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Synthesis and conformational analysis of naphth[1′,2′:5,6][1,3]oxazino[3,2-*c*][1,3]benzoxazine and naphth[1′,2′:5,6][1,3]oxazino[3,4-*c*][1,3]benzoxazine derivatives

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Abstract—A new functional group, the hydroxy group, was inserted into a Betti base by reaction with salicylaldehyde, and the naphthoxazine derivatives thus obtained were converted by ring-closure reactions with formaldehyde, acetaldehyde, propionaldehyde or phosgene to the corresponding naphth[1′2′:5,6][1,3]oxazino[3,2-*c*][1,3]benzoxazine derivatives. Further, the conformational analysis of these polycyclic compounds by NMR spectroscopy and an accompanying molecular modelling are reported; especially, both quantitative anisotropic ring current effects of the aromatic moieties in these compounds and steric substituent effects were employed to determine the stereochemistry of the naphthoxazinobenzoxazine derivatives.

1. Introduction

The Betti reaction is a convenient method with which to prepare α-aminobenzylnaphthol derivatives. Earlier, this three-component modified Mannich reaction with 2-naphthol, benzaldehyde and ammonia resulted in 1,3-diphenylnaphthoxazine, which on subsequent hydrolysis, gave the desired 1-α-aminobenzyl-2-naphthol (Betti base, **1**, cf. Scheme 1).[1,2] The reaction can be extended by using substituted benzaldehydes[3–5] or formaldehyde[3] instead of benzaldehyde, and 1-naphthol[6] instead of 2-naphthol.

Replacement of ammonia with chiral amines led to non-racemic *N*-substituted Betti base derivatives, which opened up a new area of application of these chiral aminonaphthols as ligands in asymmetric transformations.[7–10]

In spite of the two potentially reactive functional groups, relatively few publications have appeared in this field. In our previous studies on the ring-closing behaviour of these versatile synthons, mainly reactions with aldehydes, phosgene and oxocarboxylic acids were carried out. Through the use of salicylaldehyde, the functionalization of the Betti bases was partially resolved. In this way, trifunctional Betti base derivatives could be prepared.[11]

Our present aim was to insert a new functional group (e.g., a hydroxy group) into Betti base derivatives, and to transform the reaction products via another ring-closure reaction to naphthoxazinobenzoxazine derivatives. A further aim was the conformational analysis of these polycyclic compounds by NMR spectroscopy and an accompanying molecular modelling. This spectroscopic and theoretical study involved the quantitative determination of the anisotropic/ring current effects of the aromatic ring moieties and steric substituent effects to reveal ^{1}H chemical shift differences due to the stereochemistry of the naphthoxazinobenzoxazine derivatives.

2. Results and discussion

2.1. Syntheses

The Betti base can be functionalized with the hydroxy group in two different ways. One possibility is the reaction of Betti base **1** with salicylaldehyde (cf. Scheme 1). On NMR spectroscopic analysis in $CDCl_3$ at 300 K, however, the naphthoxazine derivative (**2**) thus obtained proved to be a three-component tautomeric mixture. The tautomeric ratios

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Keywords: Conformational analysis; Naphthoxazinobenzoxazine; NMR; Ring current effect; Steric substituent effect; Molecular modelling.

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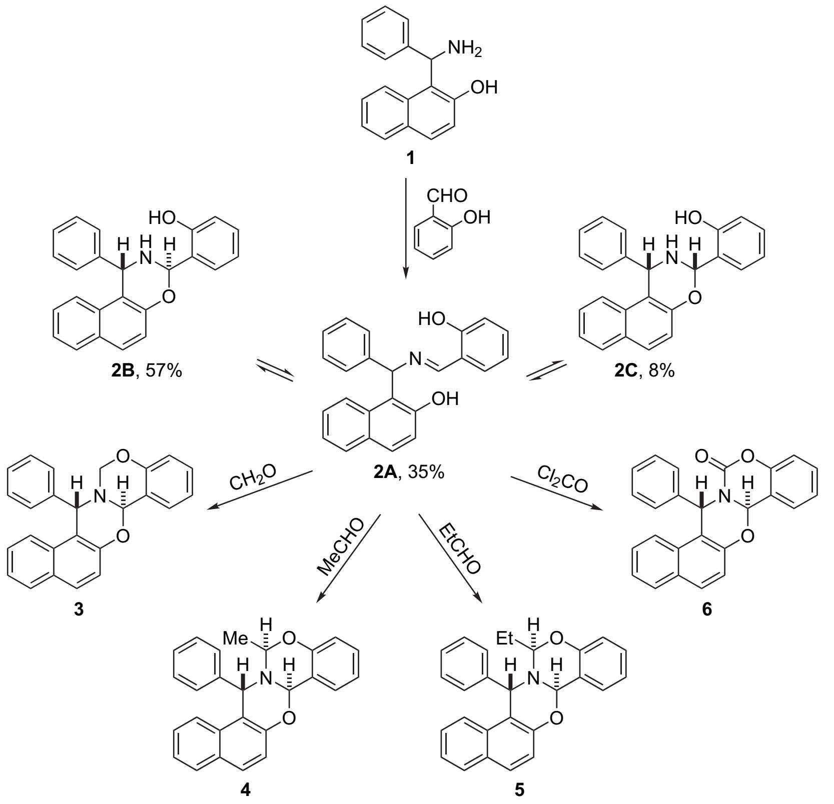


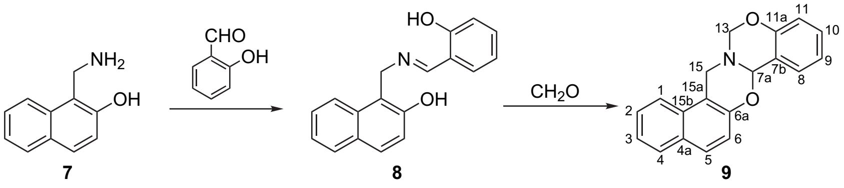
Scheme 1.

are depicted in Scheme 1. Compound **2** could be converted by the ring-closure reactions with formaldehyde,[11] acetaldehyde,[11] propionaldehyde or phosgene to the desired naphth[1′,2′:5,6][1,3]oxazino[3,2-*c*][1,3]benzoxazine derivatives **3–6**. The relative configurations of **3–6** are also depicted in Scheme 1; no minor diastereomers were detected even in the crude products. Similar high diastereoselectivity has often been observed in the analogous ring closures of aminoalcohols, and explained as a result of kinetic control governing the second ring closures of the tautomeric cyclic intermediates.[12,13]

