_3-propionyloxadiazinone **7**, the solid state structure of which was confirmed by X-ray crystallography (Fig. 2).[13]

The X-ray crystal structure revealed that oxadiazinone **7** adopts a twist boat conformation in which the N_4-bornyl substituent and the C_5-methyl group have a 1,2-*trans*-diaxial relationship. As this conformation has been observed for related oxadiazinones,[1a,d] we were more concerned with the positioning of the bornyl group. The X-ray crystal structure revealed that the bulk of the N_4-bornyl substituent is positioned directly under the N_3-propionyl substituent. It was thought that this arrangement would be ideal for asymmetric induction in the titanium mediated aldol addition reaction of the



Scheme 1. Oxadiazinone synthesis.

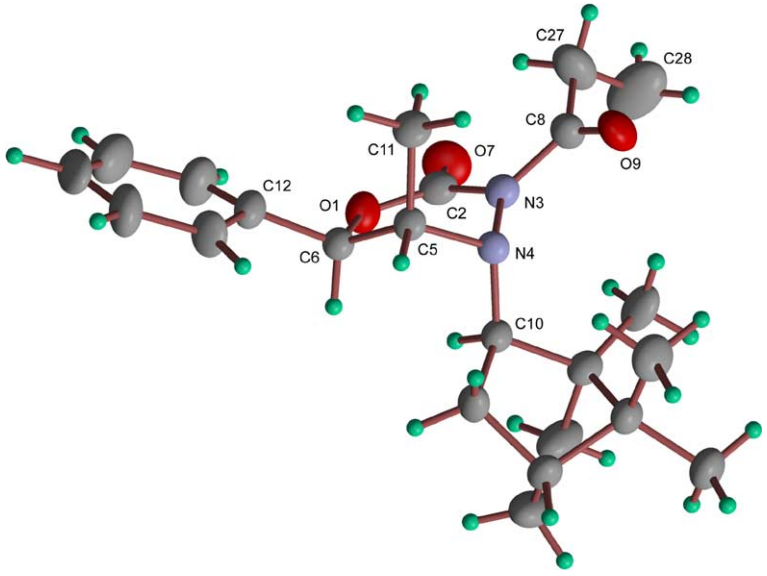


Figure 2. Oxadiazinone acylation and RASTEP view of **7** showing the atom labelling scheme. Non-hydrogen atoms are represented by Gaussian ellipsoids at the 50% probability level. Hydrogen atoms have been drawn arbitrarily small and are not labelled.

N_4-bornyloxadiazinone provided that solid state conformation was a reflection of the solution conformation.

To address the conformational preferences of oxadiazinone **7** in the solution state, two different computational approaches were employed, including the AM1 semiempirical method and density functional theory (DFT). Calculations were performed in the gas phase and in solution phase through the use of continuum solvent techniques. Semiempirical calculations were performed using the Spartan 5.1 and Spartan 02 software packages running on SGI O2 workstations.[14] DFT calculations were performed with the PQS 3.1 software package running on a Linux workstation.[15] The optimized structures obtained were verified as local minima by determination of vibrational frequencies. A conformation search was carried out in the gas phase using the AM1 semiempirical method to determine low-energy conformations of oxadiazinone **7**.[16] In the AM1 search, 18 conformers were found to exist within 5 kcal/mol of the lowest energy conformer. About half of the low-energy conformers had carbonyl orientations that were either nearly parallel or anti-parallel. Several of the lowest energy gas phase conformers from the AM1 conformation search were then optimized with the B3LYP/DZP density functional method. The lowest energy structure obtained using density functional theory (DFT) had a dihedral angle between the carbonyl groups of 174°, a nearly anti-parallel alignment (Fig. 3a). The DFT conformer most closely resembling the one found in the X-ray crystal structure had a gas phase energy 1.1 kcal/mol above the lowest energy conformer and a carbonyl dihedral angle of 160° (Fig. 3b); this result compares favourably to the X-ray crystal structure carbonyl dihedral angle of 167.0 (3)°. The only significant difference between the lowest energy conformer and the one resembling the X-ray crystal structure is the orientation of the ethyl side chain attached to C_8 (see Fig. 2).

