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Preparation of 2-alkenylperhydro-1,3-benzoxazines and application for 2-isoxazolines synthesis

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ABSTRACT

Various 2-substituted-*N*-benzyl-4,4,7-trimethyl-*trans*-octahydro-1,3-benzoxazines **2** were prepared from the condensation of (−)-8-benzylaminomenthol **1** derived from (+)-pulegone, with acrolein, crotonaldehyde, cinnamaldehyde, 2(*E*)-*N*,*N*-diisopropyl-4-oxobut-2-enamide, ethyl (2*E*)-4-oxobut-2-enoate, and 2-furaldehyde in 71–96% yield. The 1,3-dipolar cycloaddition with aceto- and benzonitrile oxide gave the corresponding 2-isoxazoline cycloadducts. The origin of the stereoselectivity (4′*S*, 5′*S*-cycloadducts up to 64% de) arises from the cycloaddition of the dipole to the top of the *Re*,*Re*-alkene face of dipolarophile **2**.

1. Introduction

The synthesis of chiral 2-isoxazolines has advanced considerably over the last decade.[1] The most direct route to generate this five-membered heterocycle consists of a 1,3-dipolar cycloaddition reaction involving a dipolarophile with a nitrile oxide as dipole. Both the regio- and stereoselectivity can, in principle, be controlled by the use of the enantiomerically pure form of at least one of these two reagents, or by the use of a chiral catalyst. An important discovery was made by Kanemasa et al. which involved Mg^{2+} directed nitrile oxide cycloadditions with chiral allylic[2] and α-silylallyl alcohols.[3] The use of chiral catalysts prepared from dialkyl zinc and diisopropyl (*R*,*R*)-tartrate allowed Inomata et al.[4] to prepare asymmetric isoxazolines up to 93% de from achiral allylic alcohols. Furthermore, Sibi et al. employed magnesium iodide and a chiral bisoxazoline to catalyze the cycloaddition of mesityl nitrile oxide with achiral pyrazolidinone crotonates[5] and α,β-disubstituted acrylimidines[6] providing various 2-isoxazolines with both high regio- and enantioselectivities. These studies have so far been limited to the use of the more stable pivalo- and aryl nitrile oxides. Aliphatic nitrile oxides are considerably more capricious than their aromatic counterparts because of their propensity to dimerise, generating furoxanes. A breakthrough was achieved by Carreira et al.,[7] who extended the Kamenasa hydroxy-directed nitrile oxide cycloaddition to the use of chiral aliphatic nitrile oxides at −78 °C. Under their conditions, the integrity of the aliphatic nitrile oxide is preserved and 2-isoxazoline cycloadducts with complete regio- and stereoselectivity were obtained from chiral allylic alcohols.[8] The substituents on these 2-isoxazolines are ideally placed for the synthesis of polyketide building blocks[9] or for the synthesis of β-aminoacids.[10]

However, those applications requiring a 2-isoxazoline with a non-propionic substitution pattern or those with reversed regiochemistry still rely on the use of other asymmetric processes. Various chiral dipolarophiles,[11–14] when reacted with more stable nitrile oxides (benzo-, mesito-, and pivalo-), produced cycloadducts with good diastereoselectivity.

A 1,3-dipolar cycloaddition reaction involving a variety of aromatic and aliphatic nitrile oxides was developed by Lassalata et al.,[15] who found that complete control of the regio- and stereoselectivity was possible when a bulky *C*-2 symmetric pyrolidine was used as the chiral auxiliary. However, under harsh acidic conditions (6 N HCl, AcOH, reflux 100 °C, 48 h), only three cycloadducts could be cleaved from their chiral auxiliary. A mixture of 2-isoxazoline regioisomers usually results if unsymmetrical 1,2-disubstituted olefins including α,β-unsaturated esters and ketones are used. The diastereoselectivity of these 1,3-dipolar cycloaddition reactions is also lower.[16] Free α,β-unsaturated aldehydes are precluded because they tend to form *bis*-cycloadducts via nitrile oxide attack on the aldehyde of the initial 2-isoxazoline product.[17a] This problem can be avoided using the corresponding acetals or thioacetals. Indeed, some of these reactions are highly regioselective; for example, using an acetal[18,19] versus a dithioacetal[19] reverses the regioselectivity in the nitrile oxide 1,3-dipolar cycloaddition reaction to cinnamaldehyde and crotonaldehyde derivatives. However, the use of an aminal in a 1,3-dipolar cycloaddition reaction has not been reported.

8-Benzylaminomenthol[20] acts as a protecting group and chiral adjuvant for acrolein in **2a**.[21] We report here the use of aminals such as perhydrobenzoxazines **2b**–**2g** to control the regio- and stereoselectivity of those 1,3-dipolar cycloaddition reaction using β-substituted, α,β-unsaturated aldehydes.

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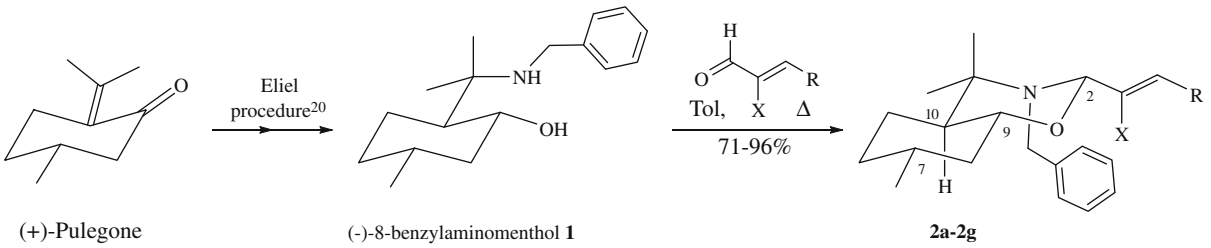
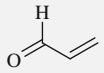
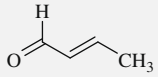
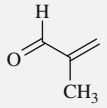
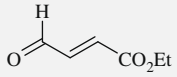
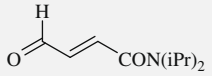
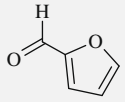
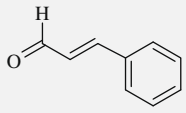


Scheme 1. Synthesis of perhydrobenzoxazines **2** from (−)-8-benzylaminomenthol **1**

Table 1
Preparation of octahydrobenzoxazines **2a**–**2g**

Entry	Aldehyde (equiv)		Method[a,b,c]	Time (h)	Product **2**	Yield (%)
1		2	A	12		15
		24	B	10	**2a** (R = X = H)	22
		15	C	20		84
2		2	A	12	**2b** (R = CH_3, X = H)	18
		8	C	15		81
3		2	A	12	**2c** (R = H, X = CH_3)	—
		15	C	24		—
4		1.2	A	48	**2d** (R = CO_2Et, X = H)	71
5		1	A	60	**2e** (R = CON(*i*Pr)$_2$, X = H)	73
6		3	A	48	**2f** (R = CHCH–O = X)	88
7		2	A	24	**2g** (R = Ph, X = H)	96

[a] Method A: a solution of aldehyde in toluene is added in one portion to **1**.
[b] Method B: a solution of **1** in neat acrolein (24 equiv) is heated to reflux.
[c] Method C: a solution of aldehyde in toluene is added slowly over 15–20 h to **1**.

2. Results and discussion

2.1. Preparation of perhydrobenzoxazines 2

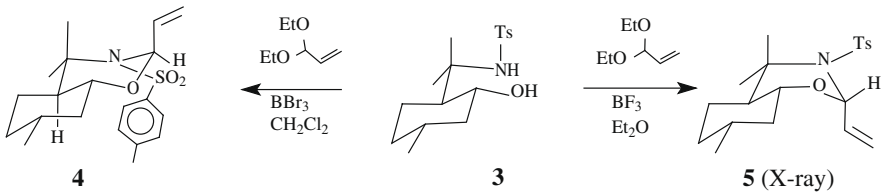
In order to study the regio- and stereoselectivity of the 1,3-dipolar cycloaddition reaction of disubstituted alkenes derived from (+)-pulegone, derivative **2** was prepared as shown in Scheme 1. The *trans*-fused octahydrobenzoxazines **2d**–**2g** were obtained in good yield from the condensation of 8-*N*-benzylaminomenthol **1,** with 1–3 equiv of the less volatile aldehydes which were added at once in refluxing toluene (Table 1, entries 4–7, method A).[20c] More volatile aldehydes such as acrolein and crotonaldehyde had lower conversion yields (entries 1 and 2, method A). A gas chromatography analysis of the latter reactions revealed that they plateaued at 15% after 12 h. A similar result was obtained using neat acrolein (Table 1, method B).[†] Compounds **2a** and **2b** were best prepared from the condensation of **1** with a large excess of volatile aldehyde, slowly added to the reaction mixture under reflux (entries 1 and 2, method C). Under these conditions, the premature polymerization of the aldehyde in the condenser is reduced. The yields ranged from 71% to 96%, with the exception of methacrolein which failed to produce **2c** (entry 3). The presence of a methyl group α to the carbonyl hampers the nucleophilic addition of the nitrogen and oxygen atoms.

2.2. Structural analysis of dipolarophiles 2

All of the optical rotations for **2** had negative values; smaller groups, **2a**,**b**,**f**: −24 to −30 and bigger groups, **2d**,**e**,**g**: −63 to −69. These amplitudes are consistent with a somewhat rigid structure having increasing mass in the same geometrical quadrant.

The rigorous establishment of the stereochemistry of these chiral auxiliaries is of paramount importance to the understanding of olefin facial discrimination. In general, tetrahydro-1,3-oxazines have been found to be mainly in a chair conformation and in room temperature solutions, an N-inversion occurs rapidly between equatorial and axial positions.[23,24] The position of the *N*-alkyl group has not been clearly defined for similar 2-substituted perhydrobenz-*2H*-1,3-oxazine derivatives. Eliel and Pedrosa first reported an equatorial;[20a,b,25] and later an axial;[20c,d] stereochemis-

[†] The use of a Lewis acid ($MgBr_2$) allowed the reaction time to be reduced to 6 h; however, the yield did not improve (21%). Furthermore, the use of a stronger Lewis Acid, $BF_3{\cdot}Et_2O$ only led to premature polymerization of the acrolein. The reaction of the *bis*-*N*,*O*-trimethylsilyl derivative of **1** with acrolein in the presence of a catalyst, trimethylsilyl trifluoromethanesulfonate, failed.[22]



Scheme 2. Synthesis of 3-*N*-tosylperhydrobenzoxazines in an all chair **4** and in a chair-boat **5** conformation; the nitrogen atom has a planar geometry.

try for the *N*-benzyl and *N*-methyl groups in compounds such as **2g**. Pedrosa et al. suggested that their *N*-acryloyl derivative was equatorial.[26] However, since the more significant resonance of the nitrogen lone pair is with the carbonyl, the nitrogen atom should be planar. An equatorial *N*-tosyl group was also cited by Ko et al.,[27] for *trans*-3-*N*-tosyl-2-benzoyloctahydro-1,3,5-benzdioxazine, but no spectroscopic evidence was presented. Ko's results clearly contrast with our findings for **4** and **5**, in which the nitrogen atom had a planar geometry (Scheme 2).[28] In addition, while compound **4** was found to have an all chair conformation, in **5**, the tetrahydro-1,3-oxazine ring is a boat in both the solid state and in solution ($CDCl_3$).

Considering the scarcity of rigorous studies of the stereochemistry of these heterocycles, we were interested in obtaining an X-ray crystal structure of **2**. A crystal suitable for X-ray analysis was obtained for (−)-**2g**, derived from cinnamaldehyde.

Figure 1 clearly shows the absolute configuration of C2, N3, C7, C9, and C10 and an almost perfect chair conformation for the fused rings. The *trans*-junction was established by torsion angles C5–C10–C9–01 = 178.9(3)° and C8–C9–C10–C4 = −173.4(3)°. The N3 is pyramidal, the *N*-benzyl is axial and the two phenyl rings are almost perpendicular to each other, dihedral angle = 91.1(1)°. This is the first example of a *trans*-fused octahydro-2*H*-1,3-benzoxazine ring system having an axial *N*-benzyl substituent. The H2 is axial, while the phenylethenyl group is equatorial and coplanar with the chair–chair ring, (i.e., H28 is eclipsed with O1) with torsion angles N3–C2–C27–C28 = −142.5(3)° and O1–C2–C27–C28 = −16.0(3)°. Note that the alkene function is not coplanar with H2 thus allylic 1,3-strain[29] between O1 and H28, and steric interaction between N3 and H27, are avoided. If H2 and H28 were eclipsed, the H27 and benzyl CH_2 interaction would be more destabilizing.

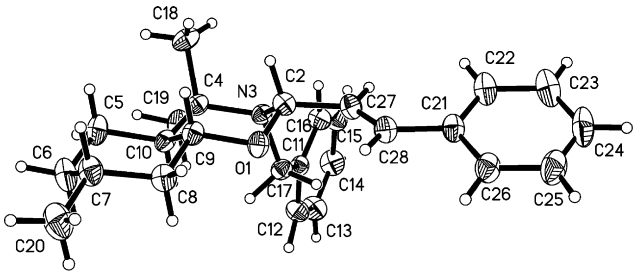


Figure 1. The structure of **(−)-2g** showing the atom-labeling scheme. Displacement ellipsoids are drawn to 30% probability level and selected H atoms are shown as spheres of arbitrary radii.

Since the stereochemistry of the $H9_{ax}$ proton has been previously established,[20a] NOEs readily confirmed a *trans*-chair-chair configuration in solution for the benzoxazine ring of **(−)-2** when this proton was irradiated (Fig. 2a); $H5_{ax}$, $H7_{ax}$, $H8_{eq}$ and, particularly, H2 (9%) were also enhanced. However, no NOE was observed for the alkene proton signals. Therefore, the stereochemistry for H2 is axial. Irradiation of H2 led to NOE enhancements of the signals assigned to $H9_{ax}$ and the axial methyl, that is, C4, H27 and H28 (Fig. 2b). Thus, H27 and H28 are almost orthogonal to $H2_{ax}$, since both showed NOEs with $H2_{ax}$ (Fig. 2b–d). Coplanarity of the phenylethenyl with $H2_{ax}$ can be ruled out, since an NOE was observed between H27 and $H2_{ax}$. Also, if the phenylethenyl moiety were coplanar with $H2_{ax}$, this would place H27 in an *anti* geometry with respect to $H2_{ax}$ and no NOE would have been seen. Furthermore, the coupling constant, J_{2-27}, (4.9 Hz), is consistent with a torsion angle of 130° for H2 and H27.[30] Irradiation of the H2 of **2a** also results in NOEs with its corresponding H27 (7%) and H28 (2%) but the intensities are switched as compared to those shown in Figure 2b. In this case, a coupling constant, J_{2-27}, of 4.3 Hz, is consistent with a torsion angle of only 40° between these protons (Fig. 2a, R = H). This conformation differs from that previously proposed.[21]

Irradiation of the benzylic proton, $N–CH_APh$, in **2g** caused an NOE which enhanced the signals attributed to $H10_{ax}$ and to the equatorial methyl at C4 (Fig. 2e). We also observed an NOE enhancement of the signals assigned to H27 and H28 (weak) upon irradiation of the other benzylic proton, $N–CH_BPh$ (Fig. 2f). Based on these results, we conclude that the *N*-benzyl substituent is mainly axial at room temperature, which is consistent with the conformation found in the solid state for (−)-**2g**.

On the other hand, an NMR study showed that the *N*-benzylic protons, AB doublets (3.6 and 4.0 ppm), separated into three sets of doublets at temperatures below −70 °C, presumably due to additional rotamers of the phenethenyl residue. A weak (1%) but reciprocal NOE also exists between the CH_{3ax}–C4 and one of the $N–CH_2–Ph$ protons (Fig. 2e). The only possible explanation for this observation is that the latter is equatorial. Thus, a rapid pyramidal inversion at the nitrogen occurs at higher temperatures.

2.3. Syntheses of 2-isoxazolines 6–9

Dipolarophiles (−)-**2** were then used in 1,3-dipolar cycloaddition reactions with both acetonitrile oxide and benzonitrile oxide; the benzonitrile oxide was generated from three different precursors: oximoyl chloride (method A),[31] nitro (method B),[32] and oxime functional groups (method C).[33] These reactions gave cycloadducts **6**–**9**, as shown in Table 2. The 1,3-dipolar cycloaddition reaction was optimized using 2-vinyl benzoxazine (−)-**2a** and benzonitrile oxide because the cycloaddition with (−)-**2a** is known to be regiospecific.[21] In order to evaluate the role played by the base, method A was used since *N*-hydroxybenzenecarboimidoyl chloride is more stable.[31a] When 5 equiv of this chloride was used with no added base[‡] or when Et_3N was added dropwise, the conversion yield and stereoselectivity were low (22% and 36%, respectively; Table 2, entries 1 and 2). Similarly, poor results were obtained if phenylnitromethane was used as the precursor (entry 6). An improvement was noted if the Et_3N (15 equiv) was added first to the reaction vessel, in which case the diastereoselectivity was 77:23 in favor of the (+)-**6a** isomer (entries 4, 5, and 7). There are several possible explanations for this result: (1) in the absence of excess base, part of the

[‡] A comparison of two ^1H NMR spectra of one of the crude reaction mixture separated by 24 h in wet $CDCl_3$, indicated that the cycloadduct had undergone partial hydrolysis to give some of the free chiral auxiliary **1**. However, the free aldehyde of the 2-isoxazoline moiety was not observed since they are known to be unstable.[17]

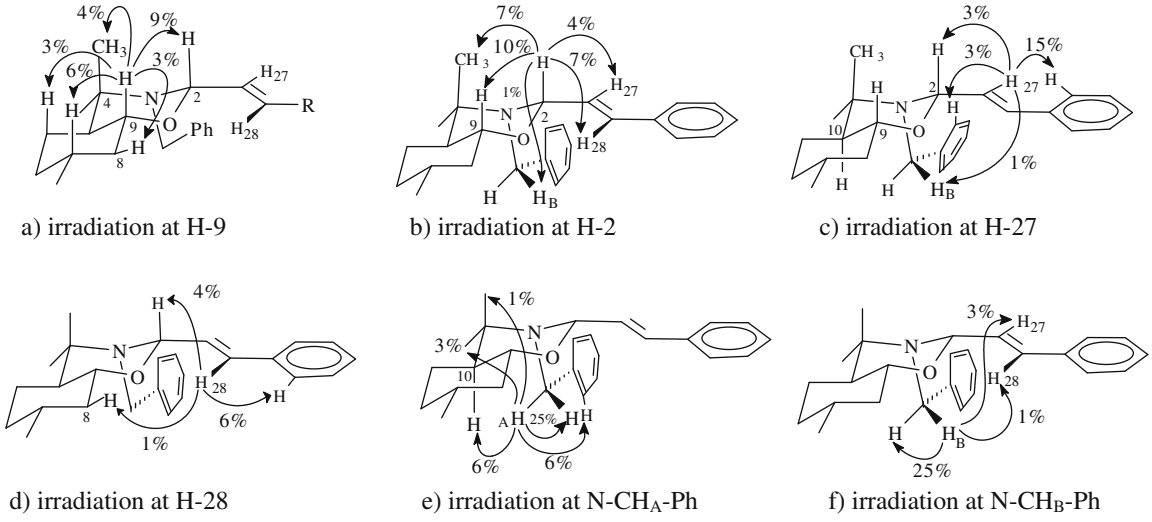


Figure 2. Summary of average NOE observed for (a) compounds **2a**–**2g** by irradiation at H9, and for compound **2g** by irradiation at: (b) H2, (c) H27, (d) H28, (e) N–CH$_A$–Ph, (f) N–CH$_B$–Ph.

auxiliary itself serves as an internal weaker base and thus generation of the nitrile oxide is not as efficient as it would be with Et_3N; (2) the corresponding ammonium salt undergoes cycloaddition more slowly than does **2a**; or (3) cycloaddition occurs for one of the two ammonium salts fixed with respect to *N*-pyramidal inversion. Such fixed geometries would result in lower overall olefin facial discrimination (Scheme 3). When a large excess of external base is used, the equilibrium shifts to the free base **2a**. Rapid *N*-pyramidal inversion shifts the position of the benzyl group, so that the less bulky alkene face is free to be attacked by the dipole. This allows for a higher ee.