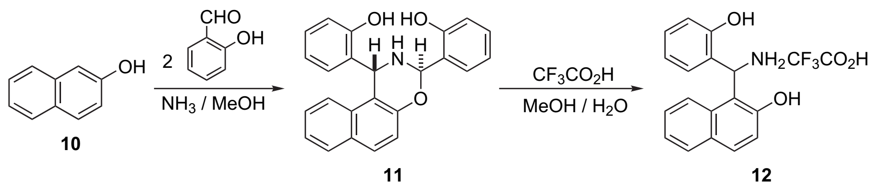
Condensation of 1-aminomethyl-2-naphthol **7** with salicylaldehyde led to the Schiff base **8**, which could be easily converted into the unsubstituted naphth[1′,2′:5,6][1,3]oxazino[3,2-*c*][1,3]benzoxazine derivative **9** (cf. Scheme 2).[11]

For the syntheses of the analogous naphth[1′,2′:5,6][1,3]oxazino[3,4-*c*][1,3]benzoxazine derivatives, the *ortho*-functionalized Betti base derivative **12** was prepared from 2-naphthol **10**, salicylaldehyde and ammonia. Subsequent acidic hydrolysis, with HCl, of the initially isolated naphthoxazine derivative **11** (cf. Scheme 3) failed; however, only the acidic hydrolysis of **11** with TFA led to the desired aminobenzylnaphthol trifluoroacetate **12**. The *ortho*-functionalized Betti base derivative **12** readily decomposes; for this reason, it was used as the trifluoroacetate in the further transformations.

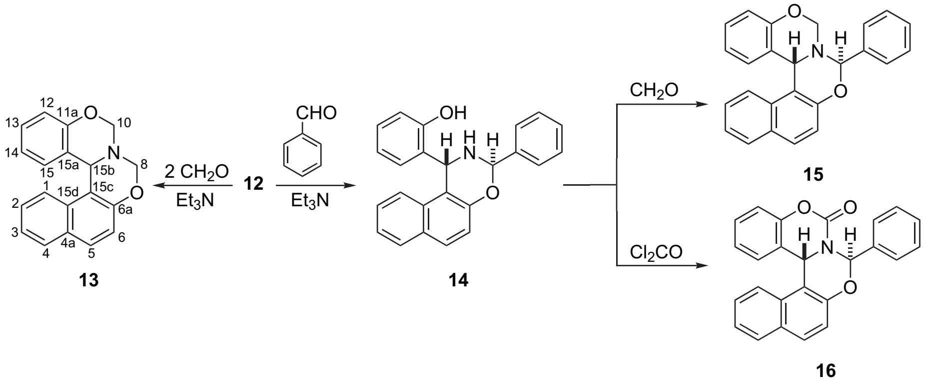
The ring-closure reaction of **12** with 2 equiv of formaldehyde led to the parent naphth[1′,2′:5,6][1,3]oxazino[3,4-*c*][1,3]benzoxazine **13** (cf. Scheme 4). For substitution of the ring system at positions 8 and 10, the aminonaphthol derivative **12** was first treated with an equivalent amount of benzaldehyde. Naphthoxazine **14** was then reacted with formaldehyde or phosgene and yielded the desired 8-phenylnaphth[1′,2′:5,6][1,3]oxazino[3,4-*c*][1,3]benzoxazine **15** and 8-phenylnaphth[1′,2′:5,6][1,3]oxazino[3,4-*c*][1,3]benzoxazin-10-one **16**, respectively (cf. Scheme 4). NMR measurements indicated that the naphthoxazinobenzoxazine derivatives **15** and **16** were obtained with practically full stereoselectivity; relative configurations are depicted in Scheme 4.



Scheme 2.



Scheme 3.



Scheme 4.

2.2. Conformational analysis

^{1}H/^{13}C NMR study of the analogous compounds **13–16**, corroborated by the results of parallel ab initio quantum chemical calculations, revealed that the naphtho-bound (unsaturated) oxazine ring prefers the 7,15b-*twisted-chair* conformation. Similarly, the corresponding benzo-bound (unsaturated) oxazine ring in **13** and **15** prefers the 11,15b-*twisted-chair* conformation. Ab initio calculations of all different configurations and their corresponding conformations led to local minima, but they were drastically higher in energy than the global energy minimum structures of **13–16** (for **13**, see Fig. 1).

In the preferred conformation, the C-15a–C-15b bond is trans to the nitrogen lone pair. In the unsubstituted derivative **13**, this conformation is proved by the NMR results: it is the only one with the possibility of ‘W’ coupling ($^4J_{\mathrm{H,H}}$) between H-15b and H-8$_{\mathrm{eq}}$, which is confirmed experimentally. The NOE enhancements given in Table 1 corroborate the present 9*S**,15b*R** configuration.

For the 8-phenyl-substituted analogue **15**, a similar global energy minimum structure was calculated. The additional phenyl substituent in position 8 is found in the *equatorial* position, as proved by NMR spectroscopy: only in this conformation is ‘W’ coupling possible but this time two ‘W’ couplings ($^4J_{\mathrm{C,H}}$, C-15c–H-10$_{\mathrm{eq}}$; *i*-C$_{\mathrm{Ph}}$–H-15b) were found in the HMBC NMR spectra. Table 1 gives the relevant

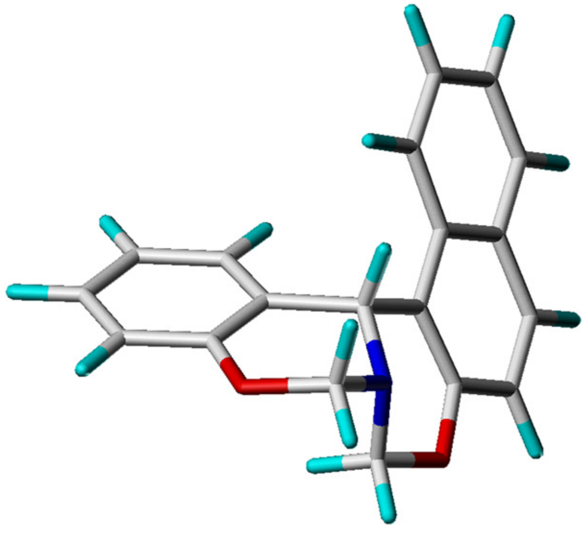


Figure 1. Global energy minimum structure of (9*S**,15b*R**)-**13**.