The effect of solvation upon the structure and energies of the conformers of oxadiazinone **7** was investigated by performing DFT calculations with the COSMO continuum solvent model[17] and a dielectric constant selected to model water. The geometries of two conformers, one with nearly parallel and one with nearly anti-parallel carbonyl groups, were optimized at the B3LYP/DZP level with the COSMO solvation model. As would be expected in a polar solvent, the conformer with the largest dipole moment exhibits the largest solvation effect. The calculated gas phase dipole moment was 7.42 Debye for the conformer with nearly parallel carbonyl groups and 3.59 Debye for the conformer with nearly anti-parallel carbonyl groups. The more favourable solvation energy of the conformer with parallel carbonyls lowers its energy relative to the conformer with anti-parallel carbonyls. In the gas phase, the conformer with parallel carbonyls is 4.4 kcal/mol higher in energy than the conformer with anti-parallel carbonyls. In solution, this trend is reversed so that the conformer with parallel carbonyls is now 0.1 kcal/mol *lower* in energy than the conformer with anti-parallel carbonyls. This computational evidence suggests that both the parallel and anti-parallel orientations of the carbonyls are possible in the solution phase.

With the N_3-acylated heterocycle in hand, we pursued the asymmetric aldol reaction. Oxadiazinone **7** was first reacted with titanium tetrachloride ($TiCl_4$) at 25 °C in tetrahydrofuran and then reacted with triethylamine at −78 °C over a 1 h period to ensure the complete formation of the enolate (Table 1).[18] The aldehyde was then added at 0 °C and the reaction allowed to warm to room temperature. The products of the asymmetric aldol reactions were obtained in good yield and in high diastereoselectivity. Aliphatic aldehydes bearing α-protons were problematic in terms of incomplete reactivity and were not pursued. Surprisingly, these results were not clearly superior to those observed for the norephedrine based N_4-isopropyl based oxadiazinone,[1a] except in the case of the formation of the aldol adduct **8d**. This was counter-intuitive as the diastereomeric ratio was expected to be greater for the N_4-bornyl system versus the N_4-isopropyl system due to the greater steric requirement. It is speculated that the aldol reactions of oxadiazinone **7** may involve alternative transition states other than the proposed chair-like Zimmerman–Traxler transition state that has been invoked for other

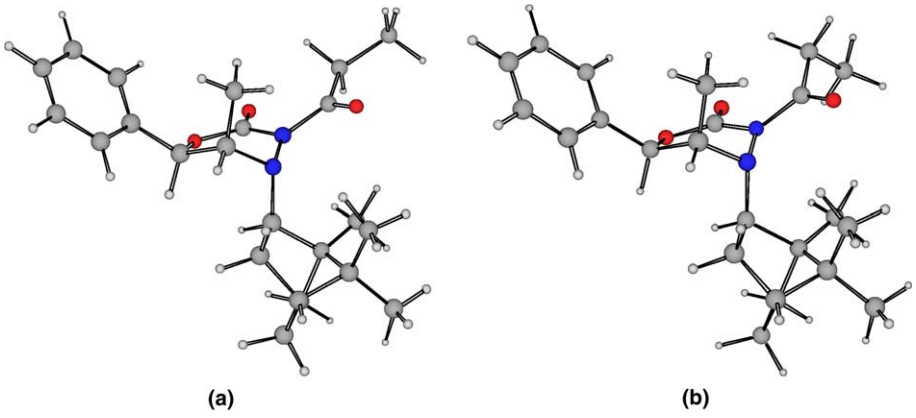
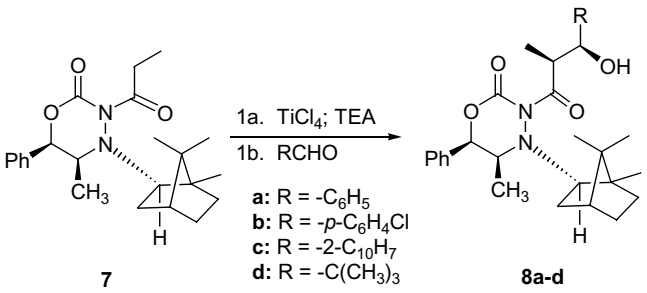


