Stereochemical aspects of novel 5,6-dihydro-4*H*-1,3-oxazines

Alan R. Katritzky,[a] Ion Ghiviriga,[b] Ke Chen,[a] Dmytro O. Tymoshenko[a] and Ashraf A. A. Abdel-Fattah[a]

[a] *Center for Heterocyclic Compounds, University of Florida, Gainesville, Florida, 32611-7200, USA*
[b] *Department of Chemistry, University of Florida, Gainesville, Florida, 32611-7200, USA*

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Novel polysubstituted 5,6-dihydro-4*H*-1,3-oxazines are synthesized by 1,4-cycloaddition of unactivated olefins with *N*-acyliminiums from benzotriazole precursors. The configuration and conformation of the products are deduced from NMR investigation. The regio- and *exo–endo* stereochemistry of the cycloaddition are discussed. Conformations of compounds of six types of substitution (6-mono; 6,6-, 5,6- and 4,6-di; 4,6,6- and 4,5,6-tri) are rationalized on the basis of axial-1,3-repulsion and the anomeric effect.

Introduction

The conformations of tetrahydro-1,3-oxazines have been much studied:[1] these rings normally assume chair structures similar to those shown by cyclohexanes. Although Δ^2-dihydro-1,3-oxazines are well-known compounds[2a,b] their stereochemistry is less documented. For *cis*-2,4,6-trisubstituted Δ^2-dihydro-1,3-oxazines[3] a quasi-equatorial position of the 4- and 6-substituents minimizes 1,3-interactions. For 2,4,5,6-tetrasubstituted compounds with alkyl substituents in positions 5 and 6, five of the ring atoms are almost planar, with the C5 atom out of the plane.[4] These investigations[3,4] along with X-ray study,[5] demonstrated the "half boat" conformations (Fig. 1).

Configurational analysis of 5,6-dihydro-4*H*-1,3-oxazines was discussed in the course of the elucidation of stereo- and regiospecificity of their preparation.[4,6–9] Generally, 5,6-dihydro-4*H*-1,3-oxazines **3** are available *via* amidomethylation of various unactivated olefins.[10] Such transformations occur *via* 1,4-polar cycloadditions of an olefin **2** to an *N*-acyliminium cation **1**, with the formation of the heterocyclic system as the primary product (Scheme 1). Regio- and stereospecificity of the process are vital for further synthetic applications of 5,6-dihydro-4*H*-1,3-oxazines **3** which are known as key intermediates for the stereoselective syntheses of *exo*,*cis*-3-carboxy-2-norborneol,† [11] 3-amino-[12a–c] and 3-amidopropanols.[13]

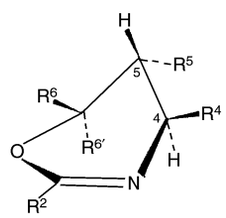


Fig. 1 Half boat conformation of Δ^2-dihydro-1,3-oxazines.

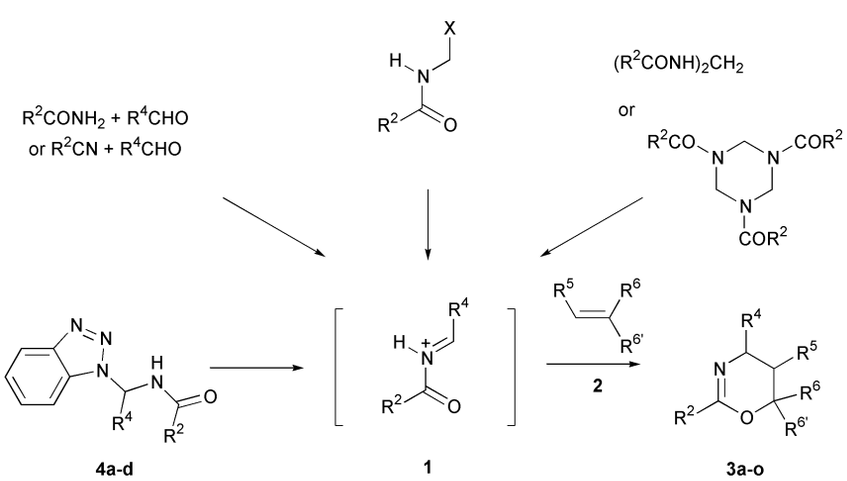
We now report on the synthesis of a series of polysubstituted 5,6-dihydro-4*H*-1,3-oxazines and the configurations and conformations of the products. These systems are readily available *via* 1,4-cycloaddition of unactivated olefins to *N*-acyliminiums **1**. Such reactive species were generated from *N*-(1-amidoalkyl)benzotriazoles which we already reported as versatile intermediates for a variety of amidoalkylations.[14–16] Extending previously documented synthetic approaches[4,17a–g] and our recent work,[18] this novel pathway provides a generalized route to 5,6-dihydro-4*H*-1,3-oxazine ring systems (Table 1).

Results and discussion

Preparation of the benzotriazole derivatives 4a–d

Adduct **4a**[19] was prepared by the literature method quoted.

† The IUPAC name for norborneol is bicyclo[2.2.1]heptan-2-ol, and the IUPAC name for the compound mentioned in ref. 11 is 3-hydroxybicyclo[2.2.1]heptane-2-carboxylic acid.



Scheme 1

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Table 1 5,6-Dihydro-4*H*-1,3-oxazines **3**. Yields and steric outcome in the amidoalkylation of alkenes with *N*-(α-amidoalkyl)benzotriazoles

Compd.	R^2	R^4	R^5	R^6	$R^{6'}$	Type	Number of stereo-isomers (isolated : total possible)		Configuration R^4–R^6	Configuration R^5–R^6	Yield[a]
3a	Ph	H	H	Ph	CH_3	ii	1 : 1		—	—	79
3b	Ph	H	H	H	$(CH_2)_{17}CH_3$	i	1 : 1		—	—	89
3c	*p*-CH_3O-C_6H_4	H	–$(CH_2)_4$–		H	iii	1 : 2		—	*cis*	84
3d	Ph	*p*-CH_3-C_6H_4	H	CH_3	Ph	v	1 : 2		*trans*	—	71
3e	Ph	*p*-CH_3-C_6H_4	–$(CH_2)_4$–		H	vi	1 : 4		*trans*	*cis*	77
3f	Ph	*p*-CH_3-C_6H_4	H	H	$(CH_2)_{17}CH_3$	iv	1 : 2		*trans*	—	75
3g	*p*-CH_3O-C_6H_4	*p*-Br-C_6H_4	H	CH_3	Ph	v	2 : 2	71%	*trans*	—	77
								29%	*cis*	—	
3h	*p*-CH_3O-C_6H_4	*p*-Br-C_6H_4	H	H	$(CH_2)_5CH_3$	iv	1 : 2		*trans*	—	65
3i	*p*-CH_3O-C_6H_4	*p*-Br-C_6H_4	–$(CH_2)_4$–		H	vi	1 : 4		*trans*	*cis*	52
3j	*p*-CH_3-C_6H_4	*p*-NO_2-C_6H_4	CH_3	H	Ph	vi	2 : 4	86%	*trans*	*cis*	60
								14%	*cis*	*cis*	
3k	Ph	CH_2CH_2Ph	H	CH_3	Ph	v	2 : 2	54%	*trans*	—	64
								46%	*cis*	—	
3l	*p*-CH_3-C_6H_4	CH_2CH_2Ph	H	H	*n*-C_4H_9	iv	2 : 2	77%	*trans*	—	15
								23%	*cis*	—	
3m	Ph	$CH(CH_3)_2$	H	CH_3	Ph	v	N/A		N/A	N/A	13
3n	Ph	*p*-CN-C_6H_4	H	H	Ph	iv	N/A		N/A	N/A	1(48)
3o	Ph	*p*-CN-C_6H_4	CH_3	H	Ph	vi	3 : 4	55%	*trans*	*cis*	1(7)
								31%	*cis*	*cis*	
								14%	*trans*	*trans*	

[a] Isolated yields. GCMS yields given in parentheses.

Compounds **4b**–**d** were synthesized by the procedure[19] similar to that used for **4a**, which was to combine benzotriazole, an aldehyde and a corresponding amide in toluene with azeotropic removal of water.