Under these conditions, the reaction of disubstituted dipolarophiles **2d**, **2e,** and **2g** with benzonitrile oxide gave all four possible diastereomers, **6**–**9**, with the exception of **8e** for which only three diastereomers were produced from **2e** (Table 2, entries 10–12). The diastereomeric ratios for **6**–**9** were determined by careful analysis of the C5′ signals of the crude reaction mixture (^{13}C NMR, see Section 4). The calculated ratios were in agreement with those isolated and the combined yields for the cycloadducts averaged 55%. Use of a Lewis acid, $MgBr_2$, as previously described by Yamamoto et al.,[34] did not affect the cycloadduct distribution ratio for the reaction of benzonitrile oxide and **2g**.

The stereochemistry was established by rigorous NOEs while that for **9g** was established unequivocally by X-ray diffraction. We were surprised to find a definite trend in the optical rotations. We observed positive rotations for **(+)-6** and **(+)-7**; due to *Re,Re* alkene facial addition, while attack on the alkene via its *Si,Si* face, produced levrorotary (−)-**8** and (−)-**9**.

2.4. Characterization of 2-isoxazolines cycloadducts 6–9

For all substituents, each of the four diastereoisomers, **6**–**9**, adopts a similar spatial arrangement. Therefore, the regio- and stereochemistries of these cycloadducts will be discussed as four diastereomer groups rather than by substituent. ^1H and ^{13}C assignments were based on COSY, DEPT, and HMQC cross peak correlations.[35]

2.4.1. Characterization of 3,5-disubstituted cycloadducts 6- and 8a,b

For **6a** and **6b**, the chemical shifts of their C4′ methylene protons were shielded (δ 2.4 and δ 3.3 ppm) relative to the C5′ methine proton (δ 4.5 ppm) for both isomers. This is consistent with a 3,5-disubstituted 2-isoxazoline but not with a 3,4-disubstituted one (Fig. 3a and b). The stereochemistry for each product was established via the following key NOEs: for all derivatives, irradiation of the signal assigned to H9 established that these compounds have a chair-chair conformation. Irradiation of the signal assigned to H2 of **6a** and **6b** showed that H2 is gauche with respect to H5′ (4% NOE), $J_{2-5'}$ = 3.6 Hz and their torsion angle is 50°.[30]

Irradiation of H4′$_\alpha$ and H5′ enhanced the signals assigned to the N–CH_2 and *o*-Ph protons. These results demonstrate that H4′$_\alpha$ and H5′ are oriented toward the *N*-benzyl and therefore, both major isomers **6a** and **6b** have a 5′*S*-stereochemistry.[§] Significant NOEs were obtained for the N–CH_2 protons with both H2 and H10, even though they are geometrically opposed. In fact, based on the various NOEs, rapid *N*-pyramidal inversion is general to all cycloadducts **6**–**9** as shown in Figures 3 and 4 (dashed lines).

For minor isomers **8a** and **8b**, $J_{2-5'}$ = 8.4 Hz but no NOE was observed between H2 and H5′. This suggests these protons are almost *anti*. Irradiation of H2 enhanced the signals attributed to H9, CH_{3ax}–C4 and H4′$_\beta$ while irradiation of H4′$_\beta$ showed NOEs with H2 (5%) and the *o*-Ph (3%) protons. Thus, the C5′ of **8a** and **8b** is *R*.

2.4.2. Characterization of 3,4,5-trisubstituted cycloadducts 6–9d,e,g

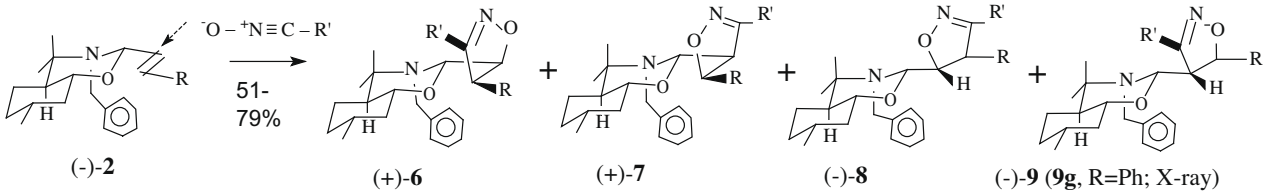
2.4.2.1. Regiochemistry studies. Figure 4 shows a summary of the significant NOEs observed for **6**–**9**, **d**–**g**. For cycloadducts **6d**–**6g** and **8d**–**8g**, irradiation of the *o*-Ph–C3′ proton signal enhanced that attributed to H4′, as well as the signal for the *o*-Ph proton at C4′, 2% for **6g** and **8g**, but no NOE was observed for H2. Therefore, the C3′ phenyl substituent is more distant from the *N*-benzyloxazine moiety than in **7d**–**7g** or **9d**–**9g**.

For regioisomers **7d**–**7g** and **9d**–**9g** the enhancements were reversed. That is, NOEs were observed between the signals attributed to the *o*-Ph–C3′ and those for H2 and H4′. However, none was seen for the proton signals attributed to the C5′ substituents (R = Ph and CON(C*H*Me_2)$_2$) upon irradiation of those for *o*-Ph–C3′.

The above C5′ phenyl regiochemistry for **7g** and **9g** is consistent with a mass peak at 106 *m/z*, corresponding to benzaldehyde less

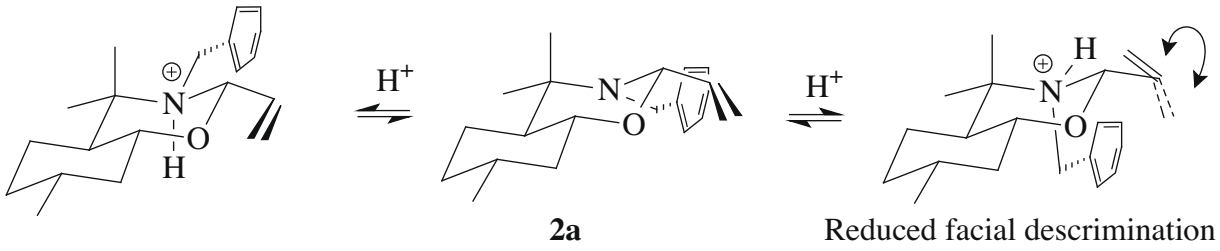
[§] An initial study found a configuration of 5′*R* for **6b** and a 5′*S* for **8b**.[21] However, further investigations of the NOEs arising from the irradiation of H4′$_\alpha$ and H4′$_\beta$ have now shown them to be 5′*S* and 5′*R*, respectively. All the NOEs observed previously are consistent with the current proposed structures. The higher diastereomeric ratio initially reported for **6b** was based on isolated yields and not on the ^{13}C NMR of the crude reaction mixture.

Table 2
Syntheses of 2-isoxazolines **6–9** from several octahydrobenzoxazines **2a**, **2d, 2e, 2g** with aceto- and benzonitrile oxides



Entry	Benzoxazines (−)-**2**	Nitrile oxide (O–N≡C–R′)	Method[a,b,c]	Et_3N (equiv)	Isolated yield (%)	2-Isoxazolines distribution (% isolated)				Selectivity[d]	
										Regio-	Stereo-
						(+)-**6**	(+)-**7**	(−)-**8**	(−)-**9**	**6**+**8**:**7**+**9**	**6**+**7**:**8**+**9** 5′*S*:5′*R*
1	**a** R = H	R′ = Ph	A	—	22	**6a** (62)	—	**8a** (38)	—	100:0	62:38
2	**a** R = H	R′ = Ph	A	5[e]	36	**6a** (62)	—	**8a** (38)	—	100:0	62:38
3	**a** R = H	R′ = Ph	A	5	68	**6a** (73)	—	**8a** (27)	—	100:0	73:27
4	**a** R = H	R′ = Ph	A	15	70	**6a** (77)	—	**8a** (23)	—	100:0	77:23
5	**a** R = H	R′ = Ph	A	20	70	**6a** (77)	—	**8a** (23)	—	100:0	77:23
6	**a** R = H	R′ = Ph	B	2	52	**6a** (71)	—	**8a** (29)	—	100:0	71:29
7	**a** R = H	R′ = Ph	B	15	75	**6a** (78)	—	**8a** (22)	—	100:0	78:22
8	**a** R = H	R′ = Ph	C	0	68	**6a** (77)	—	**8a** (23)	—	100:0	77:23
9	**a** R = H	R′ = CH_3	B	1.6	27	**6b**(75)	—	**8b** (25)	—	100:0	75:25
10	**d** R = CO_2Et	R′ = Ph	A	20	59	**6d** (31)	**7d** (16)	**8d** (7)	**9d** (5)	64:36	82:18
11	**e** R = CO N(iPr)$_2$	R′ = Ph	A	20	51	**6e** (6)	**7e** (30)	—	**9e** (15)	12:88	71:29
12	**g** R = Ph	R′ = Ph	A[f]	20	52	**6g** (8)	**7g** (20)	**8g** (6)	**9g** (18)	28:72	55:45

[a] Method A: to **2** (1 equiv) and Et_3N (0–20 equiv) in CH_2Cl_2 was added PhCCl=NOH (5 equiv) dropwise over 8 h).
[b] Method B: to **2a** (1 equiv) and Et_3N (1.6–15 equiv) in CH_2Cl_2 was added a nitroalkane (2–5 equiv) and phenylisocyanate (4–10 equiv).
[c] Method C: to **2a** (0.2 mmol) and benzaldehyde oxime (3 equiv) in CH_2Cl_2 (4 mL) was added a 5% NaOCl solution (3 mL) and was stirred for 48 h.
[d] Determined from the integration of the ^{13}C NMR′s of the crude reaction mixture.
[e] Dropwise addition.
[f] Heated to reflux.



Scheme 3. Protonation of dipolarophile **2a**. Distribution of the two ammonium salts with either an *N*-equatorial or *N*-axial benzyl group.

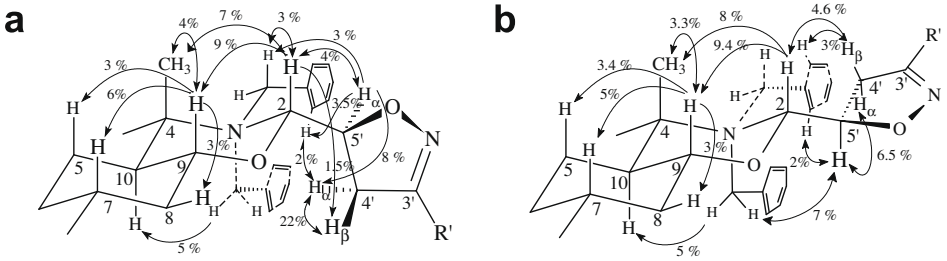


Figure 3. (a) Summary of average NOE for major (5′*S*)-**6a** (R′ = Ph) and **6b** (R′ = CH_3). (b) Summary of average NOE for minor (5′*R*)-**8a** (R′ = Ph) and **8b** (R′ = CH_3). Note: Pyramidal inversion of the *N*-benzyl group is indicated by dashed lines.

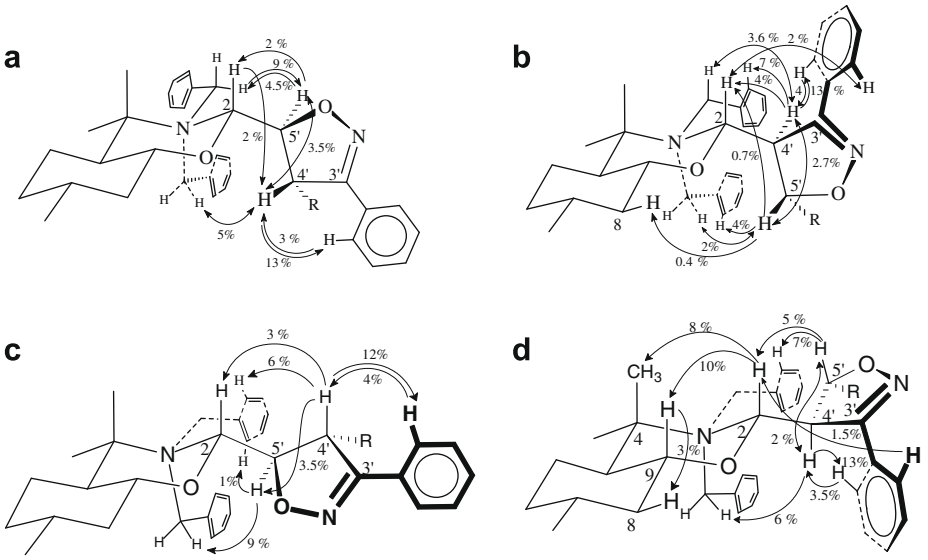


Figure 4. (a) Summary of average NOE for (4′*S*, 5′*S*)-**6d**, (R = CO_2Et), **6e** (R = CON*i*Pr_2), and **6g** (R = Ph). (b) Summary of average NOE for (4′*S*, 5′*S*)-**7d**, (R = CO_2Et), **7e** (R = CON*i*Pr_2) and **7g** (R = Ph). (c) Summary of averaged NOE for (4′*R*,5′*R*)-**8d**, (R = CO_2Et) and **8g** (R = Ph). (d) Summary of averaged NOE for (4′*R*,5′*R*)-**9d**, (R = CO_2Et), **9e** (R=CON*i*Pr_2) and **9g** (R = Ph). Note: Pyramidal inversion of the *N*-benzyl group is indicated by dashed lines.

one proton. This ion arises from the fragmentation of the 2-isoxazoline ring at C5′–C4′ and N–O;[17,36] however, it was not seen for **6g** and **8g**.

2.4.2.2. Stereochemistry studies at C4′ and C5′. Since the *trans* geometry of the alkene is transposed in the cycloadducts, this section will focus on the isoxazoline carbon directly linked to the benzoxazine moiety. For **9d**, -**e** and -**g**, strong mutual NOEs were observed for the signals assigned to H2 and H5′ and those assigned to H5′ and the peak for the *o*-NBn protons (Fig. 4d). However, there was no NOE between H2 and H4′ and $J_{2-4'}$ averaged 10 Hz, hence H2 and H4′ are *anti*. A significant NOE was also observed between the signal for H4′ and one of the doublets associated with the benzylic protons. Therefore, the absolute configuration at both C4′ and C5′ stereocenters is (*R*), which is in agreement with the X-ray structure for **9g** (Fig. 5).

Figure 5 shows one of the two independent molecules seen in the crystallographic results. The two molecules are almost identical, except for the dihedral angle between the phenyl ring located on C3′ and the plane formed by four of the atoms of the five-membered ring. The five-membered ring has an envelope conformation with the C5′ pointing out of the plane and toward its phenyl substituent. The fused rings adopt chair conformations with a *trans*-junction as shown in Figure 5. The environment around the N3 atom is pyramidal and the *N*-benzyl group is axial, as observed in crystal of **2g**.

$J_{2-4'}$ for isomer **7** was found to be small (ave. 1.7 Hz); therefore, the torsion angle between H2 and H4′ should be 65°.[30] Also, irradi-

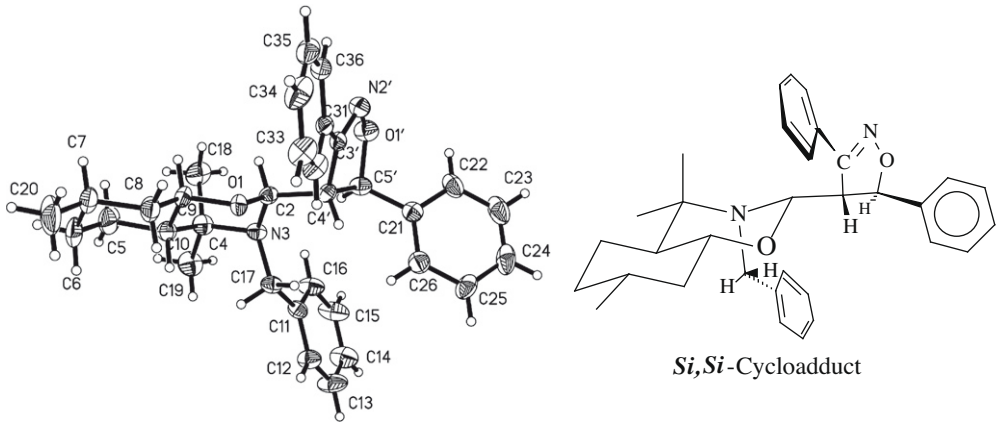


Figure 5. The structure of one of the two independent cycloadduct (−)-**9g**, showing the atom-labeling scheme. Displacement ellipsoids are drawn to 30% probability level and selected H atoms are shown as spheres of arbitrary radii.

ation of the signal assigned to H4′ led to strong NOEs with the resonances assigned to *o*-NBn, N–C*H*$_2$Ph, H2, and H5′ (Fig. 4b). Hence, H4′ is oriented toward the *N*-benzyl moiety. Long range NOEs (weak) were observed between the signals for H5′ and H8$_{eq}$ therefore, H5′ must be oriented toward H8$_{eq}$. Since the structure for **9** has been established by X-ray crystallography and **7** has the same regiochemistry as **9**, the stereocenters C4′ and C5′ of 7 must be (*S*).