Figure 3. (a) Lowest energy gas phase structure of oxadiazinone **7** determined using the B3LYP/DZP method. (b) Gas phase conformer of oxadiazinone **7** closest to the X-ray crystal structure determined using the B3LYP/DZP method.

Table 1. Asymmetric aldol reaction of the N_4-bornyloxadiazinone



Entry	Compound	RCHO	Yield[a]	Dr[b]
1	**8a**	C_6H_5CHO	80	⩾49:1
2	**8b**	*p*-ClC_6H_4CHO	67	⩾49:1
3	**8c**	2-$C_{10}H_7CHO$	88	⩾49:1
4	**8d**	$(CH_3)_3CCHO$	68	⩾49:1

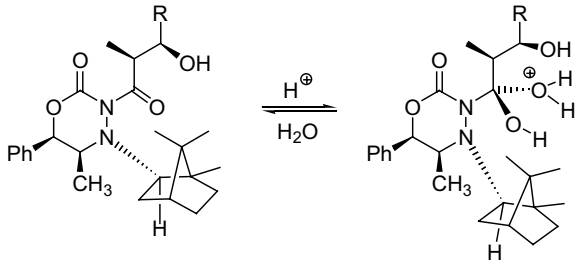
[a] Yield represent purification by column chromatography or recrystallization.

[b] Diastereomeric ratio of crude reaction mixture (major diastereomers:minor diastereomers). The individual minor diastereomers were not characterized.

oxadiazinones. The absolute stereochemistry of the aldol adduct N_3-side chain of oxadiazinone **8c** was determined by single crystal X-ray crystallography favouring the *syn*-diastereomer (Fig. 4). By analogy, it is proposed that **8a**, **8b** and **8d** possess the same absolute stereochemistry as **8c**.[19]

With the aldol adducts **8a**–**d** in hand, hydrolysis of the N_3-side chain was pursued. Unfortunately, it was not possible to hydrolyze the adducts under either acidic or basic conditions as had been done with previous oxadiazinone aldol adducts.[1] All reaction attempts afforded complex mixtures, which suggested that retro-aldol and elimination reactions were dominant reaction pathways. When comparing the ease of hydrolysis for oxadiazinone based aldol adducts, a trend emerged that was dependent on the size of the N_4-substituent (Table 2). The most successful hydrolysis occurred when the N_4-substituent was small (**9**, R = –CH_3).[1c] The hydrolysis of the N_4-isopropyl oxadiazinone proved to be not as straightforward.[1a] The dominant problem was the hydrolysis of the cleaved oxadiazinone and hydrolysis of the oxadiazinone ring prior to the cleavage of the aldol side chain. The least successful hydrolysis occurred when the N_4-substituent was large (**8a**, R = –$C_{10}H_{17}$).

The failure of oxadiazinones **8a**–**d** to undergo clean hydrolysis can be attributed to the steric environment created by the presence of the N_4-bornyl substituent. The N_3-carbonyl moiety must undergo a hybridization change from a trigonal planar carbonyl to a tetrahedral intermediate; may not be viable due to the proximity of the N_4-bornyl substituent (Scheme 2). This suggests that the process of hydrolysis becomes increasingly difficult as larger groups are introduced at the N_4-nitrogen.



Scheme 2.