Preparation of 5,6-dihydro-4*H*-1,3-oxazines. Treatment of adducts **4a**–**d** with Lewis acids in refluxing dichloromethane or 1,2-dichloroethane afforded the corresponding 5,6-dihydro-4*H*-1,3-oxazines **3a**–**o** (Scheme 1, Table 1). This synthetic route improved the previously reported[14] yield of compound **3b** from 50 to 89% and extended the methodology to novel 4-unsubstituted derivative **3c**. Further application of this methodology to **4b**–**d** derived from aromatic aldehydes allowed us to synthesize previously unreported 4-substituted 5,6-dihydro-4*H*-1,3-oxazines **3d**–**o**. The yields were rather independent of the substituents in the 4-aryl ring, and both strong electron withdrawing (**3j**, R^4 = *p*-$NO_2C_6H_4$) and electron donating groups (**3d**–**f**, R^4 = *p*-MeC_6H_4) led to 52–77% yields. Exceptional behavior was observed in the case of 4-(*p*-cyanophenyl)-5,6-dihydro-4*H*-1,3-oxazine (**3n**), which, according to GC-MS, was obtained in 48% yield. Apparently, because of the high sensitivity of the 5,6-dihydro-4*H*-1,3-oxazine ring to acidic conditions and of the cyano group to basic ones, isolation of **3n** by chromatography on neutral alumina was achieved only in 1% yield.

Although the present route is favorable for the synthesis of 4-aryl-5,6-dihydro-4*H*-1,3-oxazines, it has limitations for other types of 4-substituents. Thus, compounds **3l**,**m** with non-aromatic carbon atoms attached at position 4 were obtained only in 15 and 13% yields respectively, which may be connected with deprotonation of the *N*-acyliminium intermediates **1**. Moreover, *N*-(1-amidoalkyl)benzotriazoles with heteroaromatic substituents (R^4 = pyridin-4-yl, thiophen-2-yl and thiophen-3-yl) did not afford the expected dihydro-oxazines **3**.

Regioselectivity and product classification

According to ^{1}H NMR, products **3a–o** were all isolated as single regioisomers; thus these cycloadditions are regiospecific and follow the rule of electrophilic addition with the more substituted side of the double bond ending up next to the oxygen.[6,8,9] Substituents in position 4 of the phenyl ring do not affect the regioselectivity of the process, which is consistent with the results reported earlier.[4]

The generalized synthetic approach now utilized allowed the synthesis of six classes of variously substituted oxazines classified according to their substitution as (i) 6-monosubstituted (**3b**), (ii) 6,6-disubstituted (**3a**), (iii) 5,6-disubstituted (**3c**), (iv) 4,6-disubstituted (**3f**,**h**,**l**,**n**), (v) 4,6,6-trisubstituted (**3d**,**g**,**k**,**m**) and (vi) 4,5,6-trisubstituted (**3e**,**i**,**j**,**o**). This classification assisted the elucidation and systematization of the configurations and conformations of polysubstituted 5,6-dihydro-4*H*-1,3-oxazines **3a–o**.

NMR study and stereochemistry

The carbons in positions 4 and 6 (C4 and C6) were easily identified by their characteristic chemical shifts, 40–50 ppm for C4 and 70–80 ppm for C6. Subsequent one bond ^{1}H–^{13}C correlation experiments then identified H4 and H6. Couplings to H4 and H6 located the proton(s) in position 5. In cases where the $J_{4,5}$ and $J_{5,6}$ coupling constants could not be measured or assigned with certainty in the proton spectrum, the DQCOSY technique was used. In every case, a multiple bond ^{1}H–^{13}C correlation experiment identified the signals of the substituents and confirmed the structural integrity of the compounds. For example, a common feature of these compounds is the long-range coupling of C2 at 155–157 ppm to H4 and the *ortho* protons of R^2, which were typically the most deshielded aromatic protons, at 8.00–8.20 ppm. Another interesting feature of compounds **3a**–**c**, which all possess a methylene group at position 4, is the large geminal coupling of the protons in position 4 (16.6 Hz), due to the hyperconjugation of the C4–H4 pseudo-axial bond with the C2=N bond.[20]

(i) The single 6-monosubstituted compound **3b** can be considered the archetype of an unconstrained oxazoline ring. The pseudo-axial–axial proton coupling constants H4a–H5a and H5a–H6a are 10.5–10.8 Hz (Table 2). As for cyclohexanes, axial protons are more shielded than those that are equatorial (by 0.10 ppm at position 4 and by 0.28 ppm in position 5). The NOESY spectrum of **3b** displayed cross-peaks between H4a and H6a, but not between H4e and the α-protons on the alkyl chain in position 6 (1.75 and 1.60 ppm), indicating that **3b** exists largely in the conformation with the alkyl chain pseudo-equatorial.

Table 2 Selected ^{1}H chemical shifts and coupling constants for compounds **3**

Compd.	δH2 [a,b]	δH4a	δH4e	δH5a	δH5e	δH6a	δH6e	Selected coupling constants [c]
3b	7.91	3.56	3.66	1.67	1.95	4.21	—	$^3J_{4a,5a}$ = 10.8, $^3J_{4a,5e}$ = 5.2, $^3J_{4e,5a}$ = 5.3, $^3J_{4e,5e}$ = 2.8, $^3J_{5a,6a}$ = 10.5, $^3J_{5e,6a}$ = 3.2
3a	8.07	3.22	3.58	2.05	2.24	7.34	1.70 [e]	$^3J_{4a,5a}$ = 9.5, $^3J_{4a,5e}$ = 5.0, $^3J_{4e,5a}$ = 4.8, $^3J_{4e,5e}$ = 4.8
3c	7.88	3.63	3.36	1.50 [e] 1.84 [f]	1.87	4.37	1.57 [d] 2.05 [e]	$^3J_{4a,5}$ = 5.4, $^3J_{4e,5}$ = 2.5, $^3J_{5,5aa}$ = 14.0, $^3J_{5,6}$ = 2.4, $^3J_{6,6aa}$ = 2.4, $^3J_{6,6ae}$ = 4.1
3e	8.08	7.09 [a]	4.62	1.56 [d] 1.72 [e]	1.85	4.24	1.45 [d] 2.10 [e]	$^3J_{4e,5}$ = 2.1, $^3J_{5,6}$ = 2.4, $^3J_{5,5aa}$ = 11.8, $^3J_{5,5ae}$ = 4.8, $^3J_{6,6aa}$ = 2.9, $^3J_{6,6ae}$ = 4.0
3i	8.03	7.08 [a]	4.83	1.51 [d] 1.84 [e]	1.89	4.12	1.39 [d] 2.10 [e]	$^3J_{4e,5}$ < 2.0, $^3J_{5,6}$ = 2.9, $^3J_{5,5aa}$ = 12.5, $^3J_{5,5ae}$ = 4.2, $^3J_{6,6aa}$ = 2.9, $^3J_{6,6ae}$ = 2.9
3o′	7.92	4.39	7.38 [a]	1.78	0.64 [c]	4.93	7.33 [a]	$^3J_{4,5}$ = 10.1, $^3J_{5,6}$ = 10.4
3o″	8.07	4.60	7.37 [a]	0.67 [c]	2.37	7.23 [a]	5.12	$^3J_{4,5}$ = 4.7, $^3J_{5,6}$ = 5.0
3o‴	8.12	5.12	7.56 [a]	0.23 [c]	2.48	5.68	7.37 [a]	$^3J_{4,5}$ = 4.6, $^3J_{5,6}$ = 2.5
3j′	7.89	4.51	7.51 [a]	1.86	0.71 [c]	4.99	7.40 [a]	$^3J_{4,5}$ = 10.2, $^3J_{5,6}$ = 10.3
3j″	8.05	4.70	7.49 [a]	0.75 [c]	2.46	7.31 [a]	5.21	$^3J_{4,5}$ = 4.8, $^3J_{5,6}$ = 4.7
3f	8.05	7.13 [a]	4.88	2.03	1.94	4.08	1.74 [g] 1.55 [f]	$^3J_{4e,5a}$ = 5.5, $^3J_{4e,5e}$ = 3.5, $^3J_{5a,6a}$ = 9.4, $^3J_{5e,6a}$ = 3.5
3h	8.00	7.23 [a]	5.15	2.13	1.92	4.09	1.76 [f] 1.58 [f]	$^3J_{4e,5a}$ = 5.4, $^3J_{4e,5e}$ = 4.6, $^3J_{5a,6a}$ = 8.3, $^3J_{5e,6a}$ = 3.5
3l′	7.84	1.99 [f,h] 1.76 [f,g]	3.57 [g]	1.76	1.76	4.24 [g]	1.54 [f,g]	$^3J_{4e,5a}$ = 5.4, $^3J_{4e,5e}$ = 4.6, $^3J_{5a,6a}$ = 8.3, $^3J_{5e,6a}$ = 3.5
3l″	7.84	1.99 [f] 1.76 [f]	3.50	1.33	1.98	4.15	1.54 [f]	$^3J_{4a,5a}$ = 11.3, $^3J_{4a,5e}$ = 5.0, $^3J_{5a,6a}$ = 12.0, $^3J_{5a,6e}$ = 2.4
3d	8.17	4.84	7.29 [a]	1.81	2.46	1.81 [c]	7.51 [a]	$^3J_{4a,5a}$ = 11.6, $^3J_{4a,5e}$ = 4.6
3g′	8.20	5.29	7.51 [a]	1.61	2.78	1.92 [c]	7.56 [a]	$^3J_{4a,5a}$ = 11.3, $^3J_{4a,5e}$ = 4.5
3g″	8.24	4.50	7.50 [a]	1.64	3.04	7.50 [a]	1.74 [c]	$^3J_{4a,5a}$ = 11.7, $^3J_{4a,5e}$ = 4.2
3k′	8.09	3.70	1.95 [f] 1.87 [f]	1.66	2.22	1.67 [c]	7.51 [a]	$^3J_{4a,5a}$ = 11.3, $^3J_{4a,5e}$ = 5.0
3k″	8.13	2.99	1.85 [f] 1.81 [f]	1.69	2.45	1.69 [c]	7.41 [a]	$^3J_{4a,5a}$ = 11.7, $^3J_{4a,5e}$ = 4.7