Isomer **6** has the reverse regiochemistry relative to **7** and **9** and similar enhancements were observed for its corresponding proton signals. But, the positions of protons H4′ and H5′ of **6** are reversed (Fig. 4a). The torsion angle between protons H2 and H5′ should be 25° since the coupling constant $J_{2-5'}$ = 7.5 Hz.[30] Also, NOEs were observed between the signals for H5′ and N–C*H*–Ph (strong) and between those for H5′ and H2. Irradiation of the signal attributed to H4′ led to the enhancement of the peaks for the H2 and N–C*H*–Ph protons. Therefore, the absolute configuration at both C4′ and C5′ is (*S*).

For isomer **8**, H5′ produced a strong NOE with the signal for one of the benzylic protons as well as one (weak) NOE with the *o*-NBn peak (Fig. 4c). For **8**, the average $J_{2-5'}$ = 7.4 Hz between H2 and H5′, which corresponds to a torsion angle of 155°.[30] Therefore, H4′ should be coplanar with H2. This conclusion is further supported by the observation of NOEs for the H2 and *o*-NBn signals upon irradiation of the H4′ doublet. H5′ is also oriented toward the *N*-benzyl group and, therefore, the stereochemistry for C4′ and C5′ of **8** is (*R*).

2.5. Isomeric control of the cycloaddition

2.5.1. Regiochemistry rational

The reaction involving the monosubstituted dipolarophile **2a,** being under steric control, gives regiospecifically the C5 aminal cycloadducts **6a** + **8a** (Table 2, entries 1–9). Using disubstituted, α,β-unsaturated amides and esters, Weidner-Wells,[36] Huisgen,[37] and Caramella[38] have shown that the nitrile oxide attacks preferentially via the oxygen onto the β-center of the alkene. This allows the preferred orbital match to occur, greater HOMO coefficient of the oxygen of the dipole with the greater LUMO coefficient located at the β-carbon of the α,β-unsaturated ester.[39] Our own results, using the α,β-unsaturated ester **2d,** are consistent with this trend; affording preferentially C4 acyl cycloadducts **6d** + **8d** (C4:C5 acyl, 1.7:1; Table 2, entry 10). In addition, Rosella and Harper[40] observed that this effect was greatly magnified for ethyl cinnamate when dissolved in an ionic liquid (ratios up to 15:1).

However, the use of a bulky amide favors the opposite regiochemistry (Table 2, entry 11), which is consistent with the tertiary crotonamides independently studied by Weidner-Wells et al.[36] and, particularly elegantly by Caramella et al.[38] For their amide, the reaction is under the steric control of one of the *N*-alkyl substituents of the almost exclusively *cisoid* amide rotamer and the phenyl of the benzonitrile oxide. Steric hindrance modifies the frontier orbital interactions which, in turn, cause a drift in the regiochemistry to increasingly favor the C5 acyl cycloadduct of 7.3:1.

As reported, in the case of cinnamaldehyde, the choice of an acetal versus a dithioacetal reverses the regioselectivity of the 1,3-dipolar cycloaddition reaction with nitrile oxide.[18,19] We found that the benzoxazine moiety of dipolarophile **2** acts as an acetal, giving cycloadducts **7g** + **9g** derived from benzonitrile oxide (C4:C5 aminal ratio: 2.6:1; Table 2 entry 12). The aminal or acetal is favored at C4, since this best avoids steric repulsion between the two phenyl substituents as was observed for **2e**.

2.5.2. Stereochemistry rational

The preferred conformation of the C2 alkenyl moiety of **2** is orthogonal to H2 (Figs. 1, 2, and 6); and, to avoid steric hindrance, cycloaddition of the nitrile oxide likely occurs from the top of the auxiliary, opposite the *N*-benzyl. When attack of the nitrile oxide occurs on the *Re,Re*-face of olefin **2** (Fig. 6, parallel to H2), major isomers **6** + **7** (4′*S*,5′*S*) are obtained. Otherwise, rapid *N*-pyramidal inversion allows for a 180° rotation of the 2-alkenyl moiety and attack occurs via the *Si,Si*-face of the alkene, which gives minor (4′*R*,5′*R*) isomers **8** + **9**.

Preliminary energy minimization calculations for the alkene rotamers of **2** (Fig. 6) supports the proposed rational for facial discrimination, with the favored rotamer having the *Re,Re* alkene face pointing to H2: 0.8 kJ/mol for **2g** (R = Ph), 1.7 kJ/mol for **2e** (R = CON(*i*Pr)$_2$), and 2.4 kJ/mol for **2d** (R = CO$_2$Et). The order of increase in the calculated energy differences for these rotamers is consistent with the observed increase in stereoselectivities of dipolarophiles **2g**, **2e,** and **2d** (de for (4′*S*,5′*S*): 10%, 42%, and 64%, respectively).

3. Conclusion

(−)-8-Benzylaminomenthol **1**, was used as a chiral adjuvant in the cycloaddition of α,β-unsaturated 1,3-dipolarophiles. The condensation of **1** with various α,β-unsaturated aldehydes gave the corresponding aminal **2** with an average isolated yield of 84%. X-ray diffraction of (−)-**2g** showed a chair–chair conformation for the hetero-ring, with stereocenters C2 and N being *S*. The phenylethenyl moiety is equatorial and coplanar to the *trans*-octahydro-

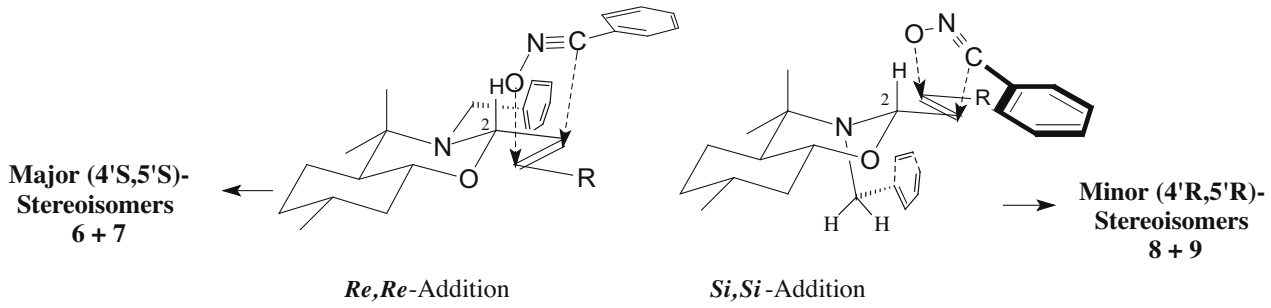


Figure 6. Suprafacial *Re*,*Re*- and *Si*,*Si*-addition of benzonitrile oxide onto dipolarophile **2**.

2*H*-1,3-benzoxazine ring; pointing away from the *N*-benzyl group. Our results in solution were consistent with the X-ray structure. However, rapid pyramidal inversion of the NBn group was observed along with the concomitant rotation of the alkenyl moiety. 1,3-Dipolar cycloadditions with nitrile oxide are regiospecific for **2a**, generating (5′*S*)-**6a** in up to 56% de when excess base is used. For **2d**–**g**, the substituent R greatly influenced the regio- and stereochemical course of the reaction. The stereochemistry for all compounds was determined by rigorous NOEs; and was unequivocally established crystallographically for (−)-**9g**. Regioselectivity is under steric control for **2a**, **2e,** and **2g** and the favored 2-isoxazoline regioisomers had the least steric interaction between the substituent derived from nitrile oxide and the substituents on the alkene (R = H, $CON(iPr)_2$ and Ph, respectively). Electronic control governs 1,3-dipolar cycloaddition reaction with **4d** ($R = CO_2Et$), favoring cycloadducts **6d** + **8d**, that is, the phenyl substituent is oriented toward the alkanoyl ester. The observed stereoselectivity (up to 64% de in favor of cycloadducts **6** and **7** arises from the addition of the dipole to the top of the *Re*,*Re*-alkene face of **2**.

4. Experimental

4.1. General information

Crystallographic data (CIF tables excluding structure factors) for the two structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC-707015 and CCDC-707016. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cabridge CB2 1EZ, UK, (fax: +44 (0)1223-336033 or e-mail: deposit@ccdc.cam.ac.Uk).

4.1.1. Instrumentation

Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 1600 FTIR instrument. ^{1}H NMR spectra were recorded using a Varian 300 BB, 300 MHz or on a Brüker AMX 2-500 MHz spectrometer. ^{13}C NMR spectra were recorded at 75 or 125 MHz. Chemical shifts are reported in parts per million (δ). ^{1}H Chemical shifts in $CDCl_3$ were referenced to residual $CHCl_3$ (7.27 ppm) while ^{13}C chemical shifts were referenced to the solvent ($CDCl_3$, 77.03 ppm). Mass spectra were obtained using a GC–MS (GCD plus gas chromatography-electron ionization detector, HPG 1800A GCD system) equipped with a 5% crosslinked PhMe silicone HP 19091 J-433 column. Elemental analyses were carried out at the chemistry department of the Université de Montréal, Montréal, P.Q., Canada; on a Fisons Instrument SPA, model EA1108. Thin-layer chromatography was performed on Silica Gel F254 (E. Merck precoated glass plates). Separations were carried out using circular chromatography (chromatotron®, model 7924, Harrison Research; E. Merck silica gel 7749).

4.1.2. Materials

Acrolein, acetaldehyde oxime, benzaldehyde oxime, benzyl bromide, borontribromide, borontrifluoride etherate, *N*-chorosuccinimide, cinnamaldehyde, crotonaldehyde, diisopropyl amine, 2-furaldehyde, fumaric acid monoethyl ester, methacrolein, and (+)-pulegone were all obtained from Aldrich Chemical Co. and were used without further purification. Phenylisocyanate was freshly distilled before use (bp 46 °C/10 mmHg). (−)-8-*N*-benzylaminomenthol **1**,[20a] *N*-hydroxybenzene-carboimidoyl chloride,[31] methyl 4-hydroxycrotonate[41] as well as methyl 4-oxo-2(*E*)-butenoate[42] were prepared as previously reported while ethyl 2(*E*)-4-(diisopropylamino)-4-oxo-butenoate was prepared from an adaptation of a general procedure previously reported.[36]

Solvents were dried by distillation as follows: THF and diethyl ether from sodium/benzophenone; dichloromethane, and toluene from P_2O_5; and finally, triethylamine from CaH_2. Unless otherwise stated, all syntheses were carried out under dry nitrogen. After reaction work-up, solutions were dried using Na_2SO_4 and the solvents were subsequently removed by rotary evaporation.

4.2. Experimental procedures

4.2.1. Typical condensation procedures for the synthesis of perhydrobenzoxazines 2a–g

Method A. Typical condensation procedure A, when less volatile aldehydes are used. To a solution of **1** (1.000 g, 3.83 mmol, 1 equiv) in toluene (10 mL), was added, all at once, 2-furaldehyde (1.10 g, 0.95 mL; 11.5 mmol, 3 equiv). The reaction was heated to reflux for 48 h or until it had finished as indicated by TLC (CH_2Cl_2–MeOH, 90:10; see times indicated in Table 1). The reaction was stopped at 8 h intervals and any condensed water was removed from the inside of the condenser. The solvent was removed under reduced pressure and the product purified by chromatography using petrol–CH_2Cl_2 (65:35). 1.144 g (88% yield) of **2f,** a yellow oil was isolated.

Method B. Typical procedure when volatile aldehydes are used. (−)-8-*N*-Benzylaminomenthol (1.00 g, 3.83 mmol, 1 equiv) was dissolved in toluene (5 mL). The solution was heated to reflux and a solution of acrolein (3.218 g, 3.80 mL, 57.46 mmol, 15 equiv) in toluene (1 mL) was slowly added with stirring over 8 h using a syringe pump. At 5 h intervals, the solution was cooled and any deposited water or white polymeric material was removed from the condenser. The reaction mixture was then heated again to reflux and followed by TLC (CH_2Cl_2, MeOH; 9:1); approx. 20 h in total. The resultant mixture was cooled, concentrated and the residue purified by chromatography using petrol–Et_2O (9:1) to give **2a** (0.963 g, 84% yield) as a pale yellow oil.

4.2.1.1. (−)-(2*S*,7*R*,9*R*,10*S*)-3-(Benzyl)-4,4,7-trimethyl-2-ethenyloctahydro-2*H*-1,3-benzoxazine 2a. See general condensation method B. R_f = 0.79 (petrol–CH_2Cl_2, 1:1); $[\alpha]_D^{23} = -23.6$ (*c* 0.865, MeOH); IR (film) *ν* 3088, 3061, 3023, 2978, 2923, 2867, 1603, 1493, 1452, 1409, 1385, 1095, 947, 940, 722, 695 and 688 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ* 0.90–1.03 (m, 2H, $H_{5ax,\ 6ax}$), 0.92 (d, *J* = 5.9 Hz, 3H, CH_3–C_7), 0.98 (s, 3H, CH_{3eq}–C_4), 1.15 (q, *J* = 11.0 Hz, 1H, H_{8ax}), 1.23 (s, 3H, CH_{3ax}–C_4), 1.43–1.78 (m, 4H, H_{5eq}, H_{6eq}, H_{10}, H_7), 1.97 (br d, *J* = 11.6 Hz, 1H, H_{8eq}), 3.55 (td, *J* = 11.0, 4.0 Hz, 1H, H_9), 3.75 (AB-d, *J* = 11.7 Hz, 1H, NCH_2Ph), 4.05 (AB-d, *J* = 11.7 Hz, 1H, NCH_2Ph), 5.09 (dt, *J* = 10.6; 1.7; Hz, 1H, $H_{2'}$), 5.14 (dt, *J* = 4.3, 1.7 Hz, 1H, H_2), 5.37 (dt, *J* = 17.4; 1.7 Hz, 1H, $H_{2'}$), 5.69 (ddd, *J* = 17.4, 10.6, 4.3 Hz, 1H, $H_{1'}$), 7.15 (t, *J* = 7.1 Hz, 1H, $H_{p\text{-Ph}}$), 7.26 (t, *J* = 7.0 Hz, 2H, $H_{m\text{-Ph}}$), 7.37 (d, *J* = 7.0 Hz, 2H, $H_{o\text{-Ph}}$); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 19.78 (*C*H_{3ax}–C_4), 22.30 (*C*H_3–C_7), 25.06 (CH_2, C_5), 27.07 (*C*H_{3eq}–C_4), 31.43 (CH, C_7), 35.11 (CH_2, C_6), 41.49 (CH_2, C_8), 46.32 (CH, C_{10}), 47.18 (N–CH_2), 56.79 (C_q, C_4), 75.79 (CH, C_9), 87.46 (CH, C_2), 117.43 (CH_2, $C_{2'}$), 125.72 (CH, $C_{p\text{-Ph}}$), 126.93 (2CH, $C_{o\text{-Ph}}$), 127.90 (2CH, $C_{m\text{-Ph}}$), 137.72 (CH, $C_{1'}$), 144.28 (C_q, C_{Ph}); GC–MS (70 eV, *m/z*, %): 299 (M^+, 1.5), 284 ($M^{+\cdot}$–CH_3, 5.5), 272 ($M^{+\cdot}$–C_2H_3, 25), 228 (10), 208 ($M^{+\cdot}$–$PhCH_2$, 3), 146 ($PhCH_2N^{+\cdot}H{=}CH{-}CH{=}CH_2$, 45), 91 ($C_7H_7^+$, 100).

4.2.1.2. (−)-(1′*E*)-(2*S*,7*R*,9*R*,10*S*)-3-(Benzyl)-4,4,7-trimethyl-2-(prop-1′-enyl)octahydro-2*H*-1,3-benzoxazine 2b. Using general condensation procedure B: **1** (1.500 g, 5.74 mmol; 1 equiv) was dissolved in toluene (10 mL) and to this was added, over 15 h, a solution of crotonaldehyde (3.214 g, 3.80 mL; 45.92 mmol, 8 equiv) in toluene (2 mL). The crude product was purified by chromatography using petrol–Et_2O (96:4) giving 1.457 g (81% yield) of **2b** as a yellow oil. R_f = 0.42 (petrol–Et_2O, 96:4); $[\alpha]_D^{23} = -31.3$ (*c* 0.193, CH_2Cl_2); IR (film) *ν* 3083, 3061, 3027, 2982, 2868, 1493, 1452, 986, 956, 727, 692 and 667 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ* 0.97 (d, *J* = 6.6 Hz, 3H, CH_3–C_7), 0.96–1.01 (m, 2H, H_{5ax} + H_{6ax}), 1.04 (s, 3H, $CH_{3\text{-}eq}$–C_4), 1.16 (q, *J* = 11.7 Hz, 1H, H_{8ax}), 1.22 (s, 3H, CH_{3ax}–C_4), 1.46–1.52 (m, 2H, H_{10} + H_7), 1.54 (d, *J* = 6.6 Hz, 3H, C=C-CH_3), 1.62–1.70 (m, 1H, H_{5eq}), 1.70–1.79 (m, 1H, H_{6eq}), 1.99 (d app., *J* = 12.5 Hz, 1H, H_{8eq}), 3.56 (td, *J* = 10.3, 3.7 Hz, 1H, H_9), 3.66 (AB-d, *J* = 17.1 Hz, 1H, NCH_2Ph), 4.05 (AB-d, *J* = 17.1 Hz, 1H, NCH_2Ph), 5.04 (d, *J* = 5.0 Hz, 1H, H_2), 5.28 (br dd, *J* = 15.4, 5.0 Hz, 1H, $H_{1'}$), 5.81 (dq, *J* = 15.4, 6.6 Hz, 1H, $H_{2'}$), 7.17 (t, *J* = 7.2 Hz, 1H, $H_{p\text{-Ph}}$), 7.28 (t, *J* = 7.3 Hz, 2H, $H_{m\text{-Ph}}$), 7.37 (d, *J* = 7.3 Hz, 2H, $H_{o\text{-Ph}}$); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 17.63 (CH_3, C=C-*C*H_3), 18.52 (*C*H_{3ax}–C_4), 22.28 (*C*H_3–C_7), 25.10 (CH_2, C_5), 27.27 (*C*H_{3eq}–C_4), 31.39 (CH, C_7), 35.09 (CH_2, C_6), 41.50 (CH_2, C_8), 46.98 (CH, C_{10}), 47.50 (NCH_2Ph), 56.75 (C_q, C_4), 75.56 (CH, C_9), 88.00 (CH, C_2), 125.66 (CH, $C_{p\text{-Ph}}$), 127.19 (2CH, $C_{o\text{-Ph}}$), 127.81 (2CH, $C_{m\text{-Ph}}$), 128.83 (CH, $C_{2'}$), 131.15 (CH, $C_{1'}$), 144.38 (C_q, C_{Ph}). GC–MS (70 eV, *m/z*, %): 313.2 (M^+, 0.8), 272.2 (M^+–HC=CH–CH_3, 9), 228 (M^+–C_4H_7NO, 6), 160 ($C_{10}H_{10}NO^+$, 18), 148 ($C_9H_{10}NO^+$, 39), 91 ($C_7H_7^+$, 100); Anal. Calcd for $C_{21}H_{31}NO$: C, 80.46; H, 9.97; N, 4.47. Found: C, 80.18; H, 10.01; N, 4.48.