3. Conclusion

A structurally novel oxadiazinone **6** has been synthesized from (1*R*,2*S*)-norephedrine and D-camphor. The oxadiazinone auxiliary was acylated to afford the N_4-bornyl-N_3-propionyloxadiazinone **7**. The structure of oxadiazinone **7** was studied in the solid state by X-ray

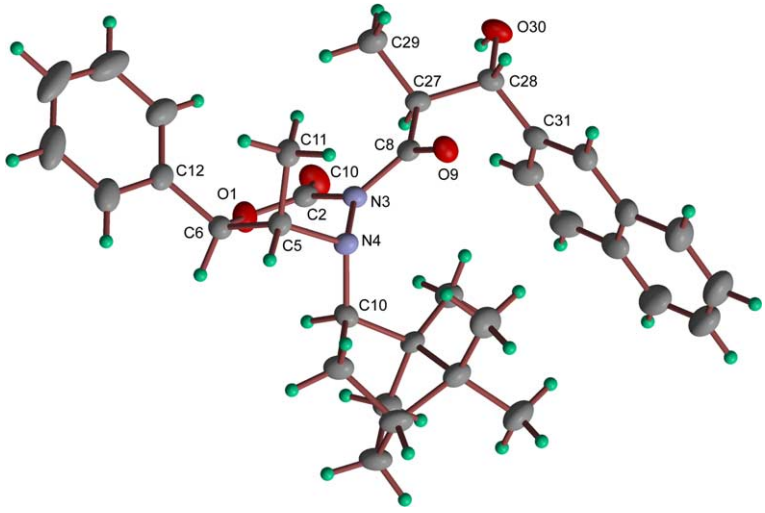
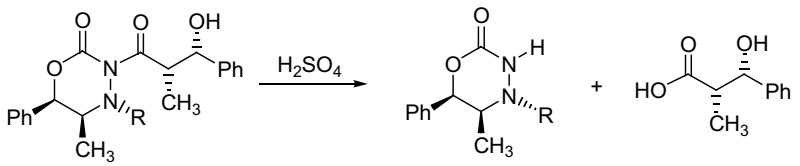


Figure 4. RASTEP view of **8c** showing the atom labelling scheme. Non-hydrogen atoms are represented by Gaussian ellipsoids at the 50% probability level. Hydrogen atoms have been drawn arbitrarily small and are not labelled.

Table 2. Comparative hydrolyses of oxadiazinone aldol adducts



8a: R = -$C_{10}H_{17}$ (-bornyl)
9: R = -CH_3
10: R = -$CH(CH_3)_2$

6: R = -$C_{10}H_{17}$ (-bornyl)
11: R = -CH_3
12: R = -$CH(CH_3)_2$

Entry	N_4-Substituent	β-Hydroxyacid (% yield)	Oxadiazinone (% yield)
1	–CH_3	71[a]	98
2	–$CH(CH_3)_2$	56[a]	46[c]
3	–$C_{10}H_{17}$ (–bornyl)	<5[b]	na[d]

[a] Yield after recrystallization.
[b] The relative amount of β-hydroxyacid was estimated from the 400 MHz ^{1}H NMR spectrum.
[c] The remainder was a mixture of hydrolyzed oxadiazinone, elimination products and retro-aldol products.
[d] Yield not determined.

crystallography and modeled in the gas and solution phases with computational methods. Oxadiazinone **7** was employed in the asymmetric aldol addition reaction with good yields and very good diastereoselectivities, although not superior to the related N_4-isopropyloxadiazinone.[1a] The absolute stereochemistry of the aldol adduct **8c** was determined by X-ray crystallographic studies. Attempts at the hydrolysis of the oxadiazinone adducts failed, presumably due to the steric environment created by the N_4-bornyl substituent. This result suggests that the steric tuning of oxadiazinones may be limited; larger substituents at the N_4-position may not necessarily give superior diastereoselectivities and the ability to hydrolyze the aldol adduct is compromised by the larger substituent. A broader study involving a systemic study of potential substituents is underway and will be disclosed.

