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Synthesis and stereochemical studies of 1- and 2-phenyl-substituted 1,3-oxazino[4,3-*a*]isoquinoline derivatives

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Abstract—Starting from the 1′- or 2′-phenyl-substituted 1-(2′-hydroxyethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline diastereomers **3** and **6**, 4-unsubstituted and 4-(*p*-nitrophenyl)- and 4-oxo-substituted 1-phenyl- and 2-phenyl-9,10-dimethoxy-2*H*,4*H*-1,6,7,11b-tetrahydro-1,3-oxazino[4,3-*a*]isoquinolines (**7**–**12**) were prepared. The relative configurations and the predominant conformations of the products were determined by NMR spectroscopy, by quantum chemical calculations and, for (2*R**,4*S**,11b*R**)-9,10-dimethoxy-4-(*p*-nitrophenyl)-2-phenyl-2*H*,4*H*-1,6,7,11b-tetrahydro-1,3-oxazino[4,3-*a*]isoquinoline (**11**), by X-ray diffraction.

1. Introduction

In consequence of their interesting biologically active properties, widespread natural occurrence and synthetic utility, considerable interest has been demonstrated towards partially saturated isoquinolines.[1–3] Their tricyclic derivatives, containing another saturated hetero-ring annelated to positions 1,2 of tetrahydroisoquinoline (azeto[2,1-*a*]isoquinolines, benzo[*e*]indolizidines, benzo[*a*]quinolizidines and their hetero analogues), have also been studied thoroughly from chemical, stereochemical and pharmacological aspects.[4–9]

Recent systematic studies on 1-, 2- and 4-substituted saturated 1,3-oxazino[4,3-*a*]-,[10–13] 1,2,3-oxathiazino[4,3-*a*]-[14] and 1,3,2-oxazaphosphorino[4,3-*a*]isoquinolines[15,16] led to the conclusion that the heteroatoms, the substituents on the saturated rings and the configurations of the substituted carbon atoms exert pronounced effects on the conformational equilibria of these compounds. Our present aims were to investigate the influence of 1- and 2-phenylsubstitution on the conformation of 1,3-oxazino[4,3-*a*]isoquinolines, and (the corresponding effects) of substituents at position 4; accordingly, the 4-unsubstituted derivatives and the 4-(*p*-nitrophenyl) and 4-oxo analogues were prepared.

Keywords: oxazines; isoquinolines; stereochemistry; molecular modelling.
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2. Results and discussion

2.1. Syntheses

The phenyl-substituted amino alcohols **3** and **6** (1′- and 2′-phenylhomocalycotomine) were prepared similarly to their methyl analogues (1′- or 2′-methylhomocalycotomine).[14] Formaldehyde addition to 1-benzyl-6,7-dimethoxy-3,4-dihydroisoquinoline (**1**) followed by $NaBH_4$ reduction and crystallization resulted in the diastereomerically pure amino alcohol **3**. This reduction of the intermediate **2** occurred with high diastereoselectivity (*de* >95%), which can be rationalized in terms of the steric effect of the phenyl substituent directing the attack of the hydride ions (Scheme 1). The relative configuration (1*R**,1′*R**) of **3** was deduced from its ring-closed derivatives (**7**–**9**).

The 2′-phenyl-substituted amino alcohol **6** was obtained from the β-amino ketone derivative **5** by $NaBH_4$ reduction. Compound **5** was formed in good yield, analogously to its methyl derivative,[12] by addition and subsequent decarboxylation of the oxo acid, prepared in situ by hydrolysis of the corresponding ethyl benzoylacetate **4**, to 6,7-dimethoxy-3,4-dihydroisoquinoline. The reduction of the amino ketone **5** resulted in a 2:1 mixture of (1*R**,2′*R**, **6**) and its (1*R**,2′*S**) isomer, from which diastereomerically pure **6** could be obtained by fractional crystallization (Scheme 1). The diastereomeric ratio could be determined from the well-separated H-2′ lines in the ^1H NMR spectrum. The relative configuration (1*R**,2′*R**) of **6** stems from literature[17] data.