4.2.1.3. (−)-(2*E*)-[(2*S*,7*R*,9*R*,10*S*)-Ethyl-3-3-(benzyl)-4,4,7-trimethyloctahydro-2*H*-1,3-benzoxazin-2-yl-prop-2-enoate 2d. Using general condensation procedure A: **1**, (1.500 g, 5.75 mmol, 1 equiv) was dissolved in toluene (12 mL) and ethyl (2*E*)-4-oxobut-2-enoate (0.861 g, 6.73 mmol, 1.2 equiv) was added. The compound, **2d,** was isolated by chromatography, using petrol–Et_2O (95:5) leaving 1.451 g (68% yield) as a white solid. mp: 102 °C; R_f = 0.52 (petrol–Et_2O, 90:10); $[\alpha]_D^{23} = -69.0$ (*c* 0.114, CH_2Cl_2); IR (KBr) *ν* 3084, 3061, 3029, 2979, 2861, 1718 (C=O); 1661, 1495, 1200, 950, 737, 696, 648 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): *δ* 0.92 (d, *J* = 6.3 Hz, 3H, CH_3–C_7), 0.96 (s, 3H, CH_{3eq}–C_4), 0.95–1.05 (m, 2H, 5_{ax} + 6_{ax}), 1.14 (t, *J* = 7.2 Hz, 3H, O–CH_2–*CH*), 1.11–1.20 (m, 1H, H_{8ax}), 1.23 (s, 3H, CH_{3ax}–C_4), 1.45–1.50 (m, 1H, H_7), 1.50–1.60 (m, 1H, H_{10}), 1.61–1.67 (m, 1H, H_{6eq}), 1.70–1.78 (m, 1H, H_{5eq}), 1.96 (d app., *J* = 12.4 Hz, 1H, H_{8eq}), 3.58 (td, *J* = 10.4, 3.8 Hz, 1H, H_9), 3.79 (AB-d, *J* = 17.3 Hz, 1H, NCH_2Ph), 3.93 (AB-d, *J* = 17.3 Hz, 1H, NCH_2Ph), 4.08 (q, *J* = 7.3 Hz, 2H, O–*C*H_2–CH_3), 5.29 (br s, 1H, H_2), 6.07 (dd, *J* = 15.7, 1.7 Hz, 1H, $H_{2'}$), 6.63 (dd, *J* = 15.7, 3.4 Hz, 1H, $H_{3'}$), 7.11 (t, *J* = 7.5 Hz, 1H, $H_{p\text{-Ph}}$), 7.22 (t, *J* = 7.5 Hz, 2H, $H_{m\text{-Ph}}$), 7.29 (d app., *J* = 7.5 Hz, 2H, $H_{o\text{-Ph}}$); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 14.09 (O–CH_2–*C*H_3), 20.97 (*C*H_{3ax}–C_4), 22.24 (*C*H_3–C_7), 24.95 (CH_2, C_6), 27.10 (*C*H_{3eq}–C_4), 31.37(CH, C_7), 35.06 (CH_2, C_5), 41.28 (CH_2, C_8), 45.42 (CH, C_{10}), 47.75 (N*C*H_2Ph), 57.04 (C_q, C_4), 60.14 (O–*C*H_2–CH_3), 76.07 (CH, C_9), 85.48 (CH, C_2), 123.07 (CH, $C_{2'}$), 125.91 (CH, $C_{p\text{-Ph}}$), 127.04 (2CH, $C_{m\text{-Ph}}$), 127.99 (2CH, $C_{o\text{-Ph}}$), 143.50 (C_q, C_{Ph}), 146.25 (CH, $C_{3'}$),166.02 (C_q, C=O); GC–MS (70 eV, *m/z*, %): 326 (M^+–C_2H_5O, 2); 272 (M^+–HC=CH–CO_2Et, 13); 91 ($C_7H_7^+$, 100); Anal. Calcd for $C_{23}H_{33}NO_3$: C, 74.36; H; 8.95; N, 3.77. Found: C, 74.03; H, 8.94; N, 3.76.

4.2.1.4. Ethyl (2*E*)-4-(diisopropylamino)-4-oxobut-2-enoate (precursor to acid). In a flask mounted with a drying tube, ethyl hydrogenofumarate (0.500 g, 3.47 mmol, 1 equiv) was dissolved in CH_2Cl_2 (4 mL) and thionyl chloride (0.802 g, 6.8 mmol, 0.492 mL, 2 equiv) was added all at once. The reaction mixture was stirred for 2 h and then diisopropylamine (0.911 g, 9.02 mmol, 1.18 mL, 2.6 equiv) was added in small amounts, to allow for safe gas evolution, over about 20 min. The resultant brown mixture was stirred at room temperature for 2 h then carefully quenched with small portions of a saturated Na_2CO_3 solution (2 mL), diluted with 1 mL of water, and extracted with CH_2Cl_2 (3 × 5 mL). The combined extracts were washed with 5 mL of water, dried over Na_2SO_4, and the solvent was removed under vacuum. The crude product was purified by chromatography (CH_2Cl_2–MeOH, 99:1) to give 0.733 g (93% yield) of the desired enoate as a yellow oil. R_f = 0.52 (CH_2Cl_2–MeOH, 96:4); IR (nujol): 2971, 2935, 2827, 1710 (O–C=O), 1626 (N–C=O), 1216 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ* 1.26 (50%, d, *J* = 6.9 Hz, 6H, N–CH–(*CH*$_3$)$_2$), 1.32 (t, *J* = 7.1 Hz, 3H, O–CH_2–*CH*$_3$), 1.40 (50%, d, *J* = 6.9 Hz, 6H, N–CH–(*CH*$_3$)$_2$), 3.72 (sep., *J* = 6.9 Hz, 1H, N–*CH*–$(CH_3)_2$), 4.00 (sep., *J* = 6.9 Hz, 1H, N–*CH*–$(CH_3)_2$), 4.25 (q, *J* = 7.1 Hz, 2H, O–*CH*$_2$–CH_3), 6.63 (d, *J* = 15.4 Hz, 1H, H_2), 7.37 (d, *J* = 15.4 Hz, 1H, H_3); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 14.16 (CH_3, O–CH_2–*C*H_3), 20.34 (50%, N–CH–(*C*H_3)$_2$), 21.30 (50%, N–CH–(*C*H_3)$_2$), 46.03 (N–*C*H–$(CH_3)_2$), 47.94 (CH, N–*C*H–$(CH_3)_2$), 60.95 (CH_2, O–*C*H_2–CH_3), 129.00 (CH, C_2), 137.28 (CH, C_3), 164.33 (C_q, *C*ON), 166.04 (C_q, *C*OO); GC–MS (70 eV, *m/z*, %): 227.1 (M^+, 1.4), 212.1 (M^+–CH_3, 5.3), 127.0 (M^+–$C_6H_{14}N$, 37), 100.0 ($C_6H_{14}N^+$, 52), 86.1 (M^+–$C_5H_{12}N$, 100).

4.2.1.5. (2*E*)-4-(Diisopropylamino)-4-oxobut-2-enoic acid (precursor to aldehyde). Ethyl (2*E*)-4-(diisopropylamino)-4-oxobut-2-enoate (0.638 g, 2.81 mmol, 1 equiv) was dissolved in a mixture of ethanol (95%, 2 mL) and $NaOH_{(aq)}$ (2 M, 1.4 mL). The resultant mixture was stirred for 15 min, acidified to pH 2, and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The corresponding acid was purified by chromatography using CH_2Cl_2–MeOH (9:1) to give 0.504 g (90% yield) as a light brown solid. Mp = 112 °C; R_f = 0.72 (CH_2Cl_2–MeOH, 4:1); IR (KBr) *ν* 3099 (CO*O*–*H*), 1731 (O*C*=O), 1603 (N*C*=O), 1250 and 1170 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ* 1.24 (50%, d, *J* = 6.6 Hz, 6H, (*CH*$_3$)$_2$CH–N), 1.38 (50%, d, *J* = 6.6 Hz, 6H, (*CH*$_3$)$_2$CH–N), 3.71 (b sep., *J* = 6.6 Hz, 1H, N–*CH*–$(CH_3)_2$), 3.98 (sep., *J* = 6.6 Hz, 1H, N–*CH*–$(CH_3)_2$), 6.60 (d, *J* = 15.7 Hz, 1H, H_2), 7.38 (d, *J* = 15.7 Hz, 1H, H_3), 10.91 (br s, 1H, COO*H*); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 20.19 (50%, ((*C*H_3)$_2$CH–N), 21.10 (50%, (*C*H_3)$_2$CH–N), 46.28 (N–CH–$(CH_3)_2$), 49.25 (N–CH–$(CH_3)_2$), 128.99 (CH, C_2), 137.99 (CH, C_3), 164.95 (C_q, *C*ON(*i*Pr)$_2$), 169.11 (C_q, *C*OOH); GC–MS (70 eV, *m/z*, %): 199 (M^+, 0.9), 184 (M^+–CH_3, 16), 181 (M^+–H_2O, 16), 142

($C_8H_{16}NO^+$, 26), 100 ($C_6H_{14}N^+$, 39), 99 ($M^+-C_6H_{14}N$, 46), 86.1 ($M^+-C_5H_{12}N$, 100), 58.1 ($C_2H_2O^+$, 36).

4.2.1.6. (2*E*)-*N*,*N*-Diisopropyl-4-oxobut-2-enamide (precursor to 2e). To a (2*E*)-4-(diisopropylamino)-4-oxobut-2-enoic acid (0.300 g, 1.5 mmol, 1 equiv) solution in CH_2Cl_2 (1 mL) was added, all at once, thionyl chloride (0.231 g, 1.66 mmol, 0.141 mL, 1.3 equiv). After stirring for 2 h, the solvent was removed under reduced pressure and then the product was dried under vacuum for 45 min. The crude acid chloride was dissolved in THF (2 mL), cooled to −78 °C and to this was added, all at once, LiAl(O–$C(CH_3)_3)_3H$ (0.5 M in diglime, 3.0 mL, 0.381 g, 1.5 mmol, 1 equiv) with stirring. The reaction mixture was slowly allowed to warm to room temperature and was stirred for a further 24 h. The product was hydrolyzed with water (10 mL) and acidified HCl (1 N, 1 mL). This mixture was extracted with CH_2Cl_2 (3 × 5 mL), washed with water (5 mL), dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The residue (containing the desired aldehyde, the corresponding alcohol, and diglyme) was separated by chromatography using a gradient: petrol–Et_2O (1:1), then Et_2O (100%) followed by Et_2O–MeOH (95:5), which gave 83 mg (30% yield) of the title aldehyde as a colorless oil. R_f = 0.45 (petrol–Et_2O, 1:1); IR (film) ν 2971, 2939, 2876, 2827, 2737, 1695 (HC=O), 1642 (NC=O), 1372, 1207, 1154 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.27 (50%, d, J = 6.6 Hz, 6H, $(CH_3)_2CH$–N), 1.42 (50%, d, J = 6.6 Hz, 6H, $(CH_3)_2CH$–N), 3.69 (50%, sept., J = 6.6 Hz, 1H, N–CH–$(CH_3)_2$), 3.98 (50%, sept., J = 6.6 Hz, 1H, N–CH–$(CH_3)_2$), 6.73 (dd, J = 15.7, 7.4 Hz, 1H, H_3), 7.19 (d, J = 15.7 Hz, 1H, H_2), 9.70 (d, J = 7.4 Hz, 1H, CHO); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.30 (50%, $(CH_3)_2CH$–N), 21.23 (50%, $(CH_3)_2CH$–N), 46.22 (N–CH–$(CH_3)_2$), 49.40 (N–CH–$(CH_3)_2$), 136.40 (CH, C_3), 143.87 (CH, C_2), 164.11 (C_q, $CON(iPr)_2$), 199.78 (C_q, COH); GC–MS (70 eV, *m*/*z*, %): 183.0 (M^+, 0.5), 168.1 (M^+-CH_3, 16), 126.1 ($M^+-C_3H_7N$, 33), 100.1 ($C_6H_{14}N^+$, 95), 86.1 ($M^+-C_5H_{12}N$, 100), 58.1 ($C_2H_2O^+$, 32).

4.2.1.7. (−)-(2*E*)-3-(2*S*,7*R*,9*R*,10*S*)-3-(Benzyl)-4,4,7-trimethyloctahydro-2*H*-1,3-benzoxazin-2-yl-*N*,*N*-diisopropylprop-2-enamide 2e. Using general condensation procedure A: **1**, (114 mg, 0.437 mmol, 1 equiv) was dissolved in toluene (5 mL) and (2*E*)-*N*,*N*-diisopropyl-4-oxobut-2-enamide (80 mg; 0,437 mmol; 1 equiv) was added. The crude reaction mixture was purified by chromatography, using petrol–Et_2O (4:1), giving 137 mg (73% yield) of **2e** as a white solid. mp: 98 °C; R_f = 0.50 (petrol–Et_2O, 1:1); $[\alpha]_D^{23} = -65.1$ (*c* 0.45, CH_2Cl_2); IR (KBr) ν 3090, 3056, 3022, 2973, 2860, 1615 (C=O), 1663, 1493, 1208, 1184, 939, 733, 696, 648 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.97 (s, 3H, CH_{3eq}–C_4), 1.00 (d, J = 6.8 Hz, 3H, CH_3–C_7), 1.00–1.05 (m, 2H, $H_{5ax+6ax}$), 1.02–1.16 (m, 6H, N–CH–$(CH_3)_2$), 1.22 (q, J = 11.4 Hz, 1H, H_{8ax}), 1.32 (s, 3H, CH_{3ax}–C_4), 1.28–1.40 (m, 6H, N–CH–$(CH_3)_2$), 1.51–1.59 (m, 1H, H_7), 1.62–1.77 (m, H_{5eq}, 3H, H_{6eq} + H_{10}), 2.01 (d app., J = 11.9 Hz, 1H, H_{8eq}), 3.61 (td, J = 10.5, 3.5 Hz, 1H, H_9), 3.68–3.52 (m, 1H, N–CH–$(CH_3)_2$), 3.89 (AB-d, J = 17.4 Hz, 1H, NCH_2Ph), 3.85–3.95 (m, 1H, N–CH–$(CH_3)_2$), 4.02 (AB-d, J = 17.4 Hz, 1H, NCH_2Ph), 5.42 (s, 1H, H_2), 6.52 (s, 2H, $H_{2'+3'}$), 7.17 (t, J = 7.1 Hz, 1H, $H_{p\text{-}Ph}$), 7.29 (t, J = 7.3 Hz, 2H, $H_{m\text{-}Ph}$), 7.40 (d, J = 7.4 Hz, 2H, $H_{o\text{-}Ph}$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.53 (50%, $(CH_3)_2CH$–N), 21.15 (50%, $(CH_3)_2CH$–N), 21.78 (CH_{3ax}–C_4), 22.30 (CH_3–C_7), 24.96 (CH_2, C_5), 26.97 (CH_{3eq}–C_4), 31.45 (CH, C_7), 35.18 (CH_2, C_6), 41.39 (CH_2, C_8), 44.83 (CH, C_{10}), 45.55 (N–CH–$(CH_3)_2$), 47.85 (NCH_2Ph), 48.14 (N–CH–$(CH_3)_2$), 56.98 (C_q, C_4), 76.33 (CH, C_9), 86.08 (CH, C_2), 125.25 (CH, $C_{2'}$), 125.83 (CH, $C_{p\text{-}Ph}$), 126.82 (2CH, $C_{o\text{-}Ph}$), 127.99 (2CH, $C_{m\text{-}Ph}$), 140.89 (CH, $C_{3'}$), 143.97 (C_q, C_{Ph}), 165.92 (C_q, C=O); GC–MS (70 eV, *m*/*z*, %): 426.2 (M^+, 2), 411 (M^+-CH_3, 4), 272.2 ($M^+-C_9H_{16}NO$, 37), 91 ($C_7H_7^+$, 100.0). Anal. Calcd for $C_{27}H_{42}N_2O_2$: C, 76.01; H, 9.92; N, 6.57. Found: C, 76.31; H, 9.95; N, 6.55.