Table 1. Calculated distances and observed NOEs in compounds **9**, **13** and **15**

Compound	Protons studied	Distances calculated	NOEs found (+) or not detected (−)
13	H-15b···H-8$_{\mathrm{eq}}$	4.094	−
	H-15b···H-8$_{\mathrm{ax}}$	3.681	−
	H-15b···H-10$_{\mathrm{ax}}$	2.345	+
	H-15b···H-10$_{\mathrm{eq}}$	3.573	−
15	H-10$_{\mathrm{eq}}$···H-8	3.215	+
	H-10$_{\mathrm{ax}}$···H-8	3.825	−
	H-15b···H-10$_{\mathrm{ax}}$	2.304	+
	H-15b···H-10$_{\mathrm{eq}}$	3.676	−
9	H-7a···H-15$_{\mathrm{ax}}$	2.624	+
	H-7a···H-15$_{\mathrm{eq}}$	3.668	−
	H-13$_{\mathrm{ax}}$···H-15$_{\mathrm{ax}}$	3.931	−
	H-13$_{\mathrm{eq}}$···H-15$_{\mathrm{ax}}$	3.465	−
	H-13$_{\mathrm{ax}}$···H-15$_{\mathrm{eq}}$	3.035	+
	H-13$_{\mathrm{eq}}$···H-15$_{\mathrm{eq}}$	2.248	+

calculated distances and observed NOEs, which confirm the calculated 8*S**,9*S**,15b*R** structure of **15**.

In the carbonyl analogue **16**, two configurations (*R***S** and *R***R**) as energy minima structures were found from the ab initio calculations, differing in energy by 5.27 kcal/mol (22.06 kJ/mol). Crucial 'W' couplings are not possible in either configuration, and were not observed. In the more stable configuration (*R***S**), the rotation of the phenyl substituent is unhindered (cf. Fig. 2); in the corresponding *R***R** configuration, however, strong hindrance of this rotation by the adjacent carbonyl group is expected. A variable-temperature NMR study gave no exchange phenomena. The suggested *R***S** configuration of **16** could finally be characterized by the trans position of H-15b and H-8 with a distance of 4.007 Å in the calculated global energy minimum structure. In the corresponding isomer (*R***R**)-**16** these protons are cis-positioned, the distance is only 3.131 Å, and the corresponding NOE between these protons could not be observed. Thus, it could be concluded that **16** exists in the *R***S** configuration; the benzo-bound oxazine ring prefers an 11,15b *boat* conformation (cf. Fig. 2).

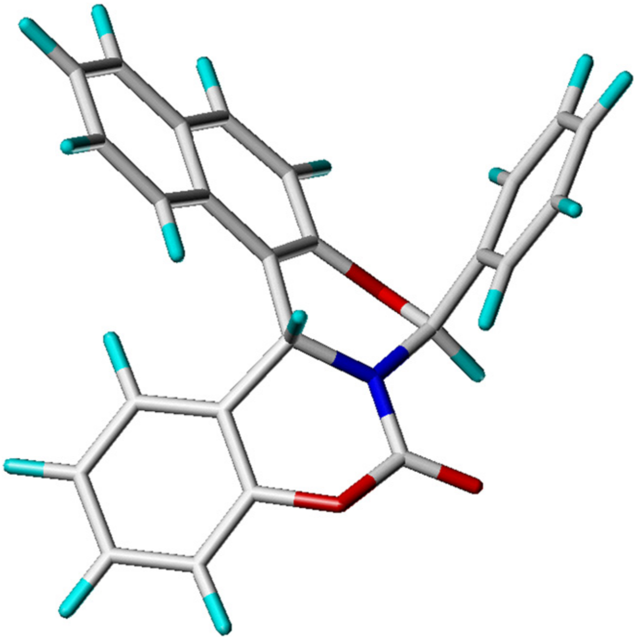


Figure 2. Global energy minimum structure of (8*S**,15b*R**)-**16**.

In the naphth[1′,2′:5,6]-[1,3]oxazino[3,2-*c*][1,3]benzoxazine derivatives **3–6** and **9**, the naphtho-bound oxazine ring was found to have a 7,15-*twisted-chair* conformation; with the exception of **6** the corresponding benzo-bound oxazine ring has a 7a,12-*twisted-chair* conformation. The ab initio calculated global energy minimum structure of **9** is depicted in Figure 3. The existence of this stereochemistry in **9** is unequivocally corroborated by the NMR spatial information (the NOEs found are given in Table 1). An assumed nitrogen inversion could not be confirmed; variable-temperature NMR measurements down to −100 °C did not reveal any dynamic effects.

The ab initio calculations on **3** led to the global energy minimum structure with the phenyl substituent in an *axial* position. This is proved by the NOEs between H-15 and H-13, similar to the spatial information in the previous structure: only an *equatorial* H-15 is close enough to the two H-13 atoms to furnish the NOE obtained. Thus, this compound can be described as (7a*R**,14*S**,15*S**)-**3**.

The corresponding ab initio calculations on **4** and **5** yielded the same result: the phenyl substituent prefers the *axial* conformation. The alkyl substituents on the oxazine ring moiety, however, were *equatorial*. These methyl and ethyl conformations are corroborated by the corresponding NOEs between H-15 and these alkyl substituents (cf. Fig. 4).

Finally, in the global energy minimum structure of **6**, the phenyl substituent on C-15 was found to be *axial* (as in **4** and **5**). The *equatorial* position of the phenyl would lead to strong steric hindrance with the nearby carbonyl group. In this structure, the benzo-bound oxazine ring is nearly planar and involves almost planar nitrogen atom bonding. Supporting information from NMR spectroscopy, such as stereospecific couplings or characteristic NOEs, could not be obtained for **6** because of the strong overlapping of the relevant proton absorptions.

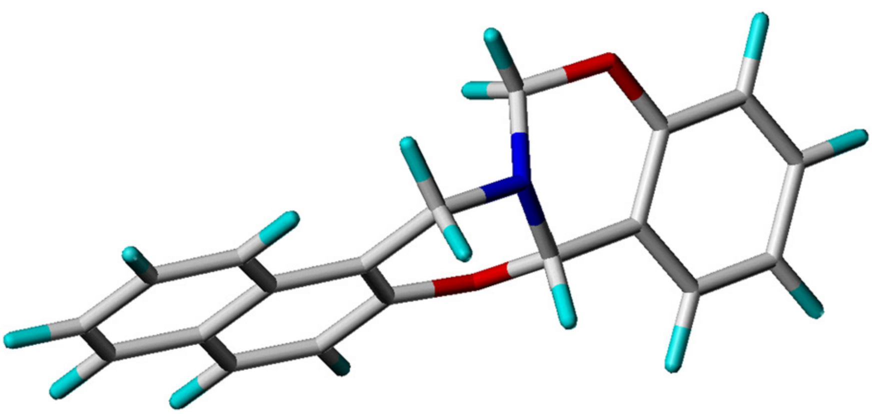


Figure 3. Global energy minimum structure of (7a*S**,14*R**)-**9**.