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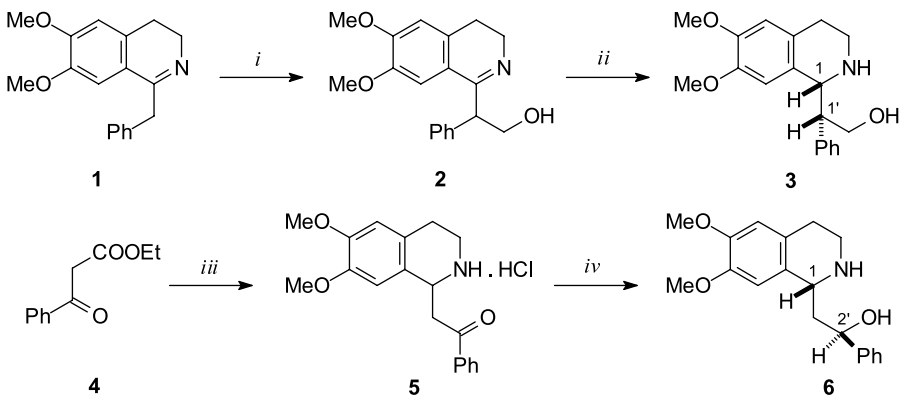


Scheme 1. *Reagents and conditions*: (i) CH_2O/NaOEt/EtOH/rt; (ii) $NaBH_4$/MeOH/0°C→rt, then crystallization; 62% (i+ii); (iii) 1. NaOH/H_2O/rt, 2. 6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride/HCl/H_2O/MeOH/rt, 74%; (iv) $NaBH_4$/MeOH/0°C→rt, then crystallization; 47%.

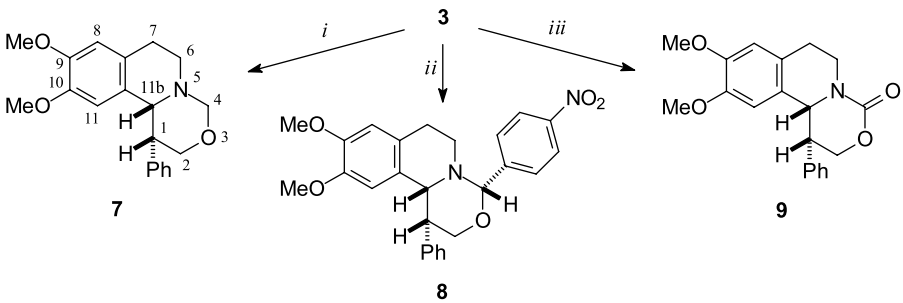
The ring-closure reaction of 1-substituted 1,2,3,4-tetrahydroisoquinoline 1,3-amino alcohols with one-carbon fragments is a common method for the synthesis of 1,3-oxazino[4,3-*a*]isoquinolines. This transformation is often applied for homocalycotomines bearing substituents in the side-chain for the purpose of determining the configuration of the substituted atoms in rigid ring-closed products.[17–20]

Treatment of amino alcohols **3** and **6** with formaldehyde gave 4-unsubstituted oxazino[4,3-*a*]isoquinolines **7** and **10** under mild conditions. The ring closures of **3** and **6** with *p*-nitrobenzaldehyde resulted in compounds **8** and **11**. In the latter reactions, the formation of C-4 epimeric pairs is possible. However, as the NMR spectra indicated, the diastereomer containing H-4 and H-11b in *cis* position was formed as the major product (*de* >99 and *de* ~95%, respectively) in both ring-closures; it could be obtained in diastereomerically pure form by crystallization.