4.2.1.8. (−)-(2*S*,7*R*,9*R*,10*S*)-3-(Benzyl)-2-(2′-furyl)-4,4,7-trimethyloctahydro-2*H*-1,3-benzoxazine 2f. See typical condensation procedure A. **2f** (1.144 g, 88%) was obtained as a yellow oil from **1** (1.000 g) and 2-furaldehyde (1.104 g); R_f = 0.42 (65:35 petrol–CH_2Cl_2); $[\alpha]_D^{23} = -24.6$ (*c* 0.74, CH_2Cl_2); IR (film) ν 3061, 3021, 2978, 2868, 1603, 1506, 1493, 1054, 733 and 696 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.00 (d, J = 6.7 Hz, 3H, CH_3–C_7), 1.04 (br d, J = 10.3 Hz, 1H, H_{6ax}), 1.06 (br d, J = 10.1 Hz, 1H, H_{5ax}), 1.09 (s, 3H, CH_{3eq}–C_4), 1.26 (q, J = 11.6 Hz, 1H, H_{8ax}), 1.34 (s, 3H, CH_{3ax}–C_4), 1.48–1.60 (m, 1H, H_7), 1.69–1.72 (m, 2H, H_{5eq} + H_{10}), 1.72–1.80 (m, 1H, H_{6eq}), 2.05 (d app., J = 11.6 Hz, 1H, H_{8eq}), 3.69 (AB-d, J = 16.9 Hz, 1H, NCH_2Ph), 3.67–3.70 (m, 1H, H_9), 4.03 (AB-d, J = 16.9 Hz, 1H, NCH_2Ph), 5.78 (s, 1H, H_2), 6.15 (dd, J = 3.0, 1.6 Hz, 1H, $H_{4'}$), 6.30 (dd, J = 3.0, 0.7 Hz, 1H, $H_{3'}$), 7.13 (t, J = 7.9 Hz, 1H, $H_{p\text{-}Ph}$), 7.15 (dd, J = 1.6, 0.7 Hz, 1H, $H_{5'}$), 7.21 (t, J = 7.8 Hz, 2H, $H_{m\text{-}Ph}$), 7.28 (d, J = 7.7 Hz, 2H, $H_{o\text{-}Ph}$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.36 (CH_{3ax}–C_4), 22.22 (CH_3–C_7), 25.01 (CH_2, C_5), 27.39 (CH_{3eq}–C_4), 31.34 (CH, C_7), 34.98 (CH_2, C_6), 41.28 (CH_2, C_8), 46.19 (CH, C_{10}), 47.89 (NCH_2Ph), 57.21 (C_q, C_4), 76.46 (CH, C_9), 84.12 (CH, C_2), 107.90 (CH, $H_{3'}$), 109.85 (CH, $H_{4'}$), 125.42 (CH, $C_{p\text{-}Ph}$), 127.00 (2CH, $C_{m\text{-}Ph}$), 127.53 (2CH, $C_{o\text{-}Ph}$), 141.57 (CH, $C_{5'}$), 143.18 (C_q, C_{Ph}), 152.47 (C_q, $C_{2'}$); GC–MS (70 eV, *m*/*z*, %): 339.2 (M^+, 4.0), 228 ($C_{16}H_{22}N^+$, 20), 186 ($M^+-C_{12}H_{12}NO$, 16), 148 ($C_{10}H_{14}N^+$, 43), 91 ($C_7H_7^+$, 100); Anal. Calcd for $C_{22}H_{29}NO_2$: C, 77.84; H, 8.61; N, 4.13. Found: C, 78.11; H, 8.63; N, 4.11.

4.2.1.9. (−)-(1′*E*)-(2*S*,7*R*,9*R*,10*S*)-3-(Benzyl)-4,4,7-trimethyl-2-2′-phenylethenyloctahydro-2*H*-1,3-benzoxazine 2g. Using general condensation procedure A: To **1**, (2.000 g; 7.66 mmol; 1 equiv) in toluene (10 mL) was added cinnamaldehyde (2.025 g; 1.93 mL; 15.31 mmol; 2 equiv). The compound, **2g,** was isolated by chromatography using petrol–Et_2O (9:1) and gave 2.760 g (96% yield) as a white solid. Crystallization from CH_2Cl_2–hexane (1:1) gave **2g** as colorless crystals. Mp. 118 °C; R_f = 0.53 (petrol–CCl_4–Et_2O, 96:20:4); $[\alpha]_D^{23} = -63.5$ (*c* 0.66, CH_2Cl_2); IR (KBr) ν 3080, 3063, 3021, 2982, 2946, 2877, 1495, 1452, 972, 956, 726, 692, 641 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ. 0.97 (d, J = 5.9 Hz, 3H, CH_3–C_7), 0.98–1.03 (m, 2H, H_{5ax} + H_{6ax}), 1.09 (s, 3H, $CH_{3\text{-}eq}$–C_4), 1.20 (q, J = 12.0 Hz, 1H, H_{8ax}), 1.27 (s, 3H, CH_{3ax}–C_4), 1.44–1.50 (m, 1H, H_7), 1.48–1.58 (m, 1H, H_{10}), 1.65–1.71 (m, 1H, H_{6eq}), 1.71–1.78 (m, 1H, H_{5eq}), 2.01 (d app., J = 12.0 Hz, 1H, H_{8eq}), 3.61 (td, J = 10.2, 3.8 Hz, 1H, H_9), 3.70 (AB-d, J = 17.2 Hz, 1H, NCH_2Ph), 4.08 (AB-d, J = 17.2 Hz, 1H, NCH_2Ph), 5.27 (d, J = 5.1 Hz, 1H, H_2), 5.91 (dd, J = 16.0, 5.1 Hz, 1H, $H_{1'}$), 6.67 (d, J = 16.0 Hz, 1H, $H_{2'}$), 7.05 (d, J = 7.2 Hz, 2H, =C–$H_{o\text{-}Ph}$), 7.14 (tapp, J = 7.3 Hz, 2H, $H_{p\text{-}Ph}$), 7.18 (t, J = 7.2 Hz, 2H, =C–$H_{m\text{-}Ph}$), 7.24 (t, J = 7.4 Hz, 2H, NC–$H_{m\text{-}Ph}$), 7.35 (d, J = 7.4 Hz, 2H, NC–$H_{o\text{-}Ph}$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.00 (CH_{3ax}–C_4), 22.28 (CH_3–C_7), 25.10 (CH_2, C_6), 27.29 (CH_{3eq}–C_4), 31.39 (CH, C_7), 35.02 (CH_2, C_5), 41.42 (CH_2, C_8), 46.82 (CH, C_{10}), 47.65 (NCH_2Ph), 56.88 (C_q, C_4), 75.76 (CH, C_9), 87.79 (CH, C_2), 125.67 (CH, $C_{p\text{-}Ph}$), 126.55 (CH, $C_{p\text{-}Ph}$), 127.29 (2CH, $C_{m\text{-}Ph}$), 127.35 (2CH, $C_{m\text{-}Ph}$), 127.93 (2CH, $C_{o\text{-}Ph}$), 128.19 (2CH, $C_{o\text{-}Ph}$), 129.51 (CH, $C_{2'}$), 131.83 (CH, $C_{1'}$), 136.72 (C_q, C_{Ph}), 143.98 (C_q, C_{Ph}); GC–MS (70 eV, *m*/*z*, %): 375 (M^+, 7); 284 ($M^+-C_7H_7$, 2); 272 (M^+–HC=CH–Ph, 12); 91 ($C_7H_7^+$, 100); Anal. Calcd for $C_{26}H_{33}NO$: C, 83.15; H, 8.86; N, 3.73. Found: C, 82.86; H, 8.82; N, 3.74.

Crystallographic studies for **2g**. Single crystals of **2g** were obtained by slow recrystallization in a 1:1 mixture of pentane and dichloromethane. The crystal belonged to the chiral orthorhombic $P2_12_12_1$ space group, but the crystallographic results did not permit determination of the absolute configuration. Nevertheless, since the stereochemistry of the C1, C2, and C5 stereocenters of the precursor (−)-8-benzylaminomenthol, **1** are known and the structure of compound **5** has already been determined, the correct enantiomer could be chosen and the stereochemistry at C7, C9, and C10 in compound **2g** was easily determined. Figure 1 shows the

structure and the labeling scheme of compound **2g**. The bond distances and angles are available in the CIF.

4.2.2. General 1,3-dipolar cycloaddition procedure for the synthesis of 2-isoxazolines cycloadducts 6–9

Method A. *N*-Hydroxybenzenecarboimidoyl chloride as precursor to phenylacetonitrile oxide. *trans*-Perhydrobenzoxazine **2** (1 equiv) and triethylamine (1–20 equiv) were dissolved in CH_2Cl_2 (2 mL) and *N*-hydroxybenzenecarboimidoyl chloride[33] (1–5 equiv) in CH_2Cl_2 (1 mL) was added over 8 h using a syringe pump. The solution was stirred for a total of 24 h and then CH_2Cl_2 (5 mL) and a saturated Na_2CO_3 solution (3 mL) were added. After stirring for 20 min, the aqueous phase was extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were washed with water (5 mL), dried over Na_2SO_4, and then the solvent was removed under reduced pressure and the crude product dried under vacuum (2 h). The residue was purified by chromatography as described for each cycloadduct, **6** through **9**.

4.2.2.1. (+)-(2*S*,5′*S*,7*R*,9*R*,10*S*)-3-(Benzyl)-2-3′-phenyl-4,5-dihydroisoxazol-5′-yl-4,4,7-trimethyloctahydro-2*H*-1,3-benzoxazine 6a and (−)-(5′*R*)-epimer 8a. Using general cycloaddition procedure A: To a solution of *trans*-perhydrobenzoxazine **2a** (71 mg, 0.24 mmol, 1 equiv) and triethylamine (0.48 g, 4.7 mmol, 20 equiv) in CH_2Cl_2 (2 mL) was added *N*-hydroxybenzenecarboimidoyl chloride[33] (0.19 g, 1.2 mmol, 5 equiv). The residue obtained was separated by chromatography using petrol–Et_2O (4:1) to give together 69.5 mg (70% yield) of cycloadducts **6a** and **8a**. The isomeric ratio was determined by integration of the ^{13}C NMR signals for $C_{5'}$ (81.50 and 81.85 ppm) and C_2 (87.64 and 88.81 ppm). The results are shown in Table 2.

Data for **6a**. Yield = 53.6 mg (54%); Yellow oil, $R_f = 0.21$ (petrol–Et_2O, 90:10); $[\alpha]_D^{23} = +13.4$ (*c* 0.264, CH_2Cl_2); IR (film) *v* 3060, 3026, 2922, 2866, 1597 (C=N), 1639, 1492, 1451, 1384, 1054, 941, 715, 696, 671 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 0.92 (d, $J = 6.1$ Hz, 3H, CH_3–C_7), 0.90–1.04 (m, 3H, $H_{8ax,5ax,6ax}$), 1.16 (s, 3H, CH_{3eq}–C_4), 1.19 (s, 3H, CH_{3ax}–C_4), 1.46 (t app., $J = 9.4$ Hz, 2H, H_{7+10}), 1.67–1.74 (m., 2H, $H_{5eq+6eq}$), 1.92 (d app., $J = 11.8$ Hz, 1H, H_{8eq}), 2.65 (dd, $J = 17.0$, 11.0 Hz, 1H, $H_{4'\alpha}$), 3.50 (dd, $J = 17.0$, 7.7 Hz, 1H, $H_{4'\beta}$), 3.51 (td, $J = 10.4$, 3.8 Hz, 1H, H_9), 3.67 (AB-d, $J = 17.6$ Hz, 1H, NCH_2Ph), 4.08 (AB-d, $J = 17.6$ Hz, 1H, NCH_2Ph), 4.62 (ddd, $J = 11.0$, 7.7, 3.9 Hz, 1H, $H_{5'}$), 4.69 (d, 3.9 Hz, 1H, H_2), 7.20 (t, $J = 7.1$ Hz, 1H, $H_{p\text{-Ph}}$), 7.32 (t, $J = 7.4$ Hz, 2H, $H_{m\text{-Ph}}$), 7.36–7.38 (m, 3H, $H_{m,\ p\text{-Ph}}$), 7.48 (d, $J = 7.4$ Hz, 2H, $H_{NC\text{-}o\text{-Ph}}$), 7.60 (dd, $J = 6.6$, 3.0 Hz, 2H, $H_{C3'\text{-}o\text{-Ph}}$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 17.27 (CH_{3ax}–C_4), 22.18 (CH_3–C_7), 25.08 (CH_2, C_5), 26.91 (CH_{3eq}–C_4), 31.16 (CH, C_7), 34.91 (CH_2, C_6), 35.75 (CH_2, $C_{4'}$), 41.16 (CH_2, C_8), 47.47 (NCH_2Ph), 48.12 (CH, C_{10}), 57.31 (C_q, C_4), 75.26 (C_q, C_9), 81.50 (CH, $C_{5'}$), 87.64 (CH, C_2), 126.32 (CH, $C_{p\text{-Ph}}$), 126.64 (2CH, $C_{3'\text{-}o\text{-Ph}}$), 127.17 (2CH, $C_{NC\text{-}o\text{-Ph}}$), 128.16 (2CH, $C_{m\text{-Ph}}$), 128.46 (2CH, $C_{m\text{-Ph}}$), 129.65 (CH, $C_{p\text{-Ph}}$), 129.82 (C_q, C_{Ph}), 142.64 (C_q, C_{Ph}), 156.51 (C_q, $C_{3'}$); Anal. Calcd for $C_{27}H_{34}N_2O_2$: C, 77.48; H, 8.19; N, 6.69 . Found: C, 77.72; H, 8.22; N, 6.71.

Data for **8a**. Yield = 15.9 mg (16%); Yellow oil, $R_f = 0.18$ (pet:Et$_2$O, 4:1); $[\alpha]_D^{23} = -90.6$ (*c* 0.145, CH_2Cl_2); IR (film) *v* 3068, 3019, 2928, 2861, 1592 (C=N), 1499, 1445, 1380, 1062, 942, 715, 695, 676 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 0.96 (d $J = 6.8$ Hz, 3H, CH_3–C_7), 0.95–0.99 (m, 2H, $H_{5ax,6ax}$), 1.20 (q app, $J = 12.0$ Hz, 1H, H_{8ax}), 1.21 (s, 3H, CH_{3eq}–C_4), 1.31 (s, 3H, CH_{3ax}–C_4), 1.48–1.58 (m, 2H, H_{7+10}), 1.63 (br d, $J = 10.5$ Hz, 1H, H_{5eq}), 1.74 (b d, $J = 7.0$ Hz, 1H, H_{6eq}), 2.09 (d app., $J = 12.1$ Hz, 1H, H_{8eq}), 2.35 (dd, $J = 17.3$, 10.7 Hz, 1H, $H_{4'\alpha}$), 3.02 (dd, $J = 17.3$, 7.1 Hz, 1H, $H_{4'\beta}$), 3.62 (td, $J = 10.9$, 3.5 Hz, 1H, H_9), 4.03 (AB-d, $J = 17.7$ Hz, 1H, NCH_2Ph), 4.13 (AB-d, $J = 17.7$ Hz, 1H, NCH_2Ph), 4.60–4.68 (m, 1H, $H_{5'}$), 4.72 (d, $J = 8.6$ Hz, 1H, H_2), 7.23 (t, $J = 7.3$ Hz, 1H, $H_{p\text{-Ph}}$), 7.33–7.36 (m, 5H, $H_{m,p\text{-Ph}}$), 7.42 (d, $J = 7.8$ Hz, 2H, $H_{NC\text{-}o\text{-Ph}}$), 7.49 (br d, $J = 7.2$ Hz, 2H, $H_{C3'\text{-}o\text{-Ph}}$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.25 (CH_{3ax}–C_4), 22.58 (CH_3–C_7), 25.05 (CH_2, C_5), 27.34 (CH_{3eq}–C_4), 31.42 (CH, C_7), 35.12 (CH_2, C_6), 37.81 (CH_2, $C_{4'}$), 41.20 (CH_2, C_8), 45.76 (CH, C_{10}), 46.31 (NCH_2Ph), 57.57 (C_q, C_4), 76.75 (CH, C_9), 81.85 (CH, $C_{5'}$), 88.81 (CH, C_2), 126.41 (CH, $C_{p\text{-Ph}}$), 126.57 (2CH, $C_{3'\text{-}o\text{-Ph}}$), 127.53 (2CH, $C_{NC\text{-}o\text{-Ph}}$), 128.24 (2CH, $C_{m\text{-Ph}}$), 128.53 (2CH, $C_{m\text{-Ph}}$), 129.52 (C_q, C_{Ph}), 129.82 (CH, $C_{p\text{-Ph}}$), 142.76 (C_q, C_{Ph}), 156.18 (C_q, $C_{3'}$); Anal. Calcd for $C_{27}H_{34}N_2O_2$: C, 77.48; H, 8.19; N, 6.69. Found: C, 77.69; H, 8.17; N, 6.70.

4.2.2.2. (+)-(2*S*,3*R*,5′*S*,7*R*,9*R*,10*S*)-3-(Benzyl)-2-3′-methyl-4,5-dihydroisoxazol-5′-yl-4,4,7-trimethyloctahydro-2*H*-1,3-benzoxazine 6b and (−)-(5′R)-epimer 8b. *Method B*: To a cooled (−30 °C) solution of nitroethane (37.5 mg, 0.50 mmol, 2.2 equiv), phenyl isocyanate (100 μL, 109.6 mg, 0.92 mmol, 4 equiv) and triethylamine (50 μL, 36.3 mg, 0.36 mmol, 1.6 equiv) in CH_2Cl_2 (2 mL), was added dipolarophile **2a** (68 mg, 0.227 mmol, 1 equiv) in CH_2Cl_2 (2 mL). The solution was allowed to warm to room temperature and stirred for 24 h. The reaction mixture was hydrolyzed with saturated NH_4Cl (5 mL). The aqueous phase was extracted with CH_2Cl_2 (2×5 mL) and the combined organic phases were washed with saturated NaCl (5 mL), dried over $MgSO_4$, concentrated under reduced pressure. The residue was separated by chromatography using hexanes–CH_2Cl_2–EtOAc, (4:1:1) to give recovered **2a** (48 mg) plus the two cycloadducts (26.5% combined yield), **6b** and **8b,** as major and minor fractions, respectively. The isomeric ratio was determined by integration of the ^{13}C NMR signals for CH_{3ax}–C_4 (15.25 and 17.03 ppm). The results are shown in Table 2.