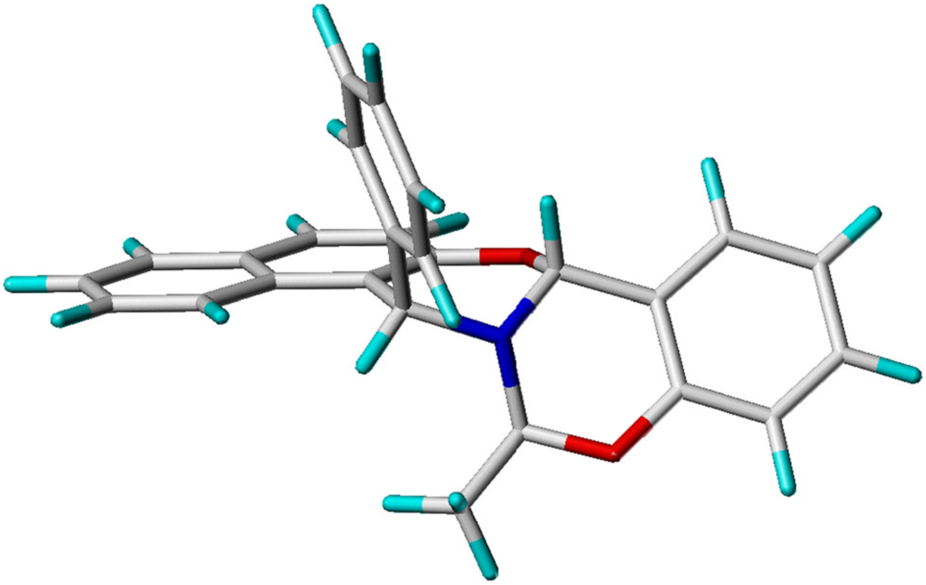


Figure 4. Global energy minimum structure of (7a*S**,13*R**,14*S**,15*S**)-**4**.

2.3. Anisotropic and steric effects

The most striking difference between the structures of the two series of compounds is the relative position of the annelated naphthalene and benzene rings. Both rings have strong ring current effects, which should mainly influence the chemical shift differences of the aromatic protons in the two series of compounds. The chemical shifts of the relevant protons are given in Table 2 together with the values calculated theoretically (i) by our method of examining only the ring current effects[14] of the aromatic moieties in the two series of compounds, and (ii) by exclusive GIAO[15] calculations.

Comparison of the experimental and theoretically calculated chemical shift differences between the relevant protons (e.g., H-15 in **13** with H-9 in **9**, etc.—cf. Table 2) demonstrates excellent agreement in both direction (high- or low-field) and amount; thus, the ^{1}H NMR spectra of corresponding compounds in the two series are correctly described by the ab initio calculations.

The coincidence between the experimental chemical shift differences and the calculated ones resulting from the present anisotropic ring current effects of both naphthyl and phenyl(s) in the corresponding molecules exclusively is less satisfactory. The sign of the differences (ring current effect influences to high- or low-field) is correct, but the values calculated in this way for the ring current effects are generally too large. Other effects on ^{1}H chemical shifts must therefore be responsible, and this was studied by a critical NBO/NCS analysis of both orbital occupations and partitions to chemical shifts (vide infra). Nevertheless, a number of conformationally relevant conclusions can be drawn.

In all three analogues examined with respect to ^{1}H chemical shift differences, δ(H-15) in series 1 is strongly high-field shifted with respect to H-8 in series 2 (cf. Figs. 1 and 3). As the reason, therefore, the ring current effect of the naphthyl moiety can readily be identified (strongly shielding H-15 in **13** with respect to the δ value of H-8 in **9**). Instead, the second proton examined, H-1 in the naphthalene moieties, is found to be low-field shifted in series 1 with respect to the position in the analogues of series 2. Both the experimental and the ring current effect on the ^{1}H chemical shifts, however, differ in size, though the direction is correctly illustrated. This is interesting, because the influence of the ring current effects on the ^{1}H chemical shifts during the stereochemical analysis usually proves to be perfect.[16] Only if strong steric hindrance is present can the ring current effect alone not explain the chemical shift differences.[14] In the pair **13–9**, for instance, the anisotropic ring current effect of the phenyl ring on H-1 is nearly zero; H-1 in **13** is positioned at the border between the high- and low-field ring current effects, as depicted in Figure 5.

Table 2. Experimental and calculated differences in chemical shift (δ) of selected pairs of protons in the two series of compounds studied

Compounds	H atoms	$\Delta\delta_{exp}$/ppm	$\Delta\delta_{calc}$/ppm (ring current effects)	$\Delta\delta_{calc}$/ppm (GIAO)	$\Delta\delta_{calc}$/ppm (total substituent effect of naphthyl/phenyl)
13–9	15–8	−0.45	−0.95	−0.28	−0.67
	1–1	+0.26	+0.04	+0.37	+0.09
15–3	15–8	−0.32	−0.72	−0.15	—
	1–1	+0.58	+0.51	+0.53	—
16–6	15–8	−1.0	−1.58	−0.81	−1.33
	1–1	+0.04	+0.81	−0.04	+0.20

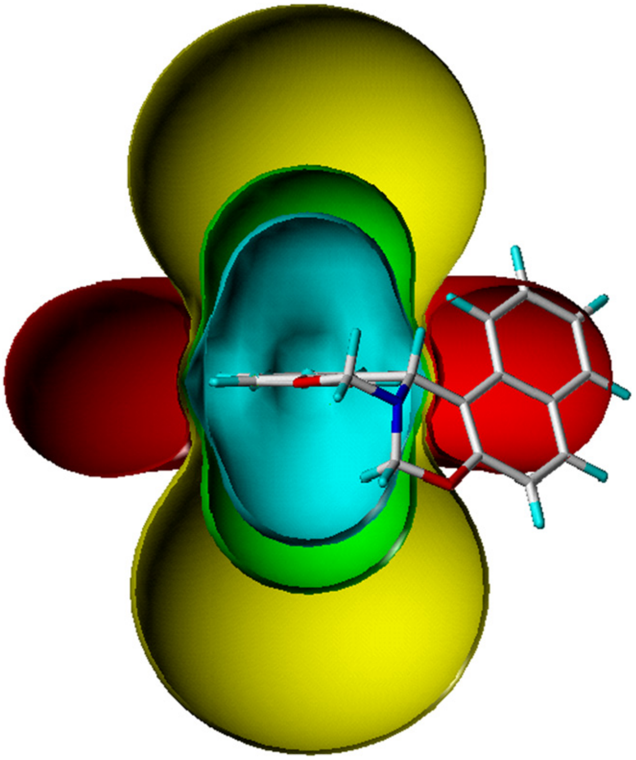


Figure 5. Ring current effect of the phenyl ring in **13**.