4. Experimental

4.1. (5*S*,6*R*,1′*R*,2′*R*,4′*R*)-3,4,5,6-Tetrahydro-5-methyl-4-(1,7,7-trimethylbicyclo[2.2.1]hept-2-yl)-6-phenyl-2*H*-1,3,4-oxadiazin-2-one 6

In a flame-dried, nitrogen purged, three necked 1 L round bottom flask fitted with a condenser and pressure equalizing addition funnel was placed lithium aluminium hydride (3.973 g, 104.7 mmol) in THF (200 mL). The reaction was heated to mild reflux and *N*-nitrosamine **5** (11.04 g, 34.90 mmol) in THF (100 mL) added to the reaction mixture over a period of 40 min. The reaction was allowed to stir overnight at reflux (70 °C). After 24 h, the reaction was cooled to 0 °C and an aqueous solution of sodium hydroxide (6 M, 400 mL) added. The white paste that formed was washed with EtOAc (3 × 500 mL) and the combined organic layers successively treated with an aqueous solution of Rochelle's salt (200 mL) and brine solution (200 mL). This process afforded the crude hydrazine, which was used immediately in the next reaction without purification. In a flame-dried, nitrogen purged 500 mL round bottom flask, hydrazine (7.84 g, 25.9 mmol) was dissolved in THF (75 mL) and to this solution was added 1,1′-carbonyldiimidazole (5.01 g, 31.1 mmol) and then *p*-toluenesulfonic acid (4.93 g, 25.9 mmol). The solution was heated to reflux and stirred under nitrogen overnight. The reaction was quenched by the addition of a saturated aqueous solution of sodium bicarbonate (100 mL). The organic products were extracted from this mixture by the use of ethyl acetate (2 × 100 mL). The combined layers were treated with a saturated aqueous solution of brine (100 mL), dried over $MgSO_4$ and the solvent removed by rotary evaporation to afford an orange oil. The solvents were removed by rotary evaporation and the crude product purified by column chromatography (EtOAc/hexanes, 1:9): 6.30 g (19.2 mmol) of the oxadiazinone were recovered (55% yield from **5**) as colourless crystals, mp 154–155 °C; $[\alpha]_D^{25} = -10.9$ (*c* 0.47, MeOH). ^{1}H NMR ($CDCl_3$): δ 0.85 (s, 3H), 0.87 (d, J = 6.6 Hz, 3H), 0.99 (s, 3H), 1.15 (s, 3H), 1.18–1.24 (m, 2H), 1.51–1.58 (m, 1H), 1.69 (dd, J = 11.9, 8.6 Hz, 1H), 1.72–1.78 (m, 2H), 1.78–1.83 (m, 1H), 3.11 (dd, J = 8.1, 5.9 Hz, 1H), 3.56 (dq, J = 3.7, 3.1 Hz, 1H), 5.71 (d, J = 3.3 Hz, 1H), 7.16 (s, 1H), 7.29–7.39 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 11.9, 14.8, 19.3, 20.4, 26.9, 34.4, 36.8, 44.7, 47.2, 49.7, 50.7, 73.8, 75.2, 125.0, 127.7, 128.3, 136.6, 152.2. IR (CCl_4): 3251, 2951, 2877, 1703, 1124 cm^{-1}. Anal. Calcd for $C_{20}H_{28}N_2O_2$: C, 73.14; H, 8.59; N, 8.53. Found: C, 72.85; H, 8.58; N, 8.59.