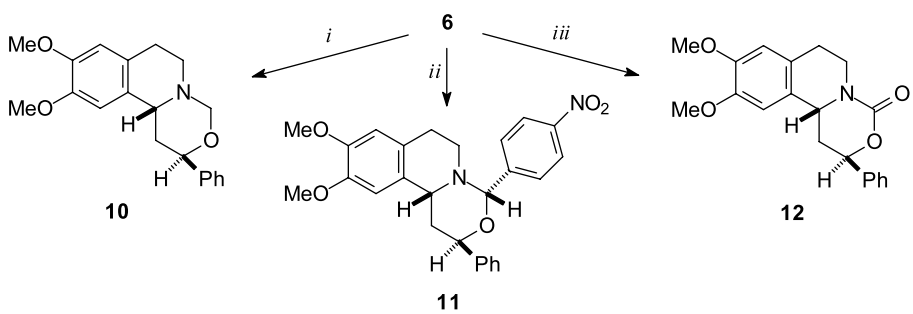
The 4-oxo derivatives **9** and **12** were synthesized in slightly different ways: the ethyl or *tert*-butyl urethanes obtained from amino alcohols **3** or **6** were treated with NaOMe or KO*t*Bu, respectively.[12,21] As the NMR data proved, the transformation **6→12** occurred without change in the configuration. Under the conditions applied in the reaction **3→9**, no cyclic product (**12**) could be obtained from **6** (Schemes 2 and 3).

2.2. NMR measurements and quantum chemical calculations

All compounds were found to have a twisted-chair conformation in the tetrahydropyridine ring and a chair (**7**, **8**, **10** and **11**) or a twisted-chair-like (**9**, **12**) conformation in the perhydrooxazine ring. The conformation of the oxazine moiety was evidenced by NOE measurements and corroborated by some ^3J(H,H) coupling constants. NOEs were observed between the axial protons or substituents:



Scheme 2. *Reagents and conditions*: (i) CH_2O/MeOH/H_2O/rt, 69%; (ii) $CHOC_6H_4NO_2$(*p*)/toluene/Δ, 72%; (iii) 1. ClCOOEt/$NaHCO_3$, 2. NaOMe/Δ, 51%.



Scheme 3. *Reagents and conditions*: (i) CH_2O//H_2O/rt, 77%; (ii) $CHOC_6H_4NO_2$(*p*)/toluene/Δ, 69%; (iii) 1. $(Boc)_2O$/EtOAc, 2. KO*t*Bu /THF/Δ, 66%.

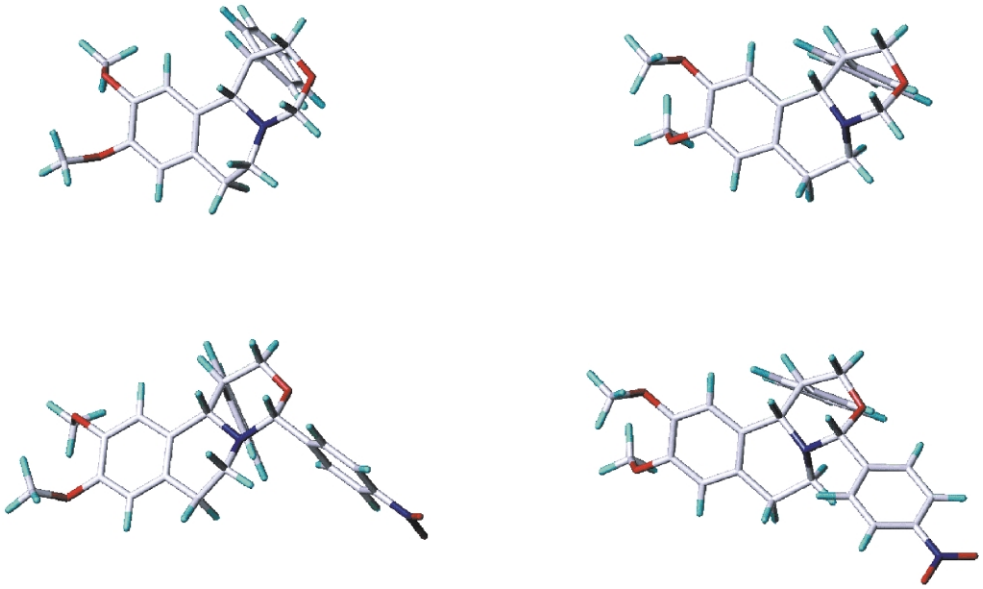


Figure 1. Calculated global energetic minimum conformations for type **A** (left) and local energetic minimum conformations (type **B**, right) for compounds **7** (ΔE=1.33 kcal/mol, top) and **8** (ΔE=0.32 kcal/mol, bottom).