In order to examine the presence of steric hindrance, partially covering the ring current effect, a critical NBO/NCS analysis of the steric hindrance differences between the corresponding derivatives in the two series of compounds was performed. The results are included in Table 2; the total partitions of naphthyl/phenyl to the chemical shifts of H-15/H-8 and H-1/H-1 in **13–9** and **16–6** were examined (the effects were not studied in the comparison of **15** and **13** because of the additional phenyl substituent on C-8). These partitions summarize the overall substituent effects of the naphthyl/phenyl moieties on the corresponding ^{1}H chemical shifts (including ring current effect partitions) and are found to be in much better accordance with both the experimental and the GIAO-calculated ^{1}H chemical shifts, corroborating the correct estimations. The differences between the ring current effect and the partitions of the overall naphthyl/phenyl ring systems originate from other substituent effects, steric hindrance, and the differences between the total substituent effects and the experimental/GIAO-calculated ^{1}H chemical shifts originate from the rest of the molecules.

The present study corroborates the importance of both anisotropic ring current effects and steric effects of nearby structural moieties in determining ^{1}H chemical shift differences of otherwise similar organic compounds.

3. Experimental

3.1. General

Melting points were determined on a Kofler micro melting apparatus and are uncorrected. Merck Kieselgel $60F_{254}$ plates were used for TLC.

The NMR spectra were recorded in $CDCl_3$ (unless specified as DMSO-d_6) solution in 5 mm tubes, at room temperature, on a BRUKER AVANCE 500 spectrometer at 500.17 (^{1}H) and 125.78 (^{13}C) MHz, with the deuterium signal of the solvent as the lock and TMS as the internal standard for ^{1}H or the solvent as the internal standard for ^{13}C. All spectra (^{1}H, ^{13}C, *gs*-H,H-COSY, *gs*-HMQC, *gs*-1D-HMQC, *gs*-HMBC and NOESY) were acquired and processed with the standard BRUKER software.

Geometry optimizations were performed without restrictions, using the Gaussian 03[17] program package. Density functional theory calculations were carried out at the B3LYP/6-31G**[18,19] level of theory. Different starting conformations were created and the results were analyzed and displayed by using the molecular modelling program SYBYL7.0.[20] Different local energy minima conformations were selected to analyze the relative stability and the geometrical parameter.

The ring current effects were calculated with the GIAO method at the HF/6-31G* level of theory, based on the calculation of NICS.[21] The studied molecules were placed at the centre of a grid ranging from −10 to 10 Å (step width 0.5 Å), resulting in a cube with 68921 lattice points. At these lattice points the magnetic shielding was calculated, and the values were transformed into SYBYL[20] contour files and displayed.

The anisotropy values in Table 2 result from NICS calculations. The ring current effects of all aromatic moieties at the positions of the studied atoms were added. Table 2 contains the differences in these values of the corresponding atoms in these pairs of molecules. Chemical shifts were calculated at the B3LYP/6-31G** level of theory, using the GIAO method.

Various platforms were used for the calculations, e.g., SGI Octane, SGI Origin workstations or Linux cluster.

Compounds **1**,[3] **2**,[11] **3**,[11] **4**,[11] **7**[3] and **8**[11] were prepared according to procedures known in the literature.

During our investigations, the assignments of the chemical shifts of **3** and **4**, which were given in Ref. 11, had to be revised. For this reason, both assignments are given, with the values obtained above. *Compound **3***: ^{1}H NMR δ 7.76 (m, 2H, H-4 and H-5), 7.32 (m, 10H, H-1, H-2, H-3, H-8, H-10 and Ph), 7.13 (d, J=8.9 Hz, 1H, H-6), 6.97 (m, 2H, H-9 and H-11), 5.61 (s, 1H, H-7a), 5.53 (s, 1H, H-15), 4.96 (d, J=−7.1 Hz, 1H, H-13) and 4.92 (d, J=−7.1 Hz, 1H, H-13); ^{13}C NMR δ 153.1 (C-11a), 150.5 (C-6a), 141.3 (*i*-Ph), 131.8 (C-15b), 130.6 (C-10), 129.7 (C-5), 129.2 (*o*-Ph), 129.0 (2C, C-4a, C-8), 128.6 (C-4), 128.4 (*m*-Ph), 127.7 (*p*-Ph or C-2), 126.8 (C-2 or *p*-Ph), 123.5 (C-3 or C-1), 122.6 (C-1 or C-3), 121.1 (C-9), 120.1 (C-7b), 119.9 (C-11), 118.9 (C-6), 111.1 (C-15a), 78.5 (C-7a, $^1J_{C,H}$=167.4 Hz), 77.7 (C-13, $^1J_{C,H}$=158.6, 155.1 Hz) and 57.7 (C-15, $^1J_{C,H}$=136.2 Hz). *Compound **4***: ^{1}H NMR δ 7.79 (d, J=7.4 Hz, 1H, H-4), 7.76 (d, J=9.0 Hz, 1H, H-5), 7.41 (d, J=7.8 Hz, 1H, H-1), 7.34 (m, 2H, H-2 and H-3), 7.28 (m, 7H, H-8, H-10 and Ph), 7.12 (d, J=8.9 Hz, 1H, H-6), 6.95 (dt, J=7.5, 0.9 Hz, 1H, H-9), 6.91 (d, J=8.0 Hz, 1H, H-11), 5.84 (s, 1H, H-15), 5.64 (s, 1H, H-7a), 5.10 (q, $J=5.5$ Hz, 1H, H-13) and 1.73 (d, $J=5.6$ Hz, 3H, Me); ^{13}C NMR δ 153.5 (C-11a), 151.2 (C-6a), 141.6 (*i*-Ph), 131.8 (C-15b), 130.4 (C-10), 129.7 (C-5), 129.2 (*o*-Ph), 128.9 (C-4a), 128.7 (2C, C-4, C-8), 128.4 (*m*-Ph), 127.5 (*p*-Ph), 127.0 (C-2), 123.5 (C-3), 122.1 (C-1), 120.8 (C-9), 120.0 (C-7b), 118.9 (C-6), 116.6 (C-11), 110.7 (C-15a), 80.9 (C-13, $^{1}J_{C,H}=155.8$ Hz), 79.2 (C-7a, $^{1}J_{C,H}=166.9$ Hz), 54.4 (C-15, $^{1}J_{C,H}=137.2$ Hz) and 19.6 (Me).