Data for **6b**. Yield = 16.1 mg (19.9%); Pale yellow oil, $R_f = 0.45$ (hexanes–CH_2Cl_2–EtOAc; 4:1:1); $[\alpha]_D^{22} = +29.3$ (*c* 0.161, MeOH); IR (film) *v* 3060, 3028, 2924, 2868, 1599 (C=N), 1603, 1493, 1452, 1385, 1324, 1063, 942, 730, 698, 664 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.92–0.98 (m, 1H, H_{5ax}), 0.94 (d, $J = 6.5$ Hz, 3H, CH_3–C_7), 0.98–1.04 (m, 1H, H_{6ax}), 1.02 (q, $J = 11.0$ Hz, 1H, H_{8ax}), 1.13 (s, 3H, CH_{3eq}–C_4), 1.16 (s, 3H, CH_{3ax}–C_4), 1.40–1.55 (m, 2H, H_{10+7}), 1.63–1.78 (m, 2H, $H_{6eq+5eq}$), 1.84 (s, 3H, CH_3–$C_{3'}$), 1.94 (br d, $J = 12.1$ Hz, 1H, H_{8eq}), 2.17 (dd, $J = 17.1$, 10.9 Hz, 1H, $H_{4'\alpha}$), 3.05 (dd, $J = 17.1$, 7.5 Hz, 1H, $H_{4'\beta}$), 3.51 (td, $J = 10.5$, 3.9 Hz, 1H, H_9), 3.60 (AB-d, $J = 17.3$ Hz, 1H, NCH_2Ph), 4.00 (AB-d, $J = 17.3$ Hz, 1H, NCH_2Ph), 4.41 (ddd, $J = 10.9$, 7.5, 3.3 Hz, 1H, $H_{5'}$), 4.60 (d, $J = 3.3$ Hz, 1H, H_2), 7.18 (t, $J = 7.1$ Hz, 1H, $H_{p\text{-Ph}}$), 7.29 (t, $J = 7.3$ Hz, 2H, $H_{m\text{-Ph}}$), 7.36 (d, $J = 7.4$ Hz, 2H, H $_{o\text{-Ph}}$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.85 (CH_3–$C_{3'}$), 15.25 (CH_{3ax}–C_4), 22.22 (CH_3–C_7), 25.08 (CH_2–C_5), 26.93 (CH_{3eq}–C_4), 31.14 (CH, C_7), 34.92 (CH_2, C_6), 39.32 (CH_2, $C_{4'}$), 41.22 (CH_2, C_8), 47.51 (NCH_2Ph), 48.28 (CH, C_{10}), 57.24 (C_q, C_4), 74.93 (CH, C_9), 80.60 (CH, $C_{5'}$), 87.72 (CH, C_2), 126.22 (CH, $C_{p\text{-Ph}}$), 127.12 (2CH, $C_{o\text{-Ph}}$), 128.11 (2CH, $C_{m\text{-Ph}}$), 144.28 (C_q, C_{Ph}), 155.38 (C_q, $C_{3'}$); GC–MS (70 eV, *m/z*, %): 272 ($M^{+\cdot}$−C_4H_6NO, 100), 136 ($C_{10}H_{16}^{+\cdot}$, 20) 91 ($C_7H_7^+$, 100), 81 ($C_6H_9^+$, 18); Anal. Calcd for $C_{22}H_{32}N_2O_2$: C, 74.12; H, 9.05; N, 7.86. Found: C, 74.35; H, 9.02; N, 7.88.

Data for **8b**. Yield = 5.4 mg (6.6%); Pale yellow oil; $R_f = 0.27$ (hexanes–CH_2Cl_2–EtOAc; 4:1:1); $[\alpha]_D^{23} = -106.1$ (*c* 0.022, MeOH); IR (film) *v* 3060, 3026, 2922, 2866, 1597 (C=N), 1639, 1492, 1451, 1384, 1323, 1054, 941, 715, 696, 671 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.94 (d, $J = 6.5$ Hz, 3H, CH_3–C_7), 0.88–1.02 (m, 2H, $H_{5ax,\ 6ax}$), 1.14 (q, $J = 11.7$ Hz, 1H, H_{8ax}), 1.15 (s, 3H, CH_{3eq}–C_4), 1.31 (s, 3H, CH_{3ax}–C_4), 1.44–1.56 (m, 2H, $H_{7,\ 10}$), 1.57–1.65 (m, 1H, H_{5eq}), 1.66–1.77 (m, 1H, H_{6eq}), 1.82 (s, 3H, CH_3–$C_{3'}$), 1.98 (dd, $J = 10.6$, 7.5 Hz, 1H, $H_{4'\beta}$), 2.07 (br d, $J = 11.8$ Hz, 1H, H_{8eq}), 2.64 (dd, $J = 18.0$, 7.5 Hz, 1H, $H_{4'\alpha}$), 3.59 (td, 1H, $J = 10.5$, 3.9 Hz, H_9), 3.95 (AB-d, $J = 17.5$ Hz, 1H, NCH_2Ph), 4.05 (AB-d, $J = 17.5$ Hz, 1H, NCH_2Ph), 4.45 (ddd, $J = 18.0$, 10.6, 8.2 Hz, 1H, $H_{5'}$), 4.65 (d, $J_{vic} = 8.2$ Hz, 1H, H_2), 7.19 (t, $J = 7.1$ Hz, 1H$_{p\text{-Ph}}$), 7.30 (t, $J = 7.2$ Hz, 2H, $H_{m\text{-Ph}}$), 7.34 (d, $J = 7.2$ Hz, 2H, H $_{o\text{-Ph}}$); ^{13}C NMR ($CDCl_3$,

75 MHz): δ 12.93 (CH_3–$C_{3'}$), 17.03 (CH_{3ax}–C_4), 22.30 (CH_3–C_7), 25.14 (CH_2, C_5), 26.99 (CH_{3eq}–C_4), 31.20 (CH, C_7), 34.98 (CH_2, C_6), 39.38 (CH_2, $C_{4'}$), 41.28 (CH_2, C_8), 47.58 (NCH_2Ph), 48.33 (CH, C_{10}), 57.24 (C_q, C_4), 74.98 (CH, C_9), 80.65 (CH, $C_{5'}$), 87.76 (CH, C_2), 126.29 (CH, $C_{p\text{-}Ph}$), 127.18 (2CH, $C_{o\text{-}Ph}$), 128.18 (2CH, $C_{m\text{-}Ph}$), 144.90 (C_q, C_{Ph}), 155.46 (C_q, $C_{3'}$); GC–MS (70 eV, *m/z*, %): 272 ($M^{+\cdot}$–C_4H_6NO, 44), 136 ($C_{10}H_{16}^{+\cdot}$, 17), 91 $C_7H_7^{+}$, 100), 81 ($C_6H_9^{+}$, 17); Anal. Calcd for $C_{22}H_{32}N_2O_2$: C, 74.12; H, 9.05; N, 7.86. Found: C, 74.30; H, 9.07; N, 7.90.

4.2.2.3. Ethyl (+)-(2*S*,4′*S*,5′*S*,7*R*,9*R*,10*S*)-5-3-(benzyl)-4,4,7-trimethyloctahydro-2*H*-1,3-benzoxazin-2-yl-3-phenyl-4,5-dihydroisoxazole-4-carboxylate 6d its diastereoisomer (−)-(4′*R*,5′*R*)-8d and regioisomers ethyl (+)-(2*S*,4′*S*,5′*S*,7*R*,9*R*,10*S*)-4-3-(benzyl)-4,4,7-trimethyl-octahydro-2*H*-1,3-benzoxazin-2-yl-3-phenyl-4,5-dihydroisoxazole-5-carboxylate 7d and (−)-(4′*R*,5′*R*)-9d. Using general cycloaddition procedure A: to *trans*-benzoxazine **2d** (50 mg, 0.135 mmol, 1 equiv) and triethylamine (0.375 mL, 0.272 g, 2.7 mmol, 20 equiv) was added phenyloximoyl chloride (105 mg, 0.674 mmol, 5 equiv). The crude products were purified by chromatography using petrol–Et_2O (90:10) and provided a total of 39.0 mg (59% conversion yield). The isomeric ratio was determined by integration of the ^{13}C NMR signals for $C_{5'}$ (85.57 (**6d**), 85.22 (**8d**), 79.61 (**7d**), and 81.32 ppm (**9d**)). The results are shown in Table 2.

Data for **6d**. Yield = 20.5 mg (31%); Yellow oil; R_f = 0.41 (CH_2Cl_2); $[\alpha]_D^{23} = +81.0$ (*c* 0.09, CH_2Cl_2); IR (film) *ν* 3068, 3021, 2984, 2929, 2861, 1735 (C=O), 1610, 1560 (C=N), 1261, 913, 738, 689, 641 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 0.88 (d, *J* = 6.9 Hz, 3H, CH_3–C_7), 0.94 (t, *J* = 7.1 Hz, 3H, O–CH_2–CH_3), 0.91–1.00 (m, 3H, $H_{5ax,\ 6ax,\ 8ax}$), 1.12 (s, 3H, CH_{3eq}–C_4), 1.16 (s, 3H, CH_{3ax}–C_4), 1.38–1.45 (m, 1H, H_7), 1.47 (td, *J* = 11.0, 2.3 Hz, 1H, H_{10}), 1.67–1.71 (m, 2H, H_{5eq} + H_{6eq}), 1.83 (d app., *J* = 12.2 Hz, 1H, H_{8eq}), 3.44 (td, *J* = 10.4, 4.1 Hz, 1H, H_9), 3.48 (AB-d, *J* = 17.8 Hz, 1H, NCH_2Ph), 3.76 (q, *J* = 7.1 Hz, 2H, O–CH_2–CH_3), 4.07 (AB-d, *J* = 17.8 Hz, 1H, NCH_2Ph), 4.65 (d, *J* = 4.3 Hz, 1H, $H_{4'}$), 4.68 (d, *J* = 3.2 Hz, 1H, H_2), 4.95 (t app., *J* = 4.3 Hz, 1H, $H_{5'}$), 7.19 (t, *J* = 7.3 Hz, 1H, $H_{NC\text{-}p\text{-}Ph}$), 7.30 (t, *J* = 7.7 Hz, 2H, $H_{NC\text{-}m\text{-}Ph}$), 7.35–7.40 (m, 3H, $H_{3'\text{-}m,p\text{-}Ph}$), 7.45 (d, *J* = 7.5 Hz, 2H, $H_{NC\text{-}o\text{-}Ph}$), 7.75 (dd., *J* = 6.6, 3.3 Hz, 2H, $H_{3'\text{-}o\text{-}Ph}$); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.61 (O–CH_2–CH_3), 17.01 (CH_{3ax}–C_4), 22.15 (CH_3–C_7), 25.02 (CH_2, C_5), 26.85 (CH_{3eq}–C_4), 31.10 (CH, C_7), 34.87 (CH_2, C_6), 40.97 (CH_2, C_8), 47.71 (NCH_2Ph), 48.00 (CH, C_{10}), 54.81 (CH, $C_{4'}$), 57.38 (C_q, C_4), 61.47 (CH_2, O–CH_2–CH_3), 75.00 (CH, C_9), 85.57 (CH, $C_{5'}$), 88.38 (CH, C_2), 126.24 (CH, $C_{NC\text{-}p\text{-}Ph}$), 126.92 (2CH, $C_{NC\text{-}o\text{-}Ph}$), 127.25 (2CH, $C_{3'\text{-}o\text{-}Ph}$), 128.33 (2CH, $C_{NC\text{-}m\text{-}Ph}$), 128.42 (2CH, $C_{3'\text{-}m\text{-}Ph}$), 128.55 ($C_q$, C_{Ph}), 129.86 (CH, $C_{3'\text{-}p\text{-}Ph}$), 142.30 ($C_q$, C_{Ph}), 154.22 (C_q, $C_{3'}$), 168.64 (C_q, C=O); Anal. Calcd for $C_{30}H_{38}N_2O_4$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.25; H, 7.75; N, 5.73.

Data for **7d**. Yield = 10.6 mg (16%); Yellow oil; R_f = 0.23 (80:20 petrol–Et_2O); $[\alpha]_D^{23} = +223$ (*c* 0.104, CH_2Cl_2); IR (film) *ν* 3061, 3027, 2980, 2925, 2869, 1737 (C=O), 1602, 1566 (C=N), 1265, 909, 732, 693, 647 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 0.88–0.98 (m, 2H, $H_{5ax,\ 6ax}$), 0.91 (d, *J* = 6.3 Hz, 3H, CH_3–C_7), 1.02 (t, *J* = 7.2 Hz, 3H, O–CH_2–CH_3), 1.03 – 1.10 (m, 1H, H_{8ax}), 1.07 (s, 3H, CH_{3ax}–C_4), 1.11 (s, 3H, CH_{3eq}–C_4), 1.32 – 1.43 (m, 1H, H_7), 1.49 (t, *J* = 10.7 Hz, 1H, H_{10}), 1.63–1.72 (m, 2H, $H_{5eq,\ 6eq}$), 1.88 (br d, *J* = 12.4 Hz, 1H, H_{8eq}), 3.32 (td, *J* = 10.4, 3.7 Hz, 1H, H_9), 3.68 (AB-d, *J* = 17.9 Hz, 1H, NCH_2Ph), 3.74–3.84 (m, 2H, O–CH_2–CH_3), 4.00 (dd, *J* = 3.3, 1.4 Hz, 1H, $H_{4'}$), 4.13 (AB-d, *J* = 17.9 Hz, 1H, NCH_2Ph), 4.74 (d, *J* = 1.4 Hz, 1H, H_2), 5.43 (d, *J* = 3.3 Hz, 1H, $H_{5'}$), 7.20 (t, *J* = 7.3 Hz, 1H, $H_{NC\text{-}p\text{-}Ph}$), 7.31 (t, *J* = 7.7 Hz, 2H, $H_{NC\text{-}m\text{-}Ph}$), 7.42–7.48 (m, 5H, $H_{C3'\text{-}m,p\text{-}Ph,\ NC\text{-}o\text{-}Ph}$), 7.77 (dd, *J* = 8.2, 1.9 Hz, 2H, $H_{C3'\text{-}o\text{-}Ph}$); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.61 (O–CH_2–CH_3), 17.09 (CH_{3ax}–C_4), 22.11 (CH_3–C_7), 24.96 (CH_2, C_5), 27.04 (CH_{3eq}–C_4), 31.10 (CH, C_7), 34.83 (CH_2, C_6), 40.96 (CH_2, C_8), 47.56 (CH, C_{10}), 48.13 (NCH_2Ph), 55.33 (CH, $C_{4'}$), 57.77 (C_q, C_4), 61.33 (CH_2, O–CH_2–CH_3), 75.22 (CH, C_9), 79.61 (CH, $C_{5'}$), 85.03 (CH, C_2), 126.39 (CH, $C_{NC\text{-}p\text{-}Ph}$), 126.64 (2CH, $C_{NC\text{-}o\text{-}Ph}$), 127.51 (2CH, $C_{3'\text{-}o\text{-}Ph}$), 128.47 (2CH, $C_{NC\text{-}m\text{-}Ph}$), 128.61 ($C_q$, C_{Ph}), 128.73 (2CH, $C_{3'\text{-}m\text{-}Ph}$), 129.98 (CH, $C_{3'\text{-}p\text{-}Ph}$), 142.24 ($C_q$, C_{Ph}), 156.92 (C_q, $C_{3'}$), 168.86 (C_q, C=O); Anal. Calcd for $C_{30}H_{38}N_2O_4$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.41; H, 7.83; N, 5.74.

Data for **8d**. Yield = 4.6 mg (7%); Yellow oil, R_f = 0.20 (80:20 petrol–Et_2O); $[\alpha]_D^{23} = -89.3$ (*c* 0.045, CH_2Cl_2); IR (film) *ν* 3061, 3028, 2979, 2924, 2869, 1737 (C=O), 1602, 1494 (C=N), 1097, 1256, 909, 732, 693, 647 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 0.89 (t, *J* = 6.8 Hz, 3H, O–CH_2–CH_3), 0.95 (d, *J* = 6.5 Hz, 3H, CH_3–C_7), 0.94–1.02 (m, 2H, $H_{5ax,\ 6ax}$), 1.13 (s, 3H, CH_{3eq}–C_4), 1.18 (q, *J* = 12.1 Hz, 1H, H_{8ax}), 1.26 (s, 3H, CH_{3ax}–C_4), 1.44–1.53 (m, 1H, H_7), 1.56 (t, *J* = 10.5 Hz, 1H, H_{10}), 1.62 (d app., *J* = 11.3 Hz, 1H, H_{5eq}), 1.72 (d app., *J* = 7.8 Hz, 1H, H_{6eq}), 2.06 (br d, *J* = 12.3 Hz, 1H, H_{8eq}), 3.54 – 3.62 (m, 2H, H_9 + O–CH_2–CH_3), 3.70 (dq, *J* = 11.3, 6.8 Hz, 1H, O–CH_2–CH_3), 4.00 (d, *J* = 18.0 Hz, 1H, NCH_2Ph), 4.15 (d, *J* = 18.0 Hz, 1H, NCH_2Ph), 4.43 (d, *J* = 3.3 Hz, 1H, $H_{4'}$), 4.63 (d, *J* = 7.8 Hz, 1H, H_2), 5.09 (dd, *J* = 7.8, 3.3 Hz, 1H, $H_{5'}$), 7.18 (t, *J* = 7.3 Hz, 1H, $H_{NC\text{-}p\text{-}Ph}$), 7.31 (t, *J* = 7.4 Hz, 2H, $H_{NC\text{-}m\text{-}Ph}$), 7.37–7.44 (m, 5H, $H_{3'\text{-}m,p\text{-}Ph,\ NC\text{-}o\text{-}Ph}$), 7.77 (dd, *J* = 7.4, 2.2 Hz, 2H, $H_{3'\text{-}o\text{-}Ph}$). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.46 (CH_3, O–CH_2–CH_3), 22.13 (CH_{3ax}–C_4), 22.21 (CH_3–C_7), 24.97 (CH_2, C_5), 26.78 (CH_{3eq}–C_4), 31.37 (CH, C_7), 35.06 (CH_2, C_6), 41.09 (CH_2, C_8), 45.50 (CH, C_{10}), 46.67 (NCH_2Ph), 55.28 (CH, $C_{4'}$), 57.77 (C_q, C_4), 61.48 (CH_2, O–CH_2–CH_3), 76.75 (CH, C_9), 85.22 (CH, $C_{5'}$), 87.19 (CH, C_2), 126.14 (CH, $C_{NC\text{-}p\text{-}Ph}$), 126.96 (2CH, $C_{NC\text{-}o\text{-}Ph}$), 127.52 (2CH, $C_{3'\text{-}o\text{-}Ph}$), 128.22 (2CH, $C_{NC\text{-}m\text{-}Ph}$), 128.38 (2CH, $C_{3'\text{-}m\text{-}Ph}$), 128.40 ($C_q$, C_{Ph}), 130.03, (CH, $C_{3'\text{-}p\text{-}Ph}$) 142.21 ($C_q$, C_{Ph}), 153.90 (C_q, $C_{3'}$), 167.30 (C_q, C=O). Anal. Calcd for $C_{30}H_{38}N_2O_4$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.40; H, 7.78; N, 5.72.