H-11b$_{axial}$↔H-4$_{axial}$ (**7**, **8**, **10** and **11**); H-4$_{axial}$↔H-*o* of the 2-phenyl substituent (**10**, **11**); H-4$_{axial}$↔H-2$_{axial}$ (**8**); H-11b$_{axial}$↔H-2$_{axial}$ (**7**, **9**); H-11b$_{axial}$↔H-*o* of the 2-phenyl substituent (**10**–**12**). *Trans*-^3J(H,H) coupling constants were found between H-11b and H-1$_{ax}$ in **10** (10.9 Hz) and **11** (10.5 Hz). In compounds **9** and **12**, the oxazine ring is flatter because of the introduction of a carbonyl group at position 4. Therefore, the hybridization of C-4 is changed from sp^3 to sp^2 and the amide bond acquires a partial double bond character, while the sp^3 hybridization at the nitrogen atom is reduced. Both changes lead to higher planarity of the perhydrooxazine ring.

In compounds **7**–**12**, the tetrahydropyridine and the perhydrooxazine rings are *cis*-fused. Three types of structures (**A**–**C**) were predicted, which differ in the direction of the lone pair on the nitrogen; *anti* to O-3 for type **A** and *syn* to O-3 for type **B**, while in type **C**, the oxazine ring is flattened and C-11b, N-5, C-4 and O-3 are lying nearly planar. Structures **A** and **B** can be conceived to be convertible into each other by nitrogen inversion. Type **A** includes compounds **7** and **8**, type **B** compounds **10** and **11**, and type **C** **9** and **12**. These assignments could be made by using the NMR results (esp. NOE measurements) and accompanying quantum chemical calculations, which also gave the corresponding global energy minima (type **A** for **7** and **8**, type **B** for **10** and **11**, and type **C** for **9** and **12**, see Figs. 1–3).