3.1.1. (7a*R,13*R**,15*S**)-13-Ethyl-15-phenylnaphth[1′,2′:5,6][1,3]oxazino[3,2-*c*][1,3]benzoxazine (5).** A mixture of compound **2** (0.50 g, 1.41 mmol) and propionaldehyde (0.13 g, 2.12 mmol) was stirred in $CHCl_3$ (25 mL) at room temperature until the TLC revealed no more starting material (20 h). The solvent was then removed under reduced pressure (the NMR spectra of the crude product showed no minor diastereomers) and the residue was crystallized from *n*-hexane–Et_2O (2:1), and recrystallized from *n*-hexane–*i*-Pr_2O (1:1). Yield: 0.41 g (74%). Mp 229–231 °C. ^{1}H NMR δ 7.79 (d, $J=7.6$ Hz, 1H, H-4), 7.78 (d, $J=9.0$ Hz, 1H, H-5), 7.44 (d, $J=8.2$ Hz, 1H, H-1), 7.35 (m, 2H, H-2 and H-3), 7.29 (m, 7H, H-8, H-10 and Ph), 7.12 (d, $J=8.9$ Hz, 1H, H-6), 6.95 (t, $J=7.5$ Hz, 1H, H-9), 6.93 (d, $J=8.4$ Hz, 1H, H-11), 5.86 (s, 1H, H-15), 5.65 (s, 1H, H-7a), 4.91 (t, $J=5.0$ Hz, 1H, H-13), 2.03 (m, 2H, CH_2) and 1.21 (t, $J=7.3$ Hz, 3H, Me); ^{13}C NMR δ 153.6 (C-11a), 151.2 (C-6a), 141.6 (*i*-Ph), 131.9 (C-15b), 130.4 (C-10), 129.7 (C-5), 129.2 (2C, *o*-Ph), 128.8 (C-4a), 128.7 (2C, C-4 and C-8), 128.4 (2C, *m*-Ph), 127.5 (*p*-Ph or C-3), 127.0 (C-2), 123.5 (C-3 or *p*-Ph), 122.0 (C-1), 120.7 (C-9), 119.9 (C-7b), 118.9 (C-6), 116.6 (C-11), 110.9 (C-15a), 84.3 (C-13, $^{1}J_{C,H}=155.5$ Hz), 79.6 (C-7a, $^{1}J_{C,H}=167.3$ Hz), 53.9 (C-15, $^{1}J_{C,H}=137.3$ Hz), 25.2 (CH_2) and 8.0 (Me). Anal. Calcd for $C_{27}H_{23}NO_2$: C, 82.42; H, 5.89; N, 3.56. Found: C, 83.03; H, 5.92; N, 3.62.

3.1.2. (7a*R,15*S**)-15-Phenylnaphth[1′,2′:5,6][1,3]oxazino[3,2-*c*][1,3]benzoxazin-13-one (6).** Naphthoxazine **2** (0.40 g, 1.13 mmol) was suspended in toluene–H_2O (20:20 mL), and Et_3N (0.25 g, 2.5 mmol) and phosgene (2.2 mL; 20% in toluene, 2.26 mmol) were added. The mixture was stirred at room temperature for 15 h, and EtOAc (40 mL) and H_2O (40 mL) were then added. The organic layer was separated, dried (Na_2SO_4) and evaporated. The oily residue crystallized on treatment with *n*-hexane (20 mL). The crystalline product was filtered off and recrystallized from *n*-hexane–*i*-Pr_2O (1:1). Yield: 0.28 g (65%). Mp 256–259 °C. ^{1}H NMR δ 7.79 (m, 2H, H-4 and H-5), 7.44 (m, 5H, H-1, H-8, H-10 and *o*-Ph), 7.33 (m, 5H, H-2, H-3, *m*- and *p*-Ph), 7.28 (s, 1H, H-15), 7.23 (t, $J=7.5$ Hz, 1H, H-9), 7.14 (d, $J=9.0$ Hz, 1H, H-6), 7.13 (d, $J=8.0$ Hz, 1H, H-11) and 6.25 (s, 1H, H-7a); ^{13}C NMR δ 151.0 (C-6a), 149.2 (C-11a), 148.3 (C-13), 140.0 (*i*-Ph), 131.5 (C-10), 131.2 (C-15b), 130.2 (C-5), 129.5 (C-4a), 128.9 (4C, *o*- and *m*-Ph), 128.6 (2C, C-4 and *p*-Ph), 127.8 (C-8), 127.1 (C-2), 124.7 (C-9), 124.2 (C-3), 123.4 (C-1), 118.2 (C-6), 116.4 (C-11), 115.1 (C-7b), 112.1 (C-15a), 76.7 (C-7a, $^{1}J_{C,H}=167.2$ Hz) and 54.8 (C-15, $^{1}J_{C,H}=144.0$ Hz). Anal. Calcd for $C_{25}H_{17}NO_3$: C, 79.14; H, 4.52; N, 3.69. Found: C, 79.85; H, 4.61; N, 3.65.

3.1.3. Naphth[1′,2′:5,6][1,3]oxazino[3,2-*c*][1,3]benzoxazine (9). To a solution of **8** (0.4 g, 1.44 mmol) in $CHCl_3$ (30 mL), 40% aqueous formaldehyde (0.5 mL) was added. The mixture was stirred at room temperature for 4 h, during which the TLC revealed no more starting material. The solvent was evaporated off at reduced pressure, and the residue was crystallized with *n*-hexane and recrystallized from *n*-hexane–*i*-Pr_2O (3:1). Yield: 0.30 g (72%). Mp 176–177 °C. ^{1}H NMR δ 7.78 (d, $J=8.1$ Hz, 1H, H-4), 7.67 (d, $J=8.9$ Hz, 1H, H-5), 7.62 (d, $J=8.4$ Hz, 1H, H-1), 7.51 (t, $J=7.6$ Hz, 1H, H-2), 7.42 (d, $J=7.2$ Hz, 1H, H-8), 7.38 (t, $J=7.2$ Hz, 1H, H-3), 7.32 (t, $J=7.9$ Hz, 1H, H-10), 7.08 (d, $J=8.9$ Hz, 1H, H-6), 7.04 (t, $J=7.4$ Hz, 1H, H-9), 6.96 (d, $J=8.2$ Hz, 1H, H-11), 5.78 (s, 1H, H-7a), 5.05 (d, $J=-7.2$ Hz, 1H, H-13), 4.85 (d, $J=-17.2$ Hz, 1H, H-15$_{ax}$), 4.73 (d, $J=-7.2$ Hz, 1H, H-13) and 4.29 (d, $J=-17.2$ Hz, 1H, H-15$_{eq}$); ^{13}C NMR δ 153.2 (C-11a), 150.2 (C-6a), 130.9 (C-15b), 130.6 (C-10), 129.0 (C-4a), 128.7 (2C, C-4 and C-8), 128.6 (C-5), 126.8 (C-2), 123.8 (C-3), 121.2 (C-9), 120.9 (C-1), 119.9 (C-7b), 118.8 (C-6), 116.9 (C-11), 111.0 (C-15a), 82.5 (C-7a, $^{1}J_{C,H}=165.4$ Hz), 77.5 (C-13, $^{1}J_{C,H}=158.6$, 155.5 Hz) and 45.6 (C-15, $^{1}J_{C,H(eq)}=136.0$ Hz, $^{1}J_{C,H(ax)}=141.5$ Hz). Anal. Calcd for $C_{19}H_{15}NO_2$: C, 78.87; H, 5.23; N, 4.84. Found: C, 78.76; H, 5.26; N, 4.86.