4.2. (5*S*,6*R*,1′*R*,2′*R*,4′*R*)-3,4,5,6-Tetrahydro-5-methyl-4-(1,7,7-trimethylbicyclo[2.2.1]hept-2-yl)6-phenyl-3-propionyl-2*H*-1,3,4-oxadiazin-2-one 7

In a flame-dried, nitrogen purged 10 mL round bottom flask fitted with a reflux condenser, the oxadiazinone (1.350 g, 4.11 mmol) was dissolved in dichloroethane (10 mL) and to this solution was added propionyl chloride (0.536 mL, 6.17 mmol). The solution was brought to reflux and then lithium hydride (0.041 g, 5.14 mmol) added. The solution was heated to reflux and stirred under nitrogen overnight. The reaction was quenched by

the addition of a saturated aqueous solution of sodium bicarbonate (50 mL). The organic products were extracted from this mixture by the use of methylene chloride (2 × 50 mL). The combined organic layers were treated with a saturated aqueous solution of brine (50 mL), dried over $MgSO_4$ and the solvent removed by rotary evaporation to afford a yellow oil. The solvents were removed by rotary evaporation and the crude product was purified by column chromatography (EtOAc/hexanes, 1:9): 88% yield as colourless crystals, mp 225–226 °C; $[\alpha]_D^{25} = -139$ (*c* 1.02, MeOH). ^{1}H NMR ($CDCl_3$): δ 0.68 (d, J = 6.6 Hz, 3H), 0.84 (s, 3H), 0.91 (s, 3H), 1.10–1.25 (m, 1H), 1.61 (t, J = 7.33 Hz, 3H), 1.20 (s, 3H), 1.47–1.53 (m, 1H), 1.72–1.81 (m, 2H), 1.97–2.02 (m, 2H), 2.80–2.98 (m, 3H), 3.21 (dd, J = 8.1, 5.9 Hz, 1H), 3.80 (quintet, J = 6.61 Hz, 1H), 6.03 (d, J = 5.5 Hz, 1H), 7.19–7.39 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 8.98, 13.0, 13.4, 19.7, 20.5, 27.1, 30.7, 35.6, 38.4, 44.9, 47.3, 49.8, 51.3, 69.8, 79.1, 124.7, 127.9, 128.5, 136.3, 149.7, 175.0. IR (CCl_4): 2928, 2879, 1731(broad), 1132 cm^{-1}. Anal. Calcd for $C_{23}H_{32}N_2O_3$: C, 71.84; H, 8.39; N, 7.29. Found: C, 71.76; H, 8.41; N, 7.37.

4.3. General procedure for the formation of the aldol adducts

In a flame-dried, nitrogen purged, 25 mL round bottom flask, the N_3-propionylated oxadiazinone (0.625 g, 1.63 mmol) was dissolved in THF (5.5 mL). To this solution was added titanium tetrachloride (0.20 mL, 1.7 mmol) by syringe. The temperature of the solution was lowered to −78 °C after 1 h of induction time. Triethylamine (0.25 mL, 1.7 mmol) was added to the solution and the system allowed to warm to 0 °C over approximately 30 min. Once the solution had reached 0 °C, the aldehyde (0.198 mL, 1.95 mmol) was added to solution by syringe and the system was allowed to warm to room temperature and run overnight. The reaction was quenched by the addition of a saturated aqueous solution of ammonium chloride (25 mL). The organic products were extracted from this mixture by the use of ethyl acetate (2 × 25 mL). The combined organic layers were treated with a saturated aqueous solution of brine (25 mL), dried over $MgSO_4$ and the solvent removed by rotary evaporation to afford a yellow oil. The solvents were removed by rotary evaporation and the crude product was purified by column chromatography (EtOAc/hexanes, 1:9).