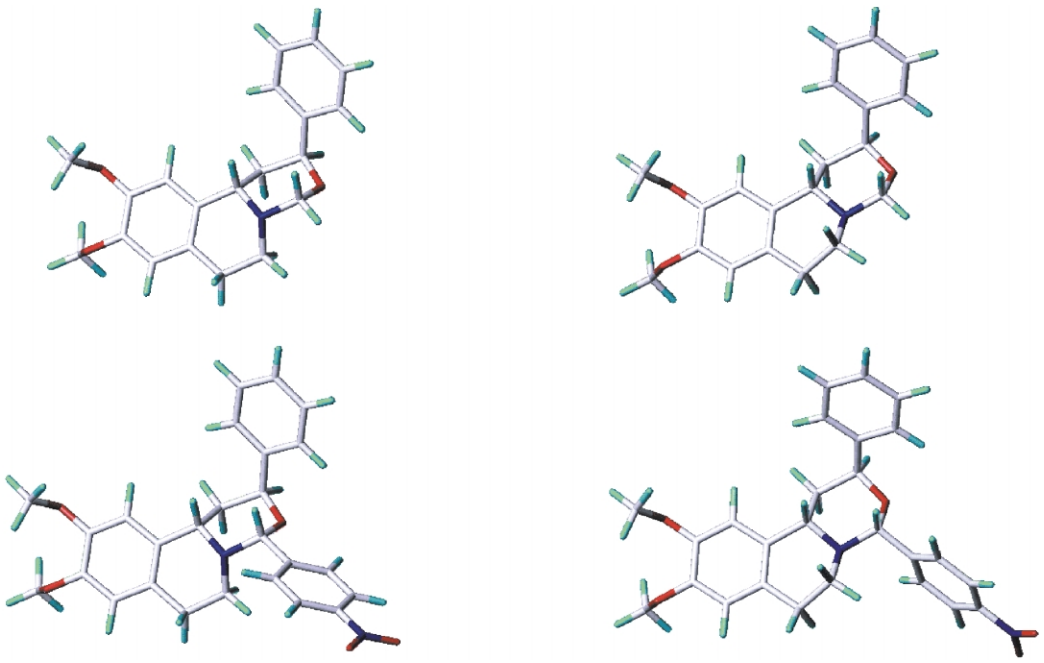


Figure 2. Calculated global energetic minimum conformations for type **B** (left) and local energetic minimum conformations (type **A**, right) for compounds **10** (ΔE=1.90 kcal/mol, top) and **11** (ΔE=2.34 kcal/mol, bottom).

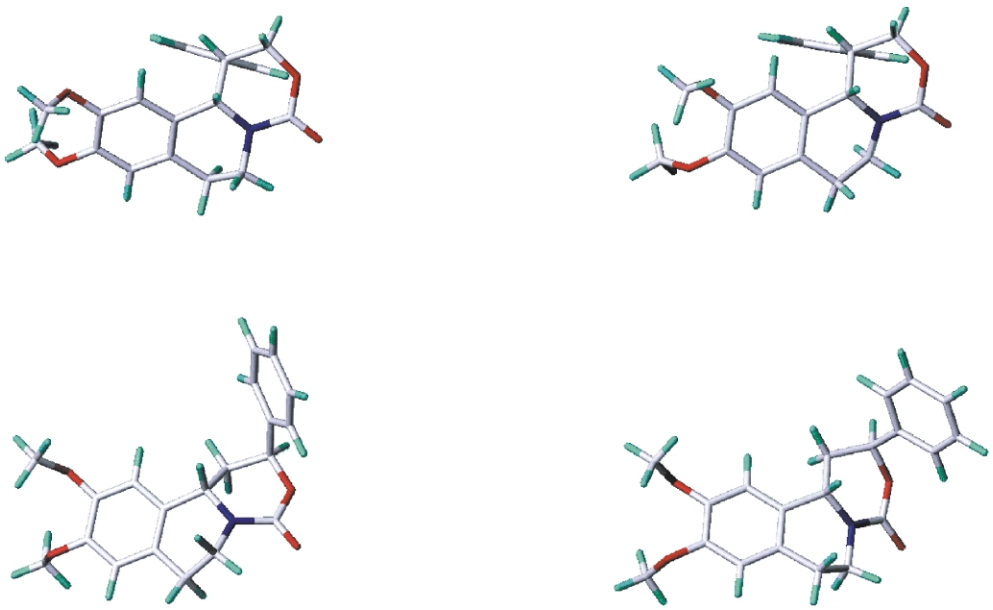


Figure 3. Calculated energetic minimum conformations for type **C** with inverted twist-chairs of the tetrahydropyridine ring (C-7 *trans* to H-11b-**Ca**, left, and C-7 *cis* to H-11b-**Cb**, right) for compounds **9** (ΔE=3.87 kcal/mol, top) and **12** (ΔE=2.13 kcal/mol, bottom).

The type **A** structure is indicated by the following NOEs (Table 1): $H6_{axial}$↔H-$11b_{axial}$ for all compounds, H-$6_{equatorial}$↔H-$4_{equatorial}$ for **7**, and H-$6_{equatorial}$↔H-2″ of the *p*-nitrophenyl substituent for **8**. Together with the NOE results (the chair conformation of the perhydrooxazine ring) and the equatorial position of H-1 (corresponding to its relatively small coupling constant $^3J_{\text{H-11b, H-1}}$ of 3.3 (**7**) and 2.4 (**8**) Hz, respectively), the relative configuration of the carbon atoms at positions 11b and 1 is proved to be R^*,R^*. In consequence of the synthetic pathway, this is also the relative configuration of the amino alcohol **3**.