[a] In ppm relative to TMS. [b] *ortho* protons of the aryl group. [c] In Hz. The proton spectra were acquired with a digital resolution of 0.1 Hz per point. [d] Methyl protons. [e] Axial proton in α position. [f] Equatorial proton in α position. [g] Proton in α position. [h] The assignment of the coupling constants and of the axial or equatorial position is uncertain—see text.

(ii) The single 6,6-disubstituted compound **3a** displays NOE's between both protons in position 4 and each of the corresponding *cis* groups in position 6, indicating that **3a** exists as a rapidly equilibrating mixture of the two possible conformations (*cf.* Table 3). The vicinal coupling constant between the proton at 3.22 ppm in position 4 and that at 2.05 ppm in position 5 is 9.5 Hz. This value is smaller than that for the $J_{4,5}$ axial–axial coupling in **3b** (10.8 Hz), which agrees with the presence of conformational averaging, but is large enough to indicate that one conformation is dominant, and that the protons at 3.22 and 2.05 ppm spend most of the time in a pseudo-axial position. The proton at 3.22 ppm displays an NOE with the *ortho* protons of the phenyl in position 6 (7.34 ppm) suggesting an axial preference for the phenyl group. The protons in position 4 in **3a**, as compared to **3b**, display strong upfield shifts, 0.34 ppm for H4a and 0.08 ppm for H4e. These shifts are not the result of conformational averaging, but of the orientation of the phenyl ring in position 6 such as to minimize the repulsive interaction with H4a. In this orientation the protons in position 5 fall in a deshielding zone, and their chemical shift is higher than in **3b** by 0.38 ppm for H5a and by 0.29 ppm for H5e. Repulsion between the axial phenyl in position 6 and the phenyl in position 2 rotates the latter more into the plane of the NCO atoms, as indicated by a downfield shift of 0.16 ppm of its *ortho* protons.

(iii) The single 5,6-disubstituted compound **3c** has a cyclohexane ring condensed in positions 5 and 6 of the oxazine ring. The protons in position 4 (3.63 and 3.36 ppm) display vicinal couplings smaller than 5.5 Hz, indicating that **3c** exists primarily in a conformation in which H5 is equatorial, and, consequently, the junction of the two rings must be *cis*. Other coupling constants (Table 2) support the conformation (Fig. 2), in which H5 is equatorial to the oxazine ring and axial to the cyclohexane ring, while H6 is axial to the oxazine ring and equatorial to the cyclohexane ring. Further support for this comes from the NOE's (Fig. 2) between the axial protons: H4 axial (3.63 ppm) and H6 (4.37 ppm) on the oxazine ring; H5 (1.87 ppm), H7 (1.57 ppm) and H9 (1.33 ppm) on the cyclohexane ring. Axial proton H7 is in position α to C6, as indicated by both coupling and NOE to H6. Equatorial proton H7 (2.05 ppm) displays a cross-peak in the NOESY spectrum with the equatorial proton in position 4 (3.36 ppm), a proof that **3c** exists as a rapid equilibrium of the two possible conformations shown in Fig. 2 and Table 3.

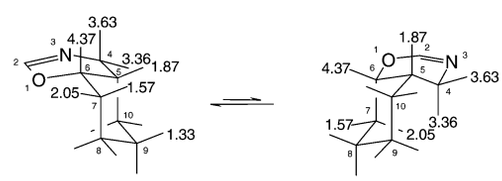
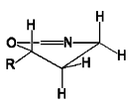
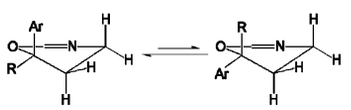
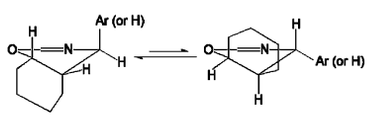
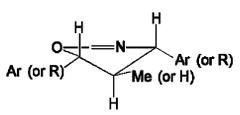
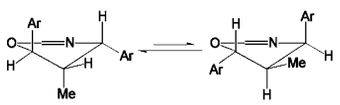
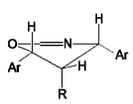
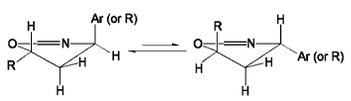
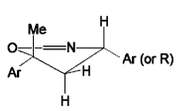
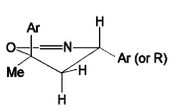


Fig. 2 Conformational equilibrium for **3c**.

(iv) The 4,6-disubstituted oxazines **3f** and **3h** were isolated as single isomers. The NOE's between H4 and the α and β protons of R^6 and between H6 and the *ortho* protons of R^4 demonstrated the *trans* relationship of R^4 and R^6, and also the presence of fast conformational equilibria for both **3f** and **3h** (see Table 3). The large coupling constants (9.4 and 8.3 Hz) between H6 and one of the protons in position 5 indicated that in the preferred conformations H6 is axial, as in **3b**. The presence of fast equilibria in **3f** and **3h** (as opposed to **3b**) indicates that an aryl in position 4 prefers an equatorial position.

The 4,6-disubstituted oxazine **3l**, in which R^4 and R^6 are both alkyl groups, was isolated as a mixture of isomers, **3l′** and **3l″**, in 1 : 0.30 ratio. Compound **3l′** is the *trans* isomer, as indicated by the NOE's between H4 and the α protons of R^6 and between H6 and the α protons of R^4. Unfortunately, it was impossible to determine with certainty which is the dominant conformer in

Table 3 Conformational preferences of oxazines **3**

Compd.	Conformation	Driving force in the conformational equilibrium
3b		Axial–axial repulsion
3a		Complex steric interactions—see text
3c, **3e**, **3i**		Axial–axial repulsion
3o′, **3j′**, **3l″**		Axial–axial repulsion
3o″, **3j″**		Anomeric effect
3o‴		Axial–axial repulsion
3f, **3h**, **3l′**		Axial–axial repulsion
3d, **3g′**, **3k′**		Axial–axial repulsion
3g″, **3k″**		Axial–axial repulsion

the fast conformational equilibrium of **3l′**. The two protons in position 5 overlapped their signals with one of the α protons in position 4 and prevented the assignment of the coupling constants. However, H4 and H6 display in **3l′** some couplings similar to those in **3f** and **3h**, suggesting that the dominant conformation has R^4 in the axial position. In the minor isomer **3l″**, both H4 and H6 display a large coupling with one of the protons in position 5, indicative of both being *pseudo*-axial. A NOE between H4 and H6 confirmed their *cis* relationship. The NOESY spectrum did not display any cross-peaks indicative of conformational exchange.