4.3.1. (5*S*,6*R*,1′*R*,2′*R*,4′*R*,2″*S*,3″*S*)-3,4,5,6-Tetrahydro-3-(3-hydroxy-2-methyl-3-phenylpropionyl)-5-methyl-6-phenyl-4-(1,7,7-trimethylbicyclo[2.2.1]hept-2-yl)-2*H*-1,3,4-oxadiazin-2-one 8a. Yield 67%; colourless crystals, mp 111–112 °C; $[\alpha]_D^{25} = -129$ (*c* 0.47, MeOH). ^{1}H NMR ($CDCl_3$): δ 0.70 (d, J = 7.0 Hz, 3H), 0.85 (s, 3H), 0.94 (s, 3H), 1.07 (d, J = 7.0 Hz, 3H), 1.10–1.28 (m, 2H), 1.22 (s, 3H), 1.49–1.70 (m, 2H), 1.74–1.83 (m, 2H), 1.98–2.05 (m, 1H), 3.24 (dd, J = 5.9, 2.2 Hz, 1H), 3.44 (br s, 1H), 3.83 (quintet, J = 6.7 Hz, 1H), 4.00 (dq, J = 2.6, 7.0 Hz, 1H), 5.28 (d, J = 2.2 Hz, 1H), 6.07 (d, J = 5.9 Hz, 1H), 7.18 (d, J = 7.3 Hz, 1H), 7.20–7.40 (m, 8H), 7.49 (d, J = 7.7 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 10.4, 13.2, 13.4, 19.7, 20.6, 27.2, 35.7, 38.4, 44.9, 45.5, 47.4, 50.1, 51.6, 69.7, 72.4, 79.7, 124.7, 126.1, 127.1, 128.07, 128.09, 128.7, 136.0, 141.3, 149.7, 178.1. IR (CCl_4): 3541, 3038, 1704 (very broad) cm^{-1}. HRMS (FAB) calcd for $C_{30}H_{39}N_2O_4$ (M+1): 491.2910. Found: 491.2915.

4.3.2. (5*S*,6*R*,1′*R*,2′*R*,4′*R*,2″*S*,3″*S*)-3-[3-(4-Chlorophenyl)-3-hydroxy-2-methylpropionyl]-3,4,5,6-tetrahydro-5-methyl-4-(1,7,7-trimethylbicyclo[2.2.1]hept-2-yl)-6-phenyl-2*H*-1,3,4-oxadiazin-2-one (8b). Yield 76%; colourless crystals, mp 134–135 °C; $[\alpha]_D^{25} = -113$ (*c* 0.65, MeOH). ^{1}H NMR ($CDCl_3$): δ 0.69 (d, J = 7.0 Hz, 3H), 0.85 (s, 3H), 0.94 (s, 3H), 1.04 (d, J = 7.0 Hz, 3H), 1.12–1.28 (m, 2H), 1.22 (s, 3H), 1.74–1.84 (m, 3H), 1.96–2.06 (m, 2H), 3.24 (dd, J = 7.7, 5.5 Hz, 1H), 3.45 (br s, 1H), 3.84 (quintet, J = 6.7 Hz, 1H), 3.89 (dq, J = 2.2, 7.0 Hz, 1H), 5.25 (d, J = 2.2 Hz, 1H), 6.07 (d, J = 5.9 Hz, 1H), 7.18 (d, J = 7.3 Hz, 1H), 7.26 (s, 1H), 7.26–7.42 (m, 7H). ^{13}C NMR ($CDCl_3$): δ 10.4, 13.1, 13.3, 19.7, 20.5, 27.1, 35.6, 38.4, 44.8, 45.4, 47.3, 50.0, 51.5, 69.6, 71.9, 79.6, 124.6, 127.6, 128.0, 128.1, 128.6, 132.7, 135.8, 139.9, 149.7, 177.6. IR (CCl_4): 3500, 1706, 754 cm^{-1}. HRMS (FAB) calcd for $C_{30}H_{38}ClN_2O_4$ (M+1): 525.2520. Found: 525.2536.