3.1.4. 1,3-Di(2-hydroxyphenyl)-2,3-dihydro-1*H*-naphth[1,2-*c*][1,3]oxazine (11). To a solution of 2-naphthol (**10**, 5.77 g, 40 mmol) in MeOH (80 mL) was added the appropriate aromatic salicylaldehyde (9.76 g, 80 mmol) and 20% methanolic ammonia solution (10 mL). The mixture was left to stand at ambient temperature for two days, during which a yellow crystalline product (**11**) separated out. The crystals were filtered off and washed with cold MeOH (2×40 mL). Yield: 8.8 g (60%). Mp 138–141 °C. The NMR spectra showed a mixture of ring (r) and chain (c) tautomers with an approximate ratio of 0.25:1. ^{1}H NMR (DMSO-d_6): δ 10.26 (br), 8.80 (s, 1H, N=CH[c]), 8.03 (d, $J=7.3$ Hz, 1H), 7.93 (m, 2.5H), 6.66–7.48 (m), 5.97 (s, 0.5H, H-1r and H-3r) and 4.52 (s, 1.25H, OH/NH); ^{13}C NMR (DMSO-d_6): δ 163.5 (N=CH), 160.9, 160.6, 155.3, 154.8, 154.0, 136.7, 132.9, 132.4, 132.2, 130.8, 130.3, 129.7, 129.5, 128.9, 128.7, 128.6, 128.5, 127.4, 126.6, 126.2, 123.6, 123.3, 122.6, 122.4, 119.7, 119.4, 119.2, 119.0, 118.7, 117.9, 117.4, 116.9, 115.6, 78.8 (C-3r), 64.2 (CH–N[c]) and 48.5 (C-1r). Anal. Calcd for $C_{24}H_{19}NO_3$: C, 78.03; H, 5.18; N, 3.79. Found: C, 77.96; H, 5.21; N, 3.81.

3.1.5. 1-α-Amino(2-hydroxyphenyl)methyl-2-naphthol trifluoroacetate (12). Naphthoxazine **11** (5 g, 10.8 mmol) was suspended in MeOH (60 mL), and H_2O (60 mL) and TFA (10 mL) were added. The mixture was stirred at 80 °C for 5 h. The solvents were evaporated off and the residue was crystallized from EtOAc. Yield: 3.84 g (93%). Mp 176–179 °C. ^{1}H NMR δ 11.04, 10.55, 8.51 (3br s, 5H, OH, NH), 7.94 (d, $J=8.6$ Hz, 1H, H-8), 7.87 (d, $J=8.9$ Hz, 1H, H-4), 7.85 (d, $J=8.3$ Hz, 1H, H-5), 7.48 (dt, $J=7.6$, 1.3 Hz, H-7), 7.32 (m, 3H, H-3, H-6 and H-6′), 7.17 (dt, $J=7.7$, 1.6 Hz, H-4′), 6.95 (dd, $J=8.1$, 0.9 Hz, H-3′), 6.75 (dt, $J=7.5$, 1.0 Hz, H-5′) and 6.38 (s, 1H, Ar-CH); ^{13}C NMR δ 158.0 (q, $^{2}J_{C,F}=31.0$ Hz, COOH), 154.8 (C-2′), 153.6 (C-2), 131.9 (C-8a), 130.4 (C-4), 129.7 (C-4′), 129.0 (C-6′), 128.6 (C-5), 128.1 (C-4a), 127.1 (C-7), 123.0 (C-6), 122.9 (C-1′), 121.7 (C-8), 119.0 (C-5′), 118.6 (C-3), 117.3 (q, $^1J_{C,F}$=300.2 Hz, CF_3), 115.4 (C-3′), 113.5 (C-1) and 46.6 (CH–NH_2). Anal. Calcd for $C_{19}H_{16}F_3NO_4$: C, 60.16; H, 4.25; N, 3.69. Found: C, 60.32; H, 4.28; N, 3.71.

3.1.6. Naphth[1′,2′:5,6][1,3]oxazino[3,4-*c*][1,3]benzoxazine (13).

A mixture of compound **12** (0.4 g, 1.05 mmol), Et_3N (0.12 g, 1.16 mmol) and 40% formaldehyde solution (0.18 g) in MeOH (25 mL) was stirred at room temperature for 24 h. The white precipitate that formed was filtered off and recrystallized from MeOH. Yield: 0.24 g (79%). Mp 109–112 °C. ^{1}H NMR δ 7.88 (d, *J*=8.5 Hz, 1H, H-1), 7.82 (d, *J*=8.1 Hz, 1H, H-4), 7.74 (d, *J*=8.8 Hz, 1H, H-5), 7.53 (t, *J*=8.3 Hz, 1H, H-2), 7.40 (t, *J*=7.1 Hz, 1H, H-3), 7.13 (t, *J*=7.7 Hz, 1H, H-13), 7.11 (d, *J*=8.9 Hz, 1H, H-6), 6.97 (d, *J*=7.8 Hz, 1H, H-15), 6.80 (dd, *J*=8.2, 0.8 Hz, 1H, H-12), 6.68 (t, *J*=7.7 Hz, 1H, H-14), 5.94 (s, 1H, H-15b), 5.51 (d, *J*=−10.7 Hz, 1H, H-10_{ax}), 5.14 (d, *J*=−10.7 Hz, 1H, H-10_{eq}), 5.04 (d, *J*=−7.6 Hz, 1H, H8_{ax}) and 4.97 (dd, *J*=−7.6, 1.1 Hz, 1H, H8_{eq}); ^{13}C NMR δ 151.5 (C-11a), 150.2 (C-6a), 132.7 (C-15d), 129.7 (C-5), 129.3 (C-15), 129.0 (C-4a), 128.8 (C-4 or C-13), 128.6 (C-13 or C-4), 126.9 (C-2), 123.6 (C-3), 122.8 (C-1), 122.3 (C-15a), 120.6 (C-14), 118.7 (C-6), 116.5 (C-12), 114.2 (C-15c), 80.5 (C-10, $^1J_{C,H(eq)}$=179.8 Hz, $^1J_{C,H(ax)}$=181.0 Hz), 76.9 (C-8, $^1J_{C,H(eq)}$=157.9 Hz, $^1J_{C,H(ax)}$=155.0 Hz) and 52.5 (C-15b). Anal. Calcd for $C_{19}H_{15}NO_2$: C, 78.87; H, 5.23; N, 4.84. Found: C, 78.97; H, 5.31; N, 4.79.

3.1.7. 1-(2-Hydroxyphenyl)-3-phenyl-2,3-dihydro-1*H*-naphth[1,2-*c*][1,3]oxazine (14).