(v) The 4,6,6-trisubstituted oxazine **3d** was isolated as a single isomer, namely that in which the aryl substituents in positions 4 and 6 are *cis* and equatorial, as demonstrated by a NOE between H4 and the methyl protons in position 6. A coupling constant of 11.6 Hz between H4 and the axial proton in position 5 also indicated that H4 is axial and that this is by far the dominant conformation. No NOE's indicative of conformational exchange were observed.

The other two 4,6,6-trisubstituted oxazines **3g** and **3k** were each isolated as mixtures of the two possible isomers, in ratios **3g′**–**3g″** of 1 : 0.40 and **3k′**–**3k″** of 1 : 0.85. In both cases, an NOE between H4 and the methyl group indicated that the major isomer is the one in which these groups are *cis* and axial, as in **3d**. For all four compounds **3g′**, **3g″**, **3k′**, **3k″**, H4 displayed one coupling constant of 11.3–11.7 Hz, indicating that they all adopt only the conformation in which H4 is axial.

(vi) Two of the 4,5,6-trisubstituted oxazines **3e** and **3i** each possess a cyclohexane-fused oxazine skeleton (as does **3c**); both **3e** and **3i** were isolated as single isomers. The protons in position 5 of **3e** and **3i** each display just one large coupling (with the cyclohexane axial proton in the position α to C5), proof that in the dominant conformation H5 is axial with respect to the cyclohexane ring. If the junctions of the oxazine and cyclohexane rings were *trans*, H5 and H6 should display a coupling constant of 10.0–14.0 Hz. A value of 2.8 Hz for this coupling demonstrates that the ring junction is *cis*, as in **3c**. H6 displays in the NOESY spectrum a cross-peak with the *ortho* protons of the aryl group in position 4, indicating that they are *cis* (and both axial). As expected for the dominant conformation shown in Table 3, H4 displays no NOE to H6, which is axial to the oxazine ring, and a large NOE to H5αe, the equatorial proton on the cyclohexane in position α to C5. However, an NOE between H4 and H6αe of the cyclohexane ring demonstrates the fast equilibrium with the other possible conformation (Fig. 2), in which these two protons are both axial. We have noticed similar NOE's in molecules which have the geometry of *cis*-decalin.[21]

The proton spectra of the two 4,5,6-trisubstituted oxazines, **3j** and **3o**, each displayed signals for mixtures of isomers. In the case of **3o** the mixture contained three isomers in a ratio **3o′**–**3o″**–**3o‴** of 1 : 0.58 : 0.25. Coupling constants of 10.1 Hz between H5 and H4 and 10.4 Hz between H5 and H6 demonstrated that in **3o′** these three protons are all *pseudo*-axial. This was confirmed by the NOE between the protons in positions 4 and 6. The *ortho* protons of the aryl rings in positions 4 and 6 (7.38 and 7.33 respectively) were identified by (a) the NOE's to H4 and H6 and (b) NOE's with both H5 and the methyl in position 5; this confirmed that the 4- and 6-aryl groups are equatorial.

In **3o″**, both H4 and H6 displayed the NOE's with two different aromatic protons (7.23 and 7.37 ppm) demonstrating that the substituents in positions 4 and 6 are *trans*, and that there is conformational exchange. The relative size of the NOE's indicated that the signal at 7.37 ppm belonged to the 4-aryl and the one at 7.23 ppm to the 6-aryl. The relative size of the NOE's of these protons with H5 and the protons of the 5-methyl indicated that R^4 and R^5 are *cis*. The lack of NOE between H4 and H6 agrees with their *trans* relationship. Of the two possible half-chair conformations, the one with R^4 axial and R^5 and R^6 equatorial should display a coupling of *ca*. 10.0 Hz between H5 and H6. An actual value of 5.0 Hz indicates that the other conformation, with two substituents in axial positions, prevails, or at least has a significant contribution to the equilibrium (*cf.* Table 3).

The NOE between H4 and H6 in **3o‴** clearly demonstrates that these protons are *cis* and both axial. Small values for the coupling constants between H5 and H4 and between H5 and H6 indicate that H5 is equatorial. NOE's with H4 and H6 identified the *ortho* protons in the 4- and 6-aryl groups as 7.56 and 7.37 ppm, respectively. Both of these protons display NOE's with H5.

Interestingly, the difference in the chemical shifts of H4 and H6 in **3o′** and **3o‴** illuminates the conformations of these molecules. Allinger and Tribble[22] have shown that an equatorial phenyl is most stable in the bisector plane of the cyclohexane chair. Two facts clearly indicate that an axial methyl in position 5 confines the equatorial aryl groups in positions 4 and 6 of **3o‴** to a plane perpendicular to the plane of the oxazine ring more than in **3o′**: (a) a deshielding of *ca*. 0.75–0.80 ppm for H4 and H6 in **3o‴**, as they are more into the plane of the geminal aryl group, and (b) a significant shielding of both the protons (0.23 *vs*. 0.64 ppm) and the carbon (11.7 *vs*. 13.0 ppm) of R^5.

Two isomers were identified in the **3j** mixture, namely **3j′** and

3j″, in a ratio of 1 : 0.16. Their stereochemistry was the same as that of **3o′** and **3o″**, respectively, as indicated by coupling constants and NOE's. It is possible that for **3j** the mixture contained other isomers also, but they were in quantities of less than 5% of the major isomer.

Steric outcome of the preparative cyclizations and mechanistic consideration

In all of the products **3a**–**o** the most substituted sp^2 carbon of the alkene ended up next to the oxygen. The regioselectivity of the reaction between an *N*-acyliminium ion and an alkene is well documented[4,6,8,9] and demonstrates that in the transition state the positive charge is delocalized from the diene into the dienophile.

The reaction has also been found to be *cis*-stereospecific[4,6,8,9]—the *cis* relationship of the R^5 and R^6 substituents in the alkene is preserved in the oxazine—proof that the formation of the two new bonds is synchronous. We found this to be true for all of the compounds of types (ii) and (vi), for which the *cis* stereospecificity is an issue (Table 1), except for **3o**, which contained 14% of the *trans* product **3o″**. It is possible that **3o″** was formed by epimerization at C6 after cyclization.[9]

Compounds of types (iv), (v) and (vi) can reveal the *exo*–*endo* specificity of the reaction. To our knowledge, this type of specificity has been previously encountered only with some intramolecular cyclizations.[8] We postulate that in the transition state the acyliminium ion **1** approaches the geometry depicted in Scheme 1, with R^4 and the acyl *anti*, and the diene system s-*cis*.

Of the compounds of type (iv), we found **3f** and **3h** to be obtained with complete stereospecificity, as the products derived from the transition state in which the repulsion between R^2 and R^6 (alkyl) is minimal. The acyliminium ion is more reactive when R^4 is an alkyl, and indeed for **3l** 23% of the other product is also obtained.

All of the examples of type (v) have been obtained from reactions of α-methylstyrene. In the case of **3d** the reaction affords entirely the product from the transition state in which the phenyl and not the methyl overlaps the aromatic R^2. A possible explanation might be the π-stacking of R^2 and R^6, in the transition state, which reduces the electron deficiency of the acyliminium ion. For **3g**, in which R^2 is *p*-anisyl instead of phenyl, this electron deficiency is reduced and 29% of the other product is formed. In the case of **3k**, there is basically no stereoselectivity of the cycloaddition because of the higher reactivity of the acyliminium ion with R^4 alkyl.

Compounds of type (vi) were obtained in the reactions of cyclohexene (**3e**, **3i**) and of *trans*-β-methylstyrene (**3j**, **3o**). The reactions of cyclohexene with acyliminium ions, in which R^4 is an aryl, resemble those of monosubstituted alkenes—the same as for **3f** and **3h**. Compounds **3e** and **3i** were derived only from the transition state in which the repulsion between R^2 and R^6 is minimized. In reactions of *trans*-β-methylstyrene to give **3j** and **3o**, minimal repulsion between R^2 and $R^{6'}$ in one transition state is counteracted with the other by π-stacking or by steric interactions of R^5 and mixtures of products **3j′** and **3j″**, and **3o′**, **3o″** and **3o‴** are formed.