4.3.3. (5*S*,6*R*,1′*R*,2′*R*,4′*R*,2″*S*,3″*S*)-3,4,5,6-Tetrahydro-3-(3-hydroxy-2-methyl-3-naphthalen-2-yl-propionyl)-5-methyl-(1,7,7-trimethylbicyclo[2.2.1]hept-2-yl)-6-phenyl-4-2*H*-1,3,4-oxadiazin-2-one 8c. Yield 88%; colourless crystals, mp 140–141 °C; $[\alpha]_D^{25} = -122$ (*c* 1.33, MeOH). ^{1}H NMR ($CDCl_3$): δ 0.71 (d, J = 7.0 Hz, 3H), 0.82 (s, 3H), 0.93 (s, 3H), 1.08 (d, J = 7.0 Hz, 3H), 1.12–1.25 (m, 2H), 1.23 (s, 3H), 1.48–1.56 (m, 1H), 1.75–1.83 (m, 3H), 1.98–2.06 (m, 1H), 3.25 (dd, J = 8.1, 5.5 Hz, 1H), 3.60 (br s, 1H), 3.84 (quintet, J = 6.7 Hz, 1H), 4.12 (dq, J = 2.0, 7.2 Hz 1H), 5.45 (s, 1H), 6.10 (d, J = 5.5 Hz, 1H), 7.18 (d, J = 7.3 Hz, 1H), 7.26–7.50 (m, 7H), 7.55 (d, J = 8.4 Hz, 1H), 7.83–7.89 (m, 2H), 7.96 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 10.5, 13.2, 13.4, 19.7, 20.4, 27.1, 35.7, 38.4, 44.9, 45.3, 47.3, 50.0, 51.6, 69.6, 72.5, 79.6, 124.3, 124.7, 125.0, 125.6, 125.8, 127.5, 127.7, 128.00, 128.03, 128.6, 132.7, 133.1, 135.9, 138.7, 149.7, 178.0. IR (CCl_4): 3482, 1729, 1696 cm^{-1}. HRMS (ESI) calcd for $C_{34}H_{41}N_2O_4$ (M+1): 541.3066. Found: 541.3066.

4.3.4. (5*S*,6*R*,1′*R*,2′*R*,4′*R*,2″*S*,3″*S*)-3,4,5,6-Tetrahydro-3-(3-hydroxy-2,4,4-trimethyl-pentanoyl)-5-methyl-6-phenyl-4-(1,7,7-trimethylbicyclo[2.2.1]hept-2-yl)-2*H*-1,3,4-oxadiazin-2-one 8d. Yield 88%; colourless crystals, mp 149–150 °C; $[\alpha]_D^{25} = -135$ (*c* 1.77, MeOH). ^{1}H NMR ($CDCl_3$): δ 0.69 (d, J = 7.2 Hz, 3H), 0.85 (s, 3H), 0.93 (s, 3H), 1.00 (s, 9H), 1.11–1.17 (m, 2H), 1.21 (d, J = 7.0 Hz, 3H), 1.22 (s, 3H), 1.26–1.32 (m, 2H), 1.47–1.54 (m, 1H), 1.73–1.82 (m, 2H), 1.96–2.04 (m, 1H), 3.21 (dd, J = 8, 6 Hz, 1H), 3.65 (s, 1H), 3.81 (quintet, J = 6.8 Hz, 1H), 4.19 (q, J = 6.6 Hz, 1H), 6.05 (d, J = 5.9 Hz, 1H), 7.19 (d, J = 7.3 Hz, 2H), 7.30–7.41 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 12.4, 13.3, 13.7, 14.1, 19.7, 20.6, 22.6, 27.1, 27.2, 31.6, 35.5, 35.7, 38.5, 39.9, 44.9, 47.4, 50.2, 51.6, 69.7, 79.7, 124.8, 128.1, 128.7, 136.1, 149.6, 179.7. IR (CCl_4): 3450, 1722 cm^{-1}. HRMS

(ESI) calcd for $C_{28}H_{43}N_2O_4$ (M+1): 471.3223. Found: 471.3217.

Acknowledgements

We thank Dr. R. C. Freeman for helpful discussions. We also thank Maria Teresa Navio of the Analytical Research and Development Department of Pfizer Global Research and Development in La Jolla, CA for optical activity measurements. Acknowledgments are also made to the donors of the American Chemical Society Petroleum Research Fund for support of this research. We acknowledge Pfizer, Inc. for significant material support. We also acknowledge continued support from Merck & Co, Inc.

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