A mixture of compound **12** (1 g, 2.64 mmol), Et_3N (0.3 g, 3.0 mmol) and benzaldehyde (0.28 g, 2.64 mmol) in MeOH (25 mL) was stirred at room temperature for 24 h. The white precipitate that separated out was filtered off and washed with MeOH. Yield: 0.87 g (93%). Mp 190–193 °C. ^{1}H NMR δ 7.81 (m, 2H, H-6 and H-7), 7.54 (d, *J*=6.8 Hz, 2H, H-2″), 7.40 (m, 6H, H-8, H-9, H-10, H-3″ and H-4″), 7.22 (m, 2H, H-5, H-4′), 7.03 (d, *J*=8.1 Hz, 1H, H-3′), 6.67 (t, *J*=7.7 Hz, 1H, H-5′), 6.62 (d, *J*=7.6 Hz, 1H, H-6′), 5.90 (s, 1H, H-1) and 5.81 (s, 1H, H-3); ^{13}C NMR δ 156.1 (C-2′), 151.7 (C-4a), 138.0 (C-1″), 131.8 (C-10a), 131.0 (C-6′), 129.9 (C-6), 129.5 (C-4′), 128.9 (C-4″), 128.8 (C-6a), 128.6 (3C, C-7 and C-3″), 127.2 (C-9), 125.9 (C-2″), 124.9 (C-1′), 123.8 (C-8), 122.7 (C-10), 119.8 (C-5′), 119.2 (C-5), 117.5 (C-3′), 112.6 (C-10b), 81.7 (C-3) and 52.5 (C-1). Anal. Calcd for $C_{24}H_{19}NO_2$: C, 81.56; H, 5.42; N, 3.96. Found: C, 81.72; H, 5.45; N, 3.95.

3.1.8. (8*R**,15b*S**)-8-Phenylnaphth[1′,2′:5,6][1,3]oxazino[3,4-*c*][1,3]benzoxazine (15).

To a solution of **14** (0.4 g, 1.1 mmol) in $CHCl_3$ (30 mL), 40% aqueous formaldehyde (0.5 mL) was added. The mixture was stirred at room temperature for 4 h, during which the TLC revealed no more starting material. The solvent was evaporated off at reduced pressure, and the residue was crystallized with Et_2O and recrystallized from *i*-Pr_2O (30 mL). Yield: 0.38 g (94%). Mp 216–219 °C. ^{1}H NMR δ 7.90 (d, *J*=8.4 Hz, 1H, H-1), 7.84 (d, *J*=8.0 Hz, 1H, H-4), 7.76 (d, *J*=8.9 Hz, 1H, H-5), 7.61 (m, 2H, *o*-Ph), 7.54 (t, *J*=8.2 Hz, 1H, H-2), 7.47 (m, 3H, *m*- and *p*-Ph), 7.41 (t, *J*=8.0 Hz, 1H, H-3), 7.17 (t, *J*=7.3 Hz, 1H, H-13), 7.14 (d, *J*=8.9 Hz, 1H, H-6), 7.00 (d, *J*=7.7 Hz, 1H, H-15), 6.86 (dd, *J*=8.2, 1.1 Hz, 1H, H-12), 6.72 (t, *J*=7.7 Hz, 1H, H-14), 6.13 (s, 1H, H-15b), 5.92 (s, 1H, H-8), 5.26 (d, *J*=−10.8 Hz, 1H, H-10_{ax}) and 4.61 (d, *J*=−10.8 Hz, 1H, H-10_{eq}); ^{13}C NMR δ 152.4 (C-11a), 150.9 (C-6a), 136.3 (*i*-Ph), 132.6 (C-15d), 129.9 (*p*-Ph), 129.7 (C-5), 129.2 (C-15), 129.0 (C-4a), 128.9 (C-13), 128.7 (3C, C-4 and *m*-Ph), 128.4 (*o*-Ph), 127.0 (C-2), 123.6 (C-3), 122.8 (C-1), 122.7 (C-15a), 120.6 (C-14), 118.7 (C-6), 116.4 (C-12), 113.9 (C-15c), 79.4 (C-10, $^1J_{C,H(eq)}$=164.0 Hz, $^1J_{C,H(ax)}$=160.7 Hz), 86.2 (C-8, $^1J_{C,H}$=157.2 Hz) and 54.2 (C-15b, $^1J_{C,H}$=141.4 Hz). Anal. Calcd for $C_{25}H_{19}NO_2$: C, 82.17; H, 5.24; N, 3.83. Found: C, 82.25; H, 5.26; N, 3.85.

3.1.9. (8*R**,15b*S**)-8-Phenylnaphth[1′,2′:5,6][1,3]oxazino[3,4-*c*][1,3]benzoxazin-10-one (16).

Naphthoxazine **14** (0.40 g, 1.13 mmol) was suspended in toluene–H_2O (20:20 mL), and Et_3N (0.25 g, 2.5 mmol) and phosgene (2.2 mL; 20% in toluene, 2.26 mmol) were added. The mixture was stirred at room temperature for 72 h, and EtOAc (40 mL) and H_2O (40 mL) were then added. The organic layer was separated, dried (Na_2SO_4) and evaporated. The oily residue crystallized on treatment with Et_2O (20 mL). The crystalline product was filtered off and recrystallized from *i*-Pr_2O (15 mL). Yield: 0.25 g (58%). Mp 270–272 °C. ^{1}H NMR δ 7.81 (d, *J*=7.0 Hz, 1H, H-4), 7.78 (d, *J*=9.3 Hz, 1H, H-5), 7.48 (d, *J*=7.2 Hz, 1H, H-1), 7.41 (m, 4H, H-2, H-3 and *o*-Ph), 7.29 (m, 6H, H-6, H-12, H-13, *m*- and *p*-Ph), 7.15 (s, 1H, H-8), 6.88 (t, *J*=7.0 Hz, 1H, H-14), 6.44 (d, *J*=7.8 Hz, 1H, H-15) and 6.36 (s, 1H, H-15b); ^{13}C NMR δ 152.3 (C-10), 151.7 (C-11a), 150.8 (C-6a), 136.0 (*i*-Ph), 131.1 (C-15d), 130.3 (C-5), 129.7 (C-4a), 129.3 (C-13), 128.9 (C-4), 128.8 (*m*-Ph), 128.5 (*p*-Ph), 127.1 (C-2), 126.1 (3C, C-15, *o*-Ph), 124.6 (C-3), 124.4 (C-14), 123.4 (C-15a), 122.7 (C-1), 120.2 (C-6), 116.7 (C-12), 111.8 (C-15c), 81.7 (C-8, $^1J_{C,H}$=164.4 Hz) and 48.9 (C-15b, $^1J_{C,H}$=143.4 Hz). Anal. Calcd for $C_{25}H_{17}NO_3$: C, 79.14; H, 4.52; N, 3.69. Found: C, 79.26; H, 4.55; N, 3.71.

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