In conclusion, we have demonstrated that *exo*–*endo* selectivity can be obtained in reactions of an acyliminium ion stabilized by an aryl R^4 with each of the following types of alkene (a) monosubstituted, (b) *cis*-disubstituted or (c) 1,1-disubstituted with one aromatic and one aliphatic substituent.

Conformational characteristics of 5,6-dihydro-4*H*-1,3-oxazines

The conformational preferences encountered in this series of 19 variously substituted oxazines are summarized in Table 3. One can identify two factors which drive the conformational equilibrium, the van der Waals repulsion and the anomeric effect.

In the case of monosubstituted (without counting R^2) oxazine **3b**, repulsion between R^6 axial and H4 axial protons drives R^6 into the equatorial position, as the only conformation. In all of the cases in which in position 6 there is a substituent *cis* to R^4 (**3o′**, **3j′**, **3l″**, **3o‴**, **3d**, **3g′**, **3k′**, **3g″**, **3k″**), repulsion between the R^4 and R^5 substituents shifts the conformational equilibrium completely towards the conformation in which R^4 and R^6 are both equatorial. The conformational equilibrium of the 4,6-disubstituted oxazines with R^4 and R^6 *trans* (**3f**, **3h**, **3l′**) is driven by steric repulsion; it appears that an R^6 in the axial position is more hindered than an axial R^4.

Axial–axial interactions of R^5 are not a factor in the conformational equilibrium of 4,5,6-trisubstituted oxazines, as demonstrated by the similarity of $^3J_{4e,5e}$ in **3c**, **3e**, **3i** on one hand and **3f**, **3h**, **3l′** on the other. As in the case of **3f**, **3h**, **3l′**, the conformational equilibria of **3c**, **3e**, **3i** are determined by the preference of the alkyl R^6 for the equatorial position.

However, for 4,6-*trans*-disubstituted derivatives **3o′** and **3j″** in which R^6 is aryl, the major conformation in the equilibrium is the one with R^6 axial. The explanation we offer is an anomeric effect, the electronegative atom geminal to the oxygen being an sp^2 carbon atom.

The explanation for the axial preference of the phenyl group in **3a** is the one offered by Hodgson *et al.*[23] for the case of 1-methyl-1-phenylcyclohexane: an equatorial phenyl has a strong interaction of the *ortho* protons with either the methyl group or the vicinal equatorial protons in positions 2 and 6, while an axial phenyl can minimize these interactions by orienting itself parallel to the plane of the bonds C3–H3a and C5–H5a.

Similar preference of an sp^2 substituent for the axial position has been found in the case of 6-methoxycarbonyl-6-methyl-4-phenyl-5,6-dihydro-4*H*-1,3-oxazine:[4] the isomer in which the methyl in position 6 and the phenyl in position 4 are *cis*, exists solely as the conformation in which these groups are both equatorial, while the isomer in which these groups are *trans* exists as a mixture of comparably populated conformers.

Conclusion

In conclusion, a novel amidoalkylation of unactivated olefins with *N*-(1-amidoalkyl)benzotriazoles to produce 5,6-dihydro-4*H*-1,3-oxazines involves regio- and *cis*-stereoselective polar [2 + 4] cycloaddition. The reaction displays *exo*–*endo* stereoselectivity in several cases. The factors, which determine this type of selectivity, have been discussed. The conformational preferences of oxazines with various substitutions have been reported. Anomeric interaction between the oxygen in position 1 and an sp^2 carbon attached to position 6 was found to play a role in these conformational equilibria.

Experimental

General

Melting points were determined on a hot-stage apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H (300 MHz) or the solvent as the internal standard for ^{13}C (75 MHz). Microanalyses were performed on a Carlo Erba-1106 elemental analyzer. Benzene and toluene were dried over molecular sieves. Column chromatography was conducted with silica gel 200–425 mesh.

General procedure for the preparation of 5,6-dihydro-4*H*-1,3-oxazines

A mixture of *N*-(benzotriazol-1-ylmethyl)benzamide (1 mmol), unactivated olefin (1 mmol) and zinc bromide (0.45 g, 2 mmol) in dry 1,2-dichloroethane (30 cm^3) was refluxed for 24 h and poured into ice–water (50 cm^3). The organic layer was washed

with 10% NaOH (30 cm^3) and water (30 cm^3) and dried over $MgSO_4$ (5 g). The solvent was evaporated and the residue was purified by column chromatography on neutral alumina using CH_2Cl_2–hexanes as an eluent.

6-Methyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3-oxazine (3a). This compound was obtained as a colorless oil (79%). Found: C, 80.96; H, 6.98. Calc. for $C_{17}H_{17}NO$: C, 81.24; H, 6.82%. δ_H(300 MHz; $CDCl_3$; Me_4Si) 8.06 (2 H, d, *J* 7.6, Ph), 7.44–7.25 (8 H, m, Ph), 3.63–3.55 (1 H, m, NCH_2), 3.28–3.18 (1 H, m, NCH_2), 2.28–2.20 (1 H, m, CCH_2), 2.14–1.92 (1 H, m, CCH_2), 1.70 (3 H, s, CCH_3); δ_C(75 MHz; $CDCl_3$; Me_4Si) 155.0 (N=C), 145.1 (ArC), 134.1 (ArC), 130.3 (ArC), 128.6 (ArC), 128.1 (ArC), 127.2 (ArC), 127.0 (ArC), 124.1 (ArC), 78.4 (C-O), 41.0 (C-N), 33.5 (CH_2), 29.7 (CH_3).

6-Octadecyl-2-phenyl-5,6-dihydro-4*H*-1,3-oxazine (3b). This compound was obtained as white prisms (89%); mp 64 °C. Found: N, 3.40. Calc. for $C_{28}H_{47}NO$: N, 3.39%. δ_H(300 MHz; $CDCl_3$; Me_4Si) 7.91 (2 H, d, *J* 6.5, Ph), 7.46–7.30 (3 H, m, Ph), 4.27–4.16 (1 H, m, OCH), 3.70–3.50 (2 H, m, NCH_2), 2.00–1.92 (1 H, m, NCH_2CH_2), 1.77–1.11 (35 H, m, NCH_2CH_2 and $(CH_2)_{17}$), 0.88 (3 H, t, *J* 6.6, CH_3); δ_C(75 MHz; $CDCl_3$; Me_4Si) 155.9 (N=C), 134.2 (ArC), 130.2 (ArC), 127.9 (ArC), 126.9 (ArC), 74.9 (C-O), 43.0 (C-N), 35.6 (N-C-*C*), 31.9 ($(CH_2)_{17}$), 29.7 ($(CH_2)_{17}$), 29.6 ($(CH_2)_{17}$), 29.4 ($(CH_2)_{17}$), 27.3 ($(CH_2)_{17}$), 25.0 ($(CH_2)_{17}$), 22.7 ($(CH_2)_{17}$), 14.1 (CH_3).

4-(4a,5,6,7,8,8a-Hexahydro-4*H*-1,3-benzoxazin-2-yl)phenyl methyl ether (3c). This compound was obtained as white prisms (84%); mp 45.0–47.0 °C. Found: N, 5.78. Calc. for $C_{15}H_{19}NO$: N, 5.71%. δ_H(300 MHz; $CDCl_3$; Me_4Si) 7.89 (2 H, d, *J* 7.1, Ph), 6.87 (2 H, d, *J* 7.4, Ph), 4.39 (1 H, dd, *J* 4.0 and 5.5, OCH), 3.82 (3 H, s, OCH_3), 3.64 (1 H, dd, *J* 4.2 and 15.9, NCH_2), 3.37 (1 H, dd, *J* 2.5 and 16.5, NCH_2), 2.05–2.04 (1 H, m, NCH_2CH), 1.88–1.87 (1 H, m, $(CH_2)_4$), 1.71–1.34 (7 H, m, $(CH_2)_4$); δ_C(75 MHz; $CDCl_3$; Me_4Si) 161.2 (N=C), 154.7 (ArCO), 128.4 (ArC), 126.6 (ArC), 113.1 (ArC), 72.5 (OCH_3), 55.2 (OCH), 48.7 (NCH_2), 32.0 (NCH_2CH), 30.4 ($(CH_2)_4$), 25.3 ($(CH_2)_4$), 24.4 ($(CH_2)_4$), 20.2 ($(CH_2)_4$).