Data for **9d**. Yield = 3.3 mg (5%); Yellow oil; R_f = 0.22 (80:20 petrol–Et_2O); $[\alpha]_D^{23} = -128.1$ (*c* 0.086, CH_2Cl_2); IR (film) *ν* 3052, 3040, 2971, 2896, 1731 (C=O), 1620, 1543 (C=N), 1260, 897, 732, 693, 647 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 0.83 (d, *J* = 6.4 Hz, 3H, CH_3–C_7), 0.87–0.94 (m, 2H, $H_{5ax,\ 6ax}$); 0.92 (q, *J* = 11.7 Hz, 1H, H_{8ax}), 1.00 (t, *J* = 7.1 Hz, 3H, O–CH_2–CH_3), 1.12 (s, 3H, CH_{3eq}–C_4), 1.27–1.34 (m, 1H, H_7), 1.33 (s, 3H, CH_{3ax}–C_4), 1.39 (d app., *J* =13.3 Hz, 1H, H_{8eq}), 1.49 (t app, *J* = 10.2 Hz, 1H, H_{10}), 1.66 (d app, *J* = 11.8 Hz, 1H, H_{5eq}), 1.63 – 1.70 (m, 1H, H_{6eq}), 3.32 (td, *J* = 10.7, 3.6 Hz, 1H, H_9), 3.78 (q, *J* = 7.1 Hz, 2H, O–CH_2–CH_3), 4.03 (AB-d, *J* = 18.1 Hz, 1H, NCH_2Ph), 4.07 (dd, *J* = 10.2, 1.9 Hz, 1H, $H_{4'}$), 4.24 (AB-d, *J* = 18.1 Hz, 1H, NCH_2Ph), 4.79 (d, *J* = 10.2 Hz, 1H, H_2), 5.13 (br s, 1H, $H_{5'}$), 7.17 (t, *J* = 7.1 Hz, 1H, $H_{NC\text{-}p\text{-}Ph}$), 7.28 (t, *J* = 7.6 Hz, 2H, $H_{NC\text{-}m\text{-}Ph}$), 7.33–7.38 (m, 3H, $H_{3'\text{-}m,p\text{-}Ph}$), 7.41 (d, *J* = 7.1 Hz, 2H, $H_{NC\text{-}o\text{-}Ph}$), 7.82 (dd, *J* = 7.6, 2.1 Hz, 2H, $H_{3'\text{-}o\text{-}Ph}$); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.68 (O–CH_2–CH_3), 22.11 (CH_3–C_7), 22.49 (CH_{3ax}–C_4), 24.79 (CH_2, C_5), 27.10 (CH_{3eq}–C_4), 31.15 (CH, C_7), 35.03 (CH_2, C_6), 40.49 (CH_2, C_8), 44.99 (CH, C_{10}), 46.05 (NCH_2Ph), 53.30 (CH, $C_{4'}$), 58.18 (C_q, C_4), 61.40 (O–CH_2–CH_3), 76.75 (CH, C_9), 81.32 (CH, $C_{5'}$), 87.48 (CH, C_2), 126.96 (CH, $C_{NC\text{-}p\text{-}Ph}$), 127.70 (2CH, $C_{NC\text{-}o\text{-}Ph}$), 128.27 (2CH, $C_{3'\text{-}o\text{-}Ph}$), 128.43 (2CH, $C_{NC\text{-}m\text{-}Ph}$), 128.70 ($C_q$, C_{Ph}), 128.91 (C_q, C_{Ph}), 129.47 (CH, $C_{3'\text{-}p\text{-}Ph}$), 129.73 (2CH, $C_{3'\text{-}m\text{-}Ph}$), 159.92 ($C_q$, $C_{3'}$), 168.34 (C_q, C=O); Anal. Calcd for $C_{30}H_{38}N_2O_4$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.41; H, 7.83; N, 5.70.

4.2.2.4. (+)-(2*S*,4′*S*,5′*S*,7*R*,9*R*,10*S*)-4-(3-(Benzyl)-4,4,7-trimethyl-octahydro-2*H*-1,3-benzoxazin-2-yl-*N*,*N*-diisopropyl-3-phenyl-4,5-dihydroisoxazole-5-carboxamide 7e, its diastereoioisomer (−)-(4′*R*,5′*R*)-9e and the regioisomer (+)-(2*S*,4′*S*,5′*S*,7*R*,9*R*,10*S*)-5-(3-(benzyl)-4,4,7-trimethyloctahydro-2*H*-1,3-benzoxazin-2-yl-*N*,*N*-diisopropyl-3-phenyl-4,5-dihydroisoxazole-4-carboxamide 6e. Using general cycloaddition procedure A: *trans*- benzoxazine **2e** (53 mg, 0,125 mmol, 1 equiv), triethylamine (252 mg, 2.5 mmol, 0.35 mL, 20 equiv) and phenyloximoyl chloride (0.095 g,

0.625 mmol, 5 equiv) at rt gave a crude oil. This was purified by chromatography using Pet/Et_2O (9:1) and the three cycloadducts were isolated in pure form with an overall yield of 51% (34.7 mg). The isomeric ratio was determined by integration of the ^{13}C NMR signals for $C_{5'}$ (79.92 (**7e**), 82.12 (**9e**) and 84.58 ppm (**6e**)) and C_2 (85.12 (**7e**), 87.68 (**9e**) and 87.05 ppm (**6e**)). The results are shown in Table 2.

Data for **6e**. Yield = 4.1 mg (6%); Yellow oil; R_f = 0.15 (100% CH_2Cl_2); $[\alpha]_D^{23} = +110.4$ (*c* 0.064, CH_2Cl_2); IR (KBr) *ν* 3068, 3017, 2961, 2943, 2867, 1648 (NC=O), 1591, 1156, 1132, 766, 678, 655 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): *δ* 0.82–0.95 (m, 2H, H_{5ax}, $_{6ax}$), 0.95 (d, *J* = 6.6 Hz, 3H, CH_3–C_7), 1.03 (s, 3H, CH_{3eq}–C_4), 1.09 (q, *J* = 11.8 Hz, 1H, H_{8ax}), 1.17 (d, *J* = 6.6 Hz, 3H, (CH_3)$_2$CH–N), 1.20 (d, *J* = 6.6 Hz, 3H, (CH_3)$_2$CH–N), 1.22 (s, 3H, CH_{3ax}–C_4), 1.26 (d, *J* = 6.6 Hz, 3H, (CH_3)$_2$CH–N), 1.28 (d, *J* = 6.6 Hz, 3H, (CH_3)$_2$CH–N), 1.40–1.53 (m, 1H, H_7), 1.55 (bt, *J* = 11.1 Hz, 1H, H_{10}), 1.62 (d app., *J* = 11.2 Hz, 1H, H_{5eq}), 1.68–1.77 (m, 1H, H_{6eq}), 1.85 (d app., *J* = 12.6 Hz, 1H, H_{8eq}), 3.34 (sept. *J* = 6.9 Hz, 1H, N–C*H*–(CH_3)$_2$), 3.51 (td, *J* = 10.9, 4.1 Hz, 1H, H_9), 3.98 (AB-d, *J* = 18.1 Hz, 1H, NCH_2Ph), 4.08 (AB-d, *J* = 18.1 Hz, 1H, NCH_2Ph), 4.67–4.53 (m, 3H, $H_{5',2}$ + N–C*H*–(CH_3)$_2$), 4.80 (d, *J* = 3.6 Hz, 1H, $H_{4'}$), 7.17 (t, *J* = 6.9 Hz, 1H, $H_{NC\text{-}p\text{-}Ph}$), 7.30 (t, *J* = 7.4 Hz, 2H, $H_{NC\text{-}m\text{-}Ph}$), 7.33–7.37 (m, 3H, $H_{3'\text{-}m,p\text{-}Ph}$), 7.51 (d, *J* = 7.4 Hz, 2H, $H_{NC\text{-}o\text{-}Ph}$), 7.62 (dd, *J* = 6.6, 3.0 Hz, 2H, $H_{3'\text{-}o\text{-}Ph}$); ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 20.07 (*C*H_{3ax}–C_4), 20.32 (CH_3, (CH_3)$_2$CH–N), 20.56 (CH_3, (CH_3)$_2$CH–N), 20.67 (CH_3, (CH_3)$_2$CH–N), 20.92 (CH_3, (CH_3)$_2$CH–N), 22.29 (CH_3–C_7), 24.85 (CH_2, C_5), 29.67 (*C*H_{3eq}–C_4), 31.25 (CH, C_7), 34.97 (CH_2, C_6), 41.20 (CH_2, C_8), 45.90 (CH, N–*C*H–(CH_3)$_2$), 46.12 (N*C*H_2Ph), 46.35 (CH, C_{10}), 48.30 (CH, N–*C*H–(CH_3)$_2$), 55.51 (CH, $C_{4'}$), 57.37 (C_q, C_4), 76.74 (CH, C_9), 84.58 (CH, $C_{5'}$), 87.05 (CH, C_2), 126.82 (CH, $C_{NC\text{-}p\text{-}Ph}$), 127.00 (2CH, C_{Ph}), 127.50 (2CH, C_{Ph}), 128.08 (2CH, C_{Ph}), 128.55 (2CH, C_{Ph}), 129.78 (CH, $C_{3'\text{-}p\text{-}Ph}$), 130.47 ($C_q$, C_{Ph}), 142.94 (C_q, C_{Ph}), 156.00 (C_q, $C_{3'}$), 167.38 (C_q, C=O); Anal. Calcd for $C_{34}H_{47}N_3O_3$: C, 74.83; H, 8.68; N, 7.70. Found: C, 74.81; H, 8.67; N, 7.68.

Data for **7e**. Yield = 20.4 mg (30%); Yellow oil; R_f = 0.41 (100% CH_2Cl_2); $[\alpha]_D^{23} = +248.3$ (*c* 0.202, CH_2Cl_2); IR (KBr) *ν* 3062, 3018, 2965, 2926, 2869, 1652 (NC=O), 1610 (C=N), 1168, 1127, 763, 687, 658 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): *δ* 0.91 (d, *J* = 6.1 Hz, 3H, CH_3–C_7), 0.83–0.95 (m, 2H, $H_{5ax,6ax}$), 0.95 (50%, d, *J* = 6.7 Hz, 6H, (CH_3)$_2$CH–N), 1.00 (s, 3H, CH_{3eq}–C_4), 1.03 (s, 3H, CH_{3ax}–C_4), 1.05 (q, *J* = 12.1 Hz, 1H, H_{8ax}), 1.16 (50%, d, *J* = 6.7 Hz, 6H, (CH_3)$_2$CH–N), 1.22 (50%, d, *J* = 6.7 Hz, 6H, (CH_3)$_2$CH–N), 1.26 (50%, d, *J* = 6.7 Hz, 6H, (CH_3)$_2$CH–N), 1.30–1.40 (m, 1H, H_7), 1.49 (br t, *J* = 11.1 Hz, 1H, H_{10}), 1.64 (d app., 1H, *J* = 11.3 Hz, H_{5eq}), 1.66 (d app., 1H, *J* = 11.2 Hz, H_{6eq}), 1.84 (d app., 1H, *J* = 12.4 Hz, H_{8eq}), 3.17–3.28 (m, 2H, H_9 + N–C*H*–(CH_3)$_2$), 3.80 (AB-d, *J* = 18.4 Hz, 1H, NCH_2Ph), 3.90 (AB-d, *J* = 18.4 Hz, 1H, NCH_2Ph), 4.28 (sept. *J* = 6.7 Hz, 1H, N–C*H*–(CH_3)$_2$), 4.74 (d, *J* = 2.0 Hz, 1H, H_2), 4.81 (dd, *J* = 4.0, 2.0 Hz, 1H, $H_{4'}$), 5.62 (d, *J* = 4.0 Hz, 1H, $H_{5'}$), 7.12 (t, *J* = 7.1 Hz, 1H, $H_{NC\text{-}p\text{-}Ph}$), 7.25 (t, *J* = 7.6 Hz, 2H, $H_{NC\text{-}m\text{-}Ph}$), 7.36–7.43 (m, 5H, $H_{NC\text{-}o\text{-}Ph}$, $_{3'\text{-}m,p\text{-}Ph}$), 7.73 (dd., *J* = 6.1, 3.3 Hz, 2H, $H_{3'\text{-}o\text{-}Ph}$); ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 15.34 (*C*H_{3ax}–C_4), 19.81 (50%, (CH_3)$_2$CH–N), 20.29 (50%, (CH_3)$_2$CH–N), 20.74 (50%, (CH_3)$_2$CH–N), 20.82 (50%, (CH_3)$_2$CH–N), 22.10 (CH_3–C_7), 24.94 (CH_2, C_5), 27.35 (*C*H_{3eq}–C_4), 31.06 (CH, C_7), 34.31 (CH_2, C_6), 41.52 (CH_2, C_8), 45.91 (N–*C*H–(CH_3)$_2$), 47.68 (N*C*H_2Ph), 48.72 (CH, C_{10}), 48.84 (N–*C*H–(CH_3)$_2$), 53.19 (CH, $C_{4'}$), 57.95 (C_q, C_4), 75.25 (CH, C_9), 79.92 (CH, $C_{5'}$), 85.12 (CH, C_2), 126.49 (CH, $C_{NC\text{-}p\text{-}Ph}$), 127.40 (2CH, C_{Ph}), 127.50 (2CH, $C_{3'\text{-}o\text{-}Ph}$), 128.16 (2CH, C_{Ph}), 128.61 (2CH, C_{Ph}), 129.66 (CH, $C_{3'\text{-}p\text{-}Ph}$), 129.86 ($C_q$, C_{Ph}), 142.30 (C_q, C_{Ph}), 158.22 (C_q, $C_{3'}$), 165.51 (C_q, C=O); Anal. Calcd for $C_{34}H_{47}N_3O_3$: C, 74.83; H, 8.68; N, 7.70. Found: C, 74.77; H, 8.70; N, 7.70.

Data for **9e**. Yield = 10.3 mg (15%); Yellow oil; R_f = 0.23 (petrol–Et_2O, 4:1); $[\alpha]_D^{23} = -212.7$ (*c* 0.103, CH_2Cl_2); IR (KBr) *ν* 3059, 3021, 2969, 2938, 2874, 1658 (NC=O), 1598 (C=N), 1160, 1129, 760, 685, 651 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): *δ* 0.82 (d, *J* = 6.3 Hz, 3H, CH_3–C_7), 0.90 (50%, d, *J* = 6.4 Hz, 6H, (CH_3)$_2$CH–N), 0.85–0.96 (m, 3H, $H_{5ax,\ 6ax,\ 8ax}$), 1.05 (s, 3H, CH_{3eq}–C_4), 1.11 (50%, d, *J* = 6.6 Hz, 6H, N–CH–(CH_3)$_2$), 1.14 (50%, d, *J* = 6.6 Hz, 6H, (CH_3)$_2$CH–N), 1.22 (50%, d, *J* = 6.4 Hz, 6H, (CH_3)$_2$CH–N), 1.24–1.38 (m, 2H, $H_{7,\ 8eq}$), 1.31 (s, 3H, CH_{3ax}–C_4), 1.43 (bt, *J* = 10.3 Hz, 1H, H_{10}), 1.50–1.59 (m, 1H, H6 eq), 1.60–1.67 (m, 1H, H_{5eq}), 3.16 (sep., *J* = 6.6 Hz, 1H, N–C*H*–(CH_3)$_2$), 3.25 (td, *J* = 10.5, 3.4 Hz, 1H, H_9), 3.95 (AB-d, *J* = 17.6 Hz, 1H, NCH_2Ph), 4.13 (sep., *J* = 6.4 Hz, 1H, N–C*H*–(CH_3)$_2$), 4.24 (AB-d, *J* = 17.6 Hz, 1H, NCH_2Ph), 4.70 (dd, *J* = 10.2, 2.2 Hz, 1H, $H_{4'}$), 4.80 (d, *J* = 10.2 Hz, 1H, H_2), 5.30 (d, *J* = 2.2 Hz, 1H, $H_{5'}$), 7.11 (t, *J* = 7.4 Hz, 1H, $H_{NC\text{-}p\text{-}Ph}$), 7.23 (t, *J* = 7.4 Hz, 2H, $H_{NC\text{-}m\text{-}Ph}$), 7.31–7.39 (m, 5H, $H_{NC\text{-}o\text{-}Ph,\ 3'\text{-}m,p\text{-}P}$), 7.82 (dd., *J* = 7.1, 2.5 Hz, 2H, $H_{3'\text{-}o\text{-}Ph}$); ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 15.34 (*C*H_{3ax}–C_4), 19.77 ((*C*H_3)$_2$CH–N), 20.08 ((*C*H_3)$_2$CH–N), 20.44 ((*C*H_3)$_2$CH–N), 20.79 ((*C*H_3)$_2$CH–N), 22.10 (CH_3–C_7), 24.94 (CH_2, C_5), 27.35 (*C*H_{3eq}–C_4), 31.10 (CH, C_7), 35.31 (CH_2, C_6), 41.24 (CH_2, C_8), 44.69 (CH, C_{10} + N*C*H_2Ph), 45.84 (N–*C*H–(CH_3)$_2$), 48.91 (N–*C*H–(CH_3)$_2$), 51.59 (CH, $C_{4'}$), 57.89 (C_q, C_4), 76.82 (CH, C_9), 82.12 (CH, $C_{5''}$), 87.68 (CH, C_2), 126.49 (CH, $C_{NC\text{-}p\text{-}Ph}$), 127.57 (2CH, C_{Ph}), 128.22 (2CH, $C_{NC\text{-}m\text{-}Ph}$), 128. (2CH, $C_{3'\text{-}o\text{-}Ph}$), 129.45 (2CH, C_{Ph}), 129.64 (CH, $C_{3'\text{-}p\text{-}Ph}$), 129.86 ($C_q$, C_{Ph}), 142.30 (C_q, C_{Ph}), 161.22 (C_q, $C_{3'}$), 165.34 (C_q, C=O); Anal. Calcd for $C_{34}H_{47}N_3O_3$: C, 74.83; H, 8.68; N, 7.70. Found: C, 74.79; H, 8.69; N, 7.71.

4.2.2.5. (−)-(2*S*,4′*R*,5′*R*,7*R*,9*R*,10*S*)-3-(Benzyl)-2-(3′,5′-diphenyl-4,5-dihydroisoxazol-4-yl)-4,4,7-trimethyloctahydro-2*H*-1,3-benzoxazine 9g, its diastereomer (+)-(4″*S*,5′*S*)-6g and regioisomers (+)-(2*S*,7*R*,9*R*,10*S*)-3-(benzyl)-2-4*S*,5*S*-(3′,5′-diphenyl-4,5-dihydroisoxazol-4-yl)-4,4,7-trimethyloctahydro-2*H*-1,3-benzoxazine 7g and (−)-(4′*R*,5′*R*)-8g.