6-Methyl-4-(4-methylphenyl)-2,6-diphenyl-5,6-dihydro-4*H*-1,3-oxazine (3d). This compound was obtained as a colorless oil (71%). Found: N, 4.26. Calc. for $C_{24}H_{23}NO$: N, 4.10%. δ_H(300 MHz; $CDCl_3$; Me_4Si) 8.18 (2 H, d, *J* 6.0, Ph), 7.50 (2 H, d, *J* 7.2, Ph), 7.43–7.20 (8 H, m, Ph), 7.14 (2 H, d, *J* 7.2, Ph), 4.84 (1 H, dd, *J* 5.0 and 11.8, NCH), 2.45 (1 H, dd, *J* 4.5 and 13.5, $NCHCH_2$), 2.32 (3 H, s, $ArCH_3$), 1.85–1.77 (1 H, m, $NCHCH_2$), 1.80 (3 H, s, CCH_3); δ_C(75 MHz; $CDCl_3$; Me_4Si) 154.8 (N=C), 146.1 (ArC), 141.3 (ArC), 136.2 (ArC), 134.3 (ArC), 130.4 (ArC), 129.0 (ArC), 128.4 (ArC), 128.0 (ArC), 127.3 (ArC), 127.2 (ArC), 126.5 (ArC), 124.0 (ArC), 77.9 (O-C), 53.8 (N-C), 43.0 ($OCCH_2$), 26.5 ($ArCH_3$), 21.0 (CCH_3).

4-(4-Methylphenyl)-2-phenyl-4a,5,6,7,8,8a-hexahydro-4*H*-1,3-benzoxazine (3e). This compound was obtained as a colorless oil (77%). Found: N, 4.70. Calc. for $C_{21}H_{23}NO$: N, 4.59%. δ_H(300 MHz; $CDCl_3$; Me_4Si) 8.09 (2 H, d, *J* 6.7, Ph), 7.47–7.38 (3 H, m, Ph), 7.18–7.09 (4 H, m, Ph), 4.59 (1 H, d, *J* 2.0, OCH), 4.21 (1 H, dd, *J* 2.7 and 6.4, NCH), 2.33 (3 H, s, $ArCH_3$), 2.07 (1 H, dd, *J* 3.4 and 13.5, NCHCH), 1.84–1.26 (8 H, m, $(CH_2)_4$); δ_C(75 MHz; $CDCl_3$; Me_4Si) 155.5 (N=C), 141.2 (ArC), 136.2 (ArC), 134.0 (ArC), 130.4 (ArC), 128.9 (ArC), 128.0 (ArC), 127.2 (ArC), 126.9 (ArC), 68.7 (O-CH), 61.0 (N-CH), 39.7 (NCHCH), 30.2 ($(CH_2)_4$), 26.8 ($(CH_2)_4$), 24.6 ($(CH_2)_4$), 21.0 ($ArCH_3$), 20.5 ($(CH_2)_4$).

6-Octadecyl-4-(4-methylphenyl)-2-phenyl-5,6-dihydro-4*H*-1,3-oxazine (3f). This compound was obtained as white prisms (75%); mp 64.0–66.0 °C. Found: N, 2.81. Calc. for $C_{35}H_{53}NO$: N, 2.78%. δ_H(300 MHz; $CDCl_3$; Me_4Si) 8.05 (2 H, d, *J* 7.4, Ph), 7.41 (3 H, dd, *J* 7.3 and 1.1, Ph), 7.14 (4 H, s, Ph), 4.88 (1 H, dd, *J* 4.0 and 5.2, NCH), 4.08 (1 H, m, OCH), 2.33 (3 H, s, $ArCH_3$), 2.02–1.92 (2 H, m, $NCHCH_2$), 1.83–1.70 (2 H, m, $(CH_2)_{17}$), 1.56–1.49 (2 H, m, $(CH_2)_{17}$), 1.43–1.11 (30 H, m, $(CH_2)_{17}$), 0.88 (3 H, t, *J* 6.3, $(CH_2)_{17}CH_3$); δ_C(75 MHz; $CDCl_3$; Me_4Si) 156.1 (N=C), 141.4 (ArC), 136.1 (ArC), 134.2 (ArC), 130.4 (ArC), 129.0 (ArC), 128.0 (ArC), 127.2 (ArC), 126.8 (ArC), 71.2 (O-CH), 54.1 (N-CH), 35.3 ($NCHCH_2$), 34.7 ($(CH_2)_{17}$), 31.9 ($(CH_2)_{17}$), 29.7 ($(CH_2)_{17}$), 29.6 ($(CH_2)_{17}$), 29.4 ($(CH_2)_{17}$), 25.1 ($(CH_2)_{17}$), 22.7 ($(CH_2)_{17}$), 21.0 ($ArCH_3$), 14.1 (CH_3).

4-(4-Bromophenyl)-2-(4-methoxyphenyl)-6-methyl-6-phenyl-5,6-dihydro-4*H*-1,3-oxazine (3g). This compound was obtained as white prisms (77%); mp 65.0–67.0 °C. Found: C, 66.28; H, 5.14; N, 3.21. Calc. for $C_{24}H_{22}BrNO_2$: C, 66.06; H, 5.08; N, 3.21%. δ_H(300 MHz; $CDCl_3$; Me_4Si) 8.17 (1 H, d, *J* 9.1, Ph), 8.13 (1 H, d, *J* 8.8, Ph), 7.53–7.23 (8 H, m, Ph), 7.09 (1 H, t, *J* 7.6, Ph), 6.97 (2 H, t, *J* 8.5, Ph), 5.22 (0.7 H, dd, *J* 4.6 and 11.4, NCH), 4.43 (0.3 H, dd, *J* 4.2 and 11.5, NCH), 3.87 (3 H, s, $ArOCH_3$), 3.00 (0.3 H, dd, *J* 4.1 and 13.5), 2.73 (0.7 H, dd, *J* 4.6 and 13.5, $NCHCH_2$), 1.87 (s, 2H), 1.69 (s, 1H), 1.65–1.51 (1 H, m, $NCHCH_2$); δ_C(75 MHz; $CDCl_3$; Me_4Si) 161.7 (N=C), 161.6 (ArC), 155.6 (ArC), 146.0 (ArC), 144.2 (ArC), 143.7 (ArC), 143.3 (ArC), 132.3 (ArC), 128.9 (ArC), 128.9 (ArC), 128.8 (ArC), 128.6 (ArC), 128.4 (ArC), 128.2 (ArC), 128.1 (ArC), 127.9 (ArC), 127.8 (ArC), 127.4 (ArC), 127.3 (ArC), 126.7 (ArC), 126.4 (ArC), 124.1 (ArC), 122.5 (ArC), 122.4 (ArC), 113.5 (ArC), 113.4 (ArC), 79.4 (O-CH), 78.2 (O-CH), 55.4 ($ArOCH_3$), 53.9 (NCH), 53.8 (NCH), 40.7 ($NCHCH_2$), 40.1 ($NCHCH_2$), 31.1 ($OCCH_3$), 26.5 ($OCCH_3$).

4-[4-(4-Bromophenyl)-6-hexyl-5,6-dihydro-4*H*-1,3-oxazin-2-yl]phenyl methyl ether (3h). This compound was obtained as a colorless oil (65%). Found: C, 64.16; H, 6.77; N, 3.55. Calc. for $C_{23}H_{28}BrNO_2$: C, 64.19; H, 6.56; N, 3.25%. δ_H(300 MHz; $CDCl_3$; Me_4Si) 8.01 (2 H, d, *J* 8.7, Ph), 7.58–7.46 (1 H, m, Ph), 7.36–7.23 (2 H, m, Ph), 7.19–7.09 (1 H, m, Ph), 6.92 (2 H, d, *J* 8.9, Ph), 5.16 (1 H, t, *J* 4.4, NCH), 4.12–4.07 (1 H, m, OCH), 3.85 (3 H, s, $ArOCH_3$), 2.19–2.09 (1 H, m, $NCHCH_2$), 1.96–0.96 (11 H, m, $NCHCH_2$ and $(CH_2)_5$), 0.90 (3 H, t, *J* 6.9, CH_2CH_3); δ_C(75 MHz; $CDCl_3$; Me_4Si) 161.6 (N=C), 156.7 (ArC), 143.1 (ArC), 132.7 (ArC), 129.3 (ArC), 128.8 (ArC), 128.2 (ArC), 127.3 (ArC), 113.3 (ArC), 71.5 (OCH), 55.3 ($ArOCH_3$), 53.9 (NCH), 35.0 ($NCHCH_2$), 32.3 ($(CH_2)_5$), 31.7 ($(CH_2)_5$), 29.2 ($(CH_2)_5$), 25.1 ($(CH_2)_5$), 22.6 ($(CH_2)_5$), 14.1 (CH_2CH_3).

4-(4-Bromophenyl)-2-(4-methoxyphenyl)-4a,5,6,7,8,8a-hexahydro-4*H*-1,3-benzoxazine (3i). This compound was obtained as a colorless oil (52%). Found: N, 3.27. Calc. for $C_{21}H_{22}BrNO_2$: N, 3.50%. δ_H(300 MHz; $CDCl_3$; Me_4Si) 8.04 (2 H, d, *J* 8.7, Ph), 7.56 (1 H, d, *J* 8.0, Ph), 7.23 (1 H, d, *J* 7.7, Ph), 7.09 (2 H, t, *J* 7.4, Ph), 6.92 (2 H, d, *J* 8.8, Ph), 4.83 (1 H, s, OCH), 4.12 (1 H, br s, NCH), 3.83 (3 H, s, $ArOCH_3$), 2.15–2.07 (1 H, m, NCHCH), 1.91–1.75 (3 H, m, $(CH_2)_4$), 1.62–1.32 (5 H, m, $(CH_2)_4$); δ_C(75 MHz; $CDCl_3$; Me_4Si) 161.6 (N=C), 156.3 (ArC), 142.7 (ArC), 132.8 (ArC), 129.3 (ArC), 128.8 (ArC), 128.1 (ArC), 127.0 (ArC), 126.1 (ArC), 123.0 (ArC), 113.3 (ArC), 67.9 (OCH), 61.3 (NCH), 55.3 ($ArCH_3$), 37.4 (NCH*C*H), 30.3 ($(CH_2)_4$), 26.4 ($(CH_2)_4$), 25.1 ($(CH_2)_4$), 20.0 ($(CH_2)_4$).

5-Methyl-2-(4-methylphenyl)-4-(4-nitrophenyl)-6-phenyl-5,6-dihydro-4*H*-1,3-oxazine (3j). This compound was obtained as a yellow oil (60%). Found: N, 6.95. Calc. for $C_{24}H_{22}N_2O_3$: N, 7.25%. δ_H(300 MHz; $CDCl_3$; Me_4Si) 8.20 (2 H, d, *J* 8.0, Ph), 8.05 (2 H, d, *J* 8.0, Ph), 7.49 (2 H, d, *J* 8.5, Ph), 7.39 (2 H, d, *J* 8.0, Ph), 7.37–7.25 (5 H, m, Ph), 5.22 (1 H, d, *J* 4.4, OCH), 4.69 (1 H, d, *J* 4.0, NCH), 2.44–2.42 (1 H, m, NCHCH), 2.42 (3 H, s, $ArCH_3$), 0.75 (3 H, d, *J* 6.9, $CHCH_3$); δ_C(75 MHz;

$CDCl_3$; Me_4Si) 155.4 (N=C), 149.4 (ArC), 146.8 (ArC), 141.4 (ArC), 140.3 (ArC), 130.3 (ArC), 128.9 (ArC), 128.8 (ArC), 128.6 (ArC), 128.4 (ArC), 128.2 (ArC), 127.3 (ArC), 125.4 (ArC), 123.5 (ArC), 123.3 (ArC), 80.2 (OCH), 55.5 (NCH), 36.6 (NCH*C*H), 21.4 ($ArCH_3$), 13.1 ($CHCH_3$).

(4*R,5*S**,6*R**)-5-Methyl-2-(4-methylphenyl)-4-(4-nitrophenyl)-6-phenyl-5,6-dihydro-4*H*-1,3-oxazine (3j′).** This compound was obtained by column separation (first fraction, alumina, hexanes–ethyl acetate 6 : 1) as a yellow oil (30%). δ_H(300 MHz; $CDCl_3$; Me_4Si) 8.20 (2 H, d, *J* 8.4, Ph), 8.05 (2 H, d, *J* 8.1, Ph), 7.49 (2 H, d, *J* 8.7, Ph), 7.42–7.34 (3 H, m, Ph), 7.31–7.25 (4 H, m, Ph), 5.22 (1 H, d, *J* 4.7, OCH), 4.69 (1 H, d, *J* 4.6, NCH), 2.49–2.38 (4 H, m, $ArCH_3$ and NCHC*H*), 0.75 (3 H, d, *J* 7.2, $CHCH_3$); δ_C(75 MHz; $CDCl_3$; Me_4Si) 155.4 (N=C), 149.4 (ArC), 146.8 (ArC), 141.3 (ArC), 140.3 (ArC), 130.3 (ArC), 129.0 (ArC), 128.8 (ArC), 128.5 (ArC), 128.2 (ArC), 127.3 (ArC), 125.4 (ArC), 123.3 (ArC), 80.2 (OCH), 55.5 (NCH), 36.6 (NCH*C*H), 21.4 ($ArCH_3$), 13.1 ($CHCH_3$).

(4*S,5*S**,6*R**)-5-Methyl-2-(4-methylphenyl)-4-(4-nitrophenyl)-6-phenyl-5,6-dihydro-4*H*-1,3-oxazine (3j″).** This compound was obtained by separation on a column (second fraction, alumina, hexanes–ethyl acetate 6 : 1) as a yellow oil (30%). δ_H(300 MHz; $CDCl_3$; Me_4Si) 8.22 (2 H, d, *J* 8.4, Ph), 7.88 (2 H, d, *J* 8.1, Ph), 7.50 (2 H, d, *J* 8.4, Ph), 7.40 (5 H, s, Ph), 7.17 (2 H, d, *J* 8.1, Ph), 5.00 (1 H, d, *J* 10.6, OCH), 4.51 (1 H, d, *J* 10.0, NCH), 2.38 (3 H, s, $ArCH_3$), 1.90–1.81 (1 H, m, NCHC*H*), 0.71 (3 H, *J* 6.9, CH_3); δ_C(75 MHz; $CDCl_3$; Me_4Si) 156.8 (N=C), 150.8 (ArC), 147.1 (ArC), 141.2 (ArC), 138.2 (ArC), 130.3 (ArC), 128.8 (ArC), 128.7 (ArC), 128.6 (ArC), 127.4 (ArC), 127.3 (ArC), 123.6 (ArC), 82.8 (O-CH), 64.1 (N-CH), 40.3 (NCH*C*H), 21.4 ($ArCH_3$), 14.0 ($CHCH_3$).

6-Methyl-4-phenethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3-oxazine (3k). This compound was obtained as a yellow oil (64%). Found: C, 84.70; H, 7.51; N, 3.64. Calc. for $C_{25}H_{25}NO$: C, 84.47; H, 7.09; N, 3.94%. δ_H(300 MHz; $CDCl_3$; Me_4Si) 8.13 (2 H, dd, *J* 2.0 and 7.4, Ph), 7.47–7.40 (3 H, m, Ph), 7.32–7.13 (10 H, m, Ph), 2.95 (2 H, m, NCH and CH_2CH_2Ph), 2.74–2.64 (1 H, m, NCHC*H*$_2$), 2.45 (1 H, dd, *J* 4.2 and 13.5, NCHC*H*$_2$), 1.83–1.75 (2 H, m, CH_2Ph), 1.69 (4 H, m, CCH_3 and CH_2CH_2Ph); δ_C(75 MHz; $CDCl_3$; Me_4Si) 153.7 (N=C), 145.0 (ArC), 142.6 (ArC), 134.0 (ArC), 130.4 (ArC), 128.6 (ArC), 128.4 (ArC), 128.2 (ArC), 128.1 (ArC), 127.2 (ArC), 127.0 (ArC), 125.6 (ArC), 124.1 (ArC), 79.0 (O-CCH_3), 49.9 (NCH), 39.7 (NCHCH_2), 38.8 (CH_2Ph), 32.2 (CH_2CH_2Ph), 31.3 (CCH_3).