Using general cycloaddition procedure A: To a solution of *trans*-benzoxazine **2g** (76.0 mg, 0.20 mmol, 1 equiv) and triethylamine (0.563 mL, 0.410 g, 4.1 mmol, 20 equiv) in CH_2Cl_2 (2 mL) was added phenyloximoyl chloride (0.155 g, 1.0 mmol, 5 equiv) and the mixture was brought to reflux. The crude products were separated sequentially by chromatography; that is, firstly, cycloadduct **8g** was isolated using petrol–Et_2O (9:1); and then **9g** was isolated as was some of **7g** using petrol–Et_2O (7:3). The final fractions, that is, **7g** and **6g** were isolated using petrol–CH_2Cl_2 (3:7). The isolated yield for all cycloadducts was 52.0 mg (52%). The isomeric ratio was determined by integration of the ^{13}C NMR signals for $C_{5'}$ (84.93 (**9g**), 83.54 (**7g**), 90.75 (**8g**), and 88.98 ppm (**6g**)). The results are shown in Table 2.

Data for **6g**. Yield = 8.0 mg (8%); Yellow oil; R_f = 0.62 (CH_2Cl_2); $[\alpha]_D^{23} = +170.3$ (*c* 0.052, CH_2Cl_2); IR (film) *ν* 3079, 3021, 2978, 2919, 2861, 1594 (C=N), 1491, 1460, 1070, 931, 719, 690, 674 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): *δ* 0.97 (d, *J* = 7.1 Hz, 3H, CH_3–C_7), 0.96–1.02 (m, 2H, $H_{5ax,\ 6ax}$), 1.03 (s, 3H, CH_{3eq}–C_4), 1.13 (q, *J* = 11.7 Hz, 1H, H_{8ax}), 1.26 (s, 3H, CH_{3ax}–C_4), 1.47–1.56 (m, 1H, H_7), 1.57 (t, *J* = 10.7 Hz, 1H, H_{10}), 1.74 (d app., *J* = 11.0 Hz, 1H, H_{5eq}), 1.73 (d app., *J* = 8.2 Hz, 1H, H_{6eq}), 1.98 (d app., *J* = 11.7 Hz, 1H, H_{8eq}), 3.61 (td, *J* = 10.4, 3.9 Hz, 1H, H_9), 3.84 (AB-d, *J* = 18.0 Hz, 1H, NCH_2Ph), 4.06 (AB-d, *J* = 18.0 Hz, 1H, NCH_2Ph), 4.50 (dd, *J* = 7.3, 4.3 Hz, 1H, $H_{5'}$), 4.76 (d, *J* = 7.3 Hz, 1H, H_2), 4.90 (d, *J* = 4.3 Hz, 1H, $H_{4'}$), 7.10 (t, *J* = 7.7 Hz, 1H, $H_{p\text{-}Ph}$), 7.13 (d, *J* = 7.4 Hz, 2H, $H_{4'\text{-}o\text{-}Ph}$), 7,16 (t, *J* = 7.7 Hz, 1H, $H_{p\text{-}Ph}$), 7.21 (t, *J* = 7.0 Hz, 2H, $H_{NC\text{-}m\text{-}Ph}$), 7.22 (t, *J* = 7.3 Hz, 2H, $H_{3'\text{-}m\text{-}Ph}$), 7.27 (t, *J* = 7.0 Hz, 2H, $H_{4'\text{-}m\text{-}Ph}$), 7.30 (t, *J* = 7.4 Hz, 1H, + $H_{p\text{-}Ph}$) 7.43 (d, *J* = 7.1 Hz, 2H, $H_{NC\text{-}o\text{-}Ph}$), 7.59 (dd, *J* = 7.7, 2.2 Hz, 2H, $H_{C3'\text{-}o\text{-}Ph}$), ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 20.50 (*C*H_{3ax}–C_4), 22.29 (*C*H_3–C_7), 24.99 (CH_2, C_5), 27.03 (*C*H_{3eq}–C_4), 31.40 (CH, C_7), 35.10 (CH_2, C_6), 41.27 (CH_2, C_8), 46.01 (CH, C_{10}), 46.63 (N*C*H_2Ph), 56.54 (CH, $C_{4'}$), 57.37 (C_q, C_4), 76.70 (CH, C_9), 87.69 (CH, C_2), 88.98 (CH, $C_{5'}$), 125.88 (CH, $C_{p\text{-}Ph}$), 127.01 (2CH, $C_{NC\text{-}o\text{-}Ph}$), 127.22 (CH, $C_{p\text{-}Ph}$), 127.35 (2CH, $C_{3'\text{-}o\text{-}Ph}$), 127.81 (2CH, $C_{4'\text{-}o\text{-}Ph}$), 127.95 (2CH, $C_{NC\text{-}m\text{-}Ph}$), 128.45 (2CH, $C_{4'\text{-}m\text{-}Ph}$), 128.95 (2CH, $C_{3'\text{-}m\text{-}Ph}$), 129.03 ($C_q$, C_{Ph}),

129.58 (CH, $C_{p\text{-Ph}}$), 139.28 (C_q, C_{Ph}), 143.12 (C_q, C_{Ph}), 158.11 (C_q, $C_{3'}$); GC–MS (70 eV, *m/z*, %): 272 ($M^+-C_{15}H_{12}NO$, 100), 91 ($C_7H_7^+$, 85); FAB$^+$ 495.2 (M+H$^+$, 16), 272.1 ($M^+-C_{15}H_{12}NO$, 100), 91.1(8); Anal. Calcd for $C_{33}H_{38}N_2O_2$: C, 80.13; H, 7.74; N, 5.66. Found: C, 80.13; H, 7.72; N, 5.66.

Data for **7g**. Yield = 20.0 mg (20%). Yellow oil; R_f = 0.58 (85:15 petrol–Et_2O); $[\alpha]_D^{23} = +136.3$ (c 0.45, CH_2Cl_2); IR (film) *v* 3076, 3021, 2987, 2931, 2859, 1593 (C=N), 1491, 1450, 1076, 937, 719, 690, 667 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.95 (d, *J* = 6.7 Hz, 3H, CH_3–C_7), 0.88–1.05 (m, 2H, 5_{ax}, 6_{ax}), 1.09 (s, 3H, CH_{3eq}–C_4), 1.15 (s, 3H, CH_{3ax}–C_4), 1.16 (q, *J* = 12.0 Hz, 1H, H_{8ax}), 1.44–1.48 (m, 1H, H_7), 1.48 (t, *J* = 11.2 Hz, 1H, H_{10}), 1.61 (br d, *J* = 12.2 Hz, 1H, H_{5eq}), 1.71 (d app., *J* = 12.2 Hz, 1H, H_{6eq}), 1.99 (br d, *J* = 12.0 Hz, 1H, H_{8eq}), 3.45 (td, *J* = 10.4, 4.5 Hz, 1H, H_9), 3.73 (dd, *J* = 6.8, 1.9 Hz, 1H, $H_{4'}$), 3.83 (AB-d, *J* = 18.4 Hz, 1H, NCH_2Ph), 3.86 (AB-d, *J* = 18.4 Hz, 1H, NCH_2Ph), 4.96 (br s, 1H, H_2), 6.05 (d, *J* = 6.8 Hz, 1H, $H_{5'}$), 7.00 (t, *J* = 7.1 Hz, 1H, $H_{p\text{-Ph}}$), 7.05 – 7.17 (m, 5H, H_{Ph}), 7.07 (d, *J* = 7.1 Hz, 2H, $H_{5'\text{-}o\text{-Ph}}$), 7.09 (d, *J* = 6.1 Hz, 2H, $H_{NC\text{-}o\text{-Ph}}$), 7.41–7.47 (m, 3H, $H_{3'\text{-}m,p\text{-Ph}}$), 7.82 (d, *J* = 7.5 Hz, 2H, $H_{3'\text{-}o\text{-Ph}}$); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 20.02 (CH_{3ax}–C_4), 22.22 (CH_3–C_7), 24.96 (CH_2, C_5), 27.07 (CH_3, C_{eq}–C_4), 31.28 (CH, C_7), 35.02 (CH_2, C_6), 41.12 (CH_2, C_8), 46.24 (CH, C_{10}), 47.53 (NCH_2Ph), 57.73 (C_q, C_4), 58.22 (CH, $C_{4'}$), 76.25 (CH, C_9), 83.54 (CH, $C_{5'}$), 85.62 (CH, C_2), 126.03 (CH, $C_{p\text{-Ph}}$), 126.36 (2CH, $C_{o\text{-Ph}}$), 126.55 (2CH, $C_{o\text{-Ph}}$), 127.46 (2CH, $C_{3'\text{-}o\text{-Ph}}$), 127.81 (CH, $C_{p\text{-Ph}}$), 128.02 (2CH, $C_{mo\text{-Ph}}$), 128.43 (2CH, $C_{mo\text{-Ph}}$), 128.63 (2CH, $C_{3'\text{-}m\text{-Ph}}$), 129.32 (CH, $C_{3'\text{-}p\text{-Ph}}$), 129.72 ($C_q$, C_{Ph}), 140.51 (C_q, C_{Ph}), 142.03 (C_q, C_{Ph}), 157.16 (C_q, $C_{3'}$). GC–MS (70 eV, *m/z*, %): 272 ($M^+-C_{15}H_{12}NO$, 92); 106 ($C_7H_6O^+$, 8.1); 91 ($C_7H_7^+$, 100); 77 ($C_6H_5^+$, 34). Anal. Calcd for $C_{33}H_{38}N_2O_2$: C, 80.13; H, 7.74; N, 5.66. Found: C, 80.09; H, 7.75; N, 5.67.

Data for **8g**. Yield = 6.0 mg (6%); Yellow oil; R_f = 0.41 (CH_2Cl_2); $[\alpha]_D^{23} = -149.9$ (*c* 0.187, CH_2Cl_2); IR (film) *v* 3091, 3029, 2980, 2939, 2865, 1589 (C=N), 1490, 1454, 1070, 930, 710, 696, 686 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.95 (d, *J* = 6.0 Hz, 3H, CH_3–C_7), 0.93–1.02 (m, 2H, 5_{ax}, 6_{ax}), 1.08 (s, 3H, CH_{3eq}–C_4), 1.15 (q, *J* = 11.7 Hz, 1H, H_{8ax}), 1.29 (s, 3H, CH_{3ax}–C_4), 1.45–1.55 (m, 1H, H_7), 1.57 (t, *J* = 11.0 Hz, 1H, H_{10}), 1.60–1.67 (m, 1H, H_{5eq}), 1.73 (d app., *J* = 6.8 Hz, 1H, H_{6eq}), 2.05 (d app., *J* = 11.7 Hz, 1H, H_{8eq}), 3.61 (td, *J* = 10.5, 3.4 Hz, 1H, H_9), 3.98 (AB-d, *J* = 18.5 Hz, 1H, NCH_2Ph), 4.04 (AB-d, *J* = 18.5 Hz, 1H, NCH_2Ph), 4.59 (dd, *J* = 7.0, 2.7 Hz, 1H, $H_{5'}$), 4.69 (d, *J* = 2.7 Hz, 1H, $H_{4'}$), 4.76 (d, *J* = 7.0 Hz, 1H, H_2), 6.69 (d, *J* = 7.7 Hz, 2H, $H_{4'\text{-}o\text{-Ph}}$), 7.01 (t, *J* = 7.4 Hz, 2H, $H_{4'\text{-}m\text{-Ph}}$), 7.05 (t, *J* = 6.6 Hz, 1H, $H_{p\text{-Ph}}$), 7.24 (t, *J* = 7.2 Hz, 1H, $H_{p\text{-Ph}}$), 7.28 (t, *J* = 6.6 Hz, 2H, $H_{3'\text{-}m\text{-Ph}}$), 7.33 (t app., *J* = 7.3 Hz, 3H, $H_{m,p\text{-Ph}}$), 7.44 (d, *J* = 7.0 Hz, 2H, $H_{o\text{-Ph}}$), 7.58 (dd, *J* = 7.4, 1.7 Hz, 2H, $H_{o\text{-Ph}}$); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 22.15 (CH_3–C_7), 22.23 (CH_{3ax}–C_4), 24.95 (CH_2, C_5), 26.44 (CH_{3eq}–C_4), 31.36 (CH, C_7), 35.12 (CH_2, C_6), 41.22 (CH_2, C_8), 44.96 (CH, C_{10}), 47.04 (NCH_2Ph), 57.72 (CH, $C_{4'}$), 57.75 (C_q, C_4), 76.87 (CH, C_9), 88.06 (CH, C_2), 90.75 (CH, $C_{5'}$), 126.27 (CH, C_{Ph}), 127.07 (2CH, C_{Ph}), 127.10 (2CH, C_{Ph}), 127.13 (CH, C_{Ph}), 127.23 (2CH, C_{Ph}), 128.18 (2CH, C_{Ph}), 128.51 (2CH, C_{Ph}), 128.70 (2CH, C_{Ph}), 128.87 (CH, C_{Ph}), 129.71 (C_q, C_{Ph}), 138.25 (C_q, C_{Ph}), 142.82 (C_q, C_{Ph}), 159.58 (C_q, $C_{3'}$), GC–MS (70 eV, *m/z*, %): 272 ($M^+-C_{15}H_{12}NO$, 58), 91 ($C_7H_2^+$, 100), 77 ($C_6H_2^+$, 11.5). FAB$^+$ (NBA, *m/z*, %): 495.3 (M+H$^+$, 46), 272.2 (100), 91.1 (38) Anal. Calcd for $C_{33}H_{38}N_2O_2$: C, 80.13; H, 7.74; N, 5.66. Found: C, 80.11; H, 7.73, N, 5.64.

Data for **9g**. Yield = 18.0 mg (18%). White crystalline solid. pf = 152 °C; R_f = 0.58 (petrol–Et_2O, 85:15); $[\alpha]_D^{23} = -146.7$ (*c* 0.31, CH_2Cl_2); IR (KBr) *v* 3060, 3027, 2979, 2923, 2864, 1589 (C=N), 1499, 1446, 1380, 1070, 942, 715, 695, 676 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.86 (d, *J* = 6.5 Hz, 3H, CH_3–C_7), 0.89– 0.96 (m, 3H, 5_{ax}, 6_{ax}, 8_{ax}), 1.17 (s, 3H, CH_{3eq}–C_4), 1.33–1.41 (m, 1H, H_7), 1.41 (s, 3H, CH_{3ax}–C_4), 1.44 (br d, *J* = 12.8 Hz, 1H, H_{8eq}), 1.54 (br t, *J* = 10.7 Hz, 1H, H_{10}), 1.58–1.63 (m, 1H, H_{5eq}), 1.71 (d app., *J* = 9.1 Hz, 1H, H_{6eq}), 3.37 (td, *J* = 10.4, 3.8 Hz, 1H, H_9), 3.74 (dd, *J* = 9.6, 1.4 Hz, 1H, $H_{4'}$), 4.11 (AB d, *J* = 18.6 Hz, 1H, NCH_2Ph), 4.27 (AB d, *J* = 18.6 Hz, 1H, NCH_2Ph), 4.96 (d, *J* = 9.6 Hz, 1H, H_2), 5.69 (d, *J* = 1.4 Hz, 1H, $H_{5'}$), 6.67 (d, *J* = 7.8 Hz, 2H, $H_{C5'\text{-}o\text{-Ph}}$), 7.01 (t, *J* = 7.6 Hz, 2H, $H_{5'\text{-}m\text{-Ph}}$), 7.08 (t, *J* = 7.6 Hz, 1H, $H_{5'\text{-}p\text{-Ph}}$), 7.16 (t, *J* = 7.4 Hz, 1H, $H_{NC\text{-}p\text{-Ph}}$), 7.28 (t, *J* = 7.6 Hz, 2H, $H_{NC\text{-}m\text{-Ph}}$), 7.34–7.40 (m, 3H, $H_{3'\text{-}m,p\text{-Ph}}$), 7.48 (d, *J* = 7.5 Hz, 2H, $H_{NC\text{-}o\text{-Ph}}$), 7.84 (dd, *J* = 7.6, 2.0, 2H, $H_{3'\text{-}o\text{-Ph}}$); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 22.14 (CH_3–C_7), 22.60 (CH_{3ax}–C_4), 24.88 (CH_2, C_5), 27.08 (CH_{3eq}–C_4), 31.18 (CH, C_7), 35.12 (CH_2, C_6), 40.60 (CH_2, C_8), 44.98 (CH, C_{10}), 46.30 (NCH_2Ph), 57.61 (C_q, C_4), 58.04 (CH, $C_{4'}$), 77.00 (CH, C_9), 84.93 (CH, $C_{5'}$), 88.10 (CH, C_2), 125.39 (2CH, $C_{5'\text{-}o\text{-Ph}}$), 126.32 (CH, $C_{NC\text{-}p\text{-Ph}}$), 127.06 (2CH, $C_{NC\text{-}o\text{-Ph}}$), 127.39 (CH, $C_{5'\text{-}p\text{-Ph}}$), 127.73 (2CH, $C_{5'\text{-}m\text{-Ph}}$), 128.07 (2CH, $C_{NC\text{-}m\text{-Ph}}$), 128.11 (2CH, $C_{3'\text{-}o\text{-Ph}}$), 128.38 (2CH, $C_{3'\text{-}m\text{-Ph}}$), 129.40 (CH, $C_{3'\text{-}p\text{-Ph}}$), 130.57 ($C_q$, C_{Ph}), 139.37 (C_q, C_{Ph}), 142.62 (C_q, C_{Ph}), 159.50 (C_q, $C_{3'}$); GC–MS (70 eV, *m/z*, %): 272 ($M^+-C_{15}H_{12}NO$, 32): 106 ($C_7H_6O^+$, 13): 91 ($C_7H_7^+$, 80): 77 ($C_6H_5^+$, 100). Anal. Calcd for $C_{33}H_{38}N_2O_2$: C, 80.13; H, 7.74; N, 5.66. Found: C, 80.07; H, 7.76; N, 5.66.

Crystallographic studies for ***9g***. The crystal **9g** was recrystallized in a dichloromethane–diisopropylether mixture and it belongs to the chiral monoclinic $P2_1$ space group. The crystallographic data were measured with Cu Kα radiation and the results permitted the determination of the absolute structure. The crystal **9g** contains two independent molecules, which are very similar, except for a few torsion angles between the five-membered ring and the phenyl group located on C3′. The H atoms were refined normally with isotropic displacement parameters. All the bond distances and angles are normal and are available in the CIF.

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