6-Butyl-2-(4-methylphenyl)-4-phenethyl-5,6-dihydro-4*H*-1,3-oxazine (3l). This compound was obtained as a colorless oil (15%). Found: C, 82.16; H, 9.05; N, 4.36. Calc. for $C_{23}H_{29}NO$: C, 82.34; H, 8.71; N, 4.18%. δ_H(300 MHz; $CDCl_3$; Me_4Si) 7.85 (2 H, dd, *J* 3.3 and 8.1, Ph), 7.34–7.14 (5 H, m, Ph), 7.16 (2 H, d, *J* 7.7, Ph), 4.26–4.20 (1 H, m, OCH), 3.60–3.54 (1 H, m, NCH), 2.90–2.77 (2 H, m, NCHC*H*$_2$), 2.35 (3 H, s, $ArCH_3$), 2.01–1.94 (2 H, m, C*H*$_2$Ph), 1.83–1.68 (3 H, m, C*H*$_2$CH$_2$Ph and CH-(C*H*$_2$)$_3$), 1.61–1.53 (2 H, m, CH(C*H*$_2$)$_3$), 1.45–1.35 (3 H, m, CH(C*H*$_2$)$_3$), 0.94 (3 H, t, *J* 6.8, CH_2CH_3); δ_C(75 MHz; $CDCl_3$; Me_4Si) 156.2 (N=C), 144.2 (ArC), 141.8 (ArC), 130.4 (ArC), 130.2 (ArC), 130.0 (ArC), 128.7 (ArC), 127.4 (ArC), 127.3 (ArC), 76.8 (O-CH), 73.9 (O-CH), 54.1 (N-CH), 51.6 (N-CH), 41.2 (NCH*C*H$_2$CH), 37.4 (CH_2Ph), 36.8 (*C*H$_2$CH$_2$Ph), 36.0 ((CH$_2$)$_3$), 34.1 ((CH$_2$)$_3$), 33.8 ((CH$_2$)$_3$), 33.0 ((CH$_2$)$_3$), 29.0 ((CH$_2$)$_3$), 28.8 ((CH$_2$)$_3$), 24.2 ($ArCH_3$), 23.2 (CH_2CH_3), 17.8 (CH_2CH_3).

4-Isopropyl-6-methyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3-oxazine (3m). This compound was obtained as a colorless oil (13%). Found: N, 4.44. Calc. for $C_{20}H_{23}NO$: N, 4.77%. δ_H(300 MHz; $CDCl_3$; Me_4Si) 8.13 (2 H, dd, *J* 2.0 and 7.2, Ph), 7.44–7.40 (3 H, m, Ph), 7.30–7.21 (5 H, m, Ph), 2.77–2.69 (1 H, m, N-CH), 2.36 (1 H, dd, *J* 4.4 and 13.4, NCHC*H*$_2$), 1.78–1.71 (1 H, m, NCHC*H*$_2$), 1.70–1.65 (4H, m, CCH_3 and C*H*(CH$_3$)$_2$), 0.98 (3 H, d, *J* 6.7, CH(C*H*$_3$)$_2$), 0.94 (3 H, d, *J* 6.7, CH(C*H*$_3$)$_2$); δ_C(75 MHz; $CDCl_3$; Me_4Si) 153.5 (N=C), 145.2 (ArC), 134.2 (ArC), 130.2 (ArC), 128.6 (ArC), 128.0 (ArC), 127.2 (ArC), 126.9 (ArC), 124.1 (ArC), 78.8 (O*C*CH$_3$), 55.3 (NCH), 36.2 (NCH*C*H$_2$), 33.3 (CCH_3), 31.5 (*C*H(CH$_3$)$_2$), 18.7 (CH(*C*H$_3$)$_2$), 18.6 (CH(*C*H$_3$)$_2$).

4-(2,6-Diphenyl-5,6-dihydro-4*H*-1,3-oxazin-4-yl)benzonitrile (3n). This compound was obtained as a colorless oil (13%). Found: C, 81.89; H, 5.34. Calc. for $C_{23}H_{18}N_2O$: C, 81.63; H, 5.36%. δ_H(300 MHz; $CDCl_3$; Me_4Si) 8.13 (2 H, d, *J* 7.8, Ph), 7.66 (2 H, d, *J* 8.1, Ph), 7.54–7.26 (10 H, m, Ph), 5.29–5.25 (1 H, m, OCH), 4.78 (1 H, t, *J* 6.0, NCH), 2.45–2.38 (1 H, m, NCHC*H*$_2$), 2.24–2.17 (1 H, m, NCHC*H*$_2$); δ_C(75 MHz; $CDCl_3$; Me_4Si) 156.7 (N=C), 149.8 (ArC), 140.5 (ArC), 133.6 (ArC), 132.6 (ArC), 131.4 (ArC), 129.1 (ArC), 128.6 (ArC), 128.5 (ArC), 127.9 (ArC), 127.7 (ArC), 125.6 (ArC), 73.6 (OCH), 53.3 (NCH), 36.6 (NCH*C*H$_2$).

4-[(4*R,5*S**,6*R**)-5-Methyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3-oxazin-4-yl]benzonitrile (3o′).** This compound was obtained by column separation (first fraction, alumina, hexanes–ethyl acetate 6 : 1) as a yellow oil (0.3% isolated yield). Found: N, 7.64. Calc. for $C_{24}H_{20}N_2O$: N, 7.95. δ_H(300 MHz; $CDCl_3$; Me_4Si) 8.15 (2 H, d, *J* 6.9, Ph), 7.64 (2 H, d, *J* 8.4, Ph), 7.51–7.25 (10 H, m, Ph), 5.20 (1 H, d, *J* 5.0, OCH), 4.67 (1 H, d, *J* 4.7, NCH), 2.44 (1 H, m, NCHC*H*), 0.74 (3 H, d, *J* 7.1, CH_3); δ_C(75 MHz; $CDCl_3$; Me_4Si) 155.3 (N=C), 147.0 (ArC), 140.1 (ArC), 133.0 (ArC), 131.9 (ArC), 130.9 (ArC), 128.7 (ArC), 128.4 (ArC), 128.2 (ArC), 128.1 (ArC), 127.3 (ArC), 125.4 (ArC), 118.9 (ArCN), 110.5 (ArC), 80.2 (OCH), 55.8 (NCH), 36.5 (NCH*C*H), 13.0 (CH_2).

4-[(4*S,5*S**,6*R**)-5-Methyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3-oxazin-4-yl]benzonitrile (3o″).** This compound was obtained by column separation (second fraction, alumina, hexanes–ethyl acetate 6 : 1) as a yellow oil (0.3% isolated yield). Found: N, 7.67. Calc. for $C_{24}H_{20}N_2O$: N, 7.95%. δ_H(300 MHz; $CDCl_3$; Me_4Si) 7.99 (2 H, d, *J* 7.4, Ph), 7.65 (2 H, d, *J* 8.1, Ph), 7.46–7.25 (10 H, m, Ph), 5.00 (1 H, d, *J* 10.3, OCH), 4.46 (1 H, d, *J* 9.9, NCH), 1.88–1.63 (1 H, m, NCHC*H*), 0.70 (3 H, d, *J* 6.6, CH_3); δ_C(75 MHz; $CDCl_3$; Me_4Si) 156.7 (N=C), 148.6 (ArC), 138.2 (ArC), 133.1 (ArC), 132.2 (ArC), 130.9 (ArC), 128.8 (ArC), 128.7 (ArC), 128.6 (ArC), 128.1 (ArC), 127.4 (ArC), 127.3 (ArC), 118.9 (CN), 111.0 (ArC), 82.8 (OCH), 64.3 (NCH), 40.2 (NCH*C*H), 14.0 (CH_3).

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