Structural proof for type **B** is provided by the following NOEs, which are fully in line with the distances obtained from the accompanying MO calculations (Table 2): H-$6_{equatorial}$↔H-$4_{equatorial}$ and H-6_{axial}↔H-1_{axial} in **10**, and H-$6_{equatorial}$↔H-2″ of the *p*-nitrophenyl substituent and $H6_{axial}$↔H-1_{axial} in **11**. Additionally, reported coupling constants of a known compound of type **B** (similar to **10**), (2*R*,11b*R*)-1,6-7-11b-tetrahydro-9,10-dimethoxy-2-(4-methoxyphenyl)-2*H*-[1,3]-oxazino[4,3-*a*]-isoquinoline,[17] are very close to the measured coupling constants of **10**.

The calculations of type **C** compounds led to two different energy minima structures, **Ca** and **Cb**, which are pseudo-rotamers of the tetrahydropyridine ring (Fig. 3). The two structures differ in some proton–proton distances, and the experimentally determined structure (by NOE measurements) was found to be **Ca** (Table 3).

The phenyl substituents in position 1 (NOEs between H-$2_{equatorial}$↔H-2′ of the phenyl substituent in **7**–**9**) or position 2 (NOEs see above, **10**–**12**) always adopt the axial position, whereas the *p*-nitrophenyl substituent (position 4) in **8** and **11** is equatorially oriented.

Significant differences in ^{13}C chemical shifts can be seen for C-11b and C-4 in the isomeric pairs **7** and **10** (−10.8 and −7.6 ppm, respectively) and **8** and **11** (−9.7 and −10.4 ppm, respectively). This may be due to a strong

Table 1. Some important calculated distances for types **A** and **B** in compounds **8** and **7** (in Å) and NOEs found

Distance		H-$11b_{axial}$↔$H6_{axial}$	H-$11b_{axial}$↔$H4_{axial}$	H-$11b_{axial}$↔$H2_{axial}$	H-6_{axial}↔$H4_{axial}$
7	Type **A**	2.59	2.41	2.52	2.73
	Type **B**	3.77	2.40	2.49	3.89
8	Type **A**	2.45	2.44	2.51	2.69
	Type **B**	3.74	2.25	2.52	3.88
NOE found?		Yes	Yes	Yes	Yes

Table 2. Some important calculated distances for types **B** and **A** in compounds **10** and **11** (in Å) and NOEs found

Distance		H-$11b_{axial}$↔H-4_{axial}	H-6_{axial}↔H-1_{axial}	H-6_{axial}↔H-4_{axial}	H-$6_{equatorial}$↔H-$4_{equatorial}$
10	Type **B**	2.39	2.27	3.83	2.27
	Type **A**	2.43	4.55	2.72	2.26
11	Type **B**	2.26	2.22	3.82	–
	Type **A**	2.45	4.54	2.72	–
NOE found?		Yes	Yes	No	Yes

Table 3. Some important calculated distances for types **Ca** and **Cb** in compounds **9** and **12** (in Å) and NOEs found

Distance		H-11b$_{axial}$↔H6$_{axial}$	H-11b$_{axial}$↔H11	H-11b$_{axial}$↔H7$_{axial}$
9	Type **Ca**	3.04	2.56	4.27
	Type **Cb**	3.88	2.85	3.50
12	Type **Ca**	2.71	2.74	4.30
	Type **Cb**	3.82	3.39	2.57
NOE found?		Yes	Yes	No

γ-effect of the axial phenyl group in position 2. The isomeric pair **9** and **12** exhibit a significant difference only for C-11b, and not for C-4 (−6.7 and −0.3 ppm, respectively). This is a further explanation of the more flattened oxazine ring in the latter two compounds relative to **7**, **8**, **10** and **11**.

The differences in ^{1}H chemical shifts of H-4$_{axial}$ between **7** and **10** (+0.54 ppm) and between **8** and **11** (+0.66 ppm) may be caused by the anisotropic effect of the phenyl ring on H-4$_{axial}$ in a preferred alignment of the phenyl substituent around the C-4–C-1′ bond (torsional angle O-3–C-2–C-*i*–C-*o*=13.6°, taken from the X-ray results for **11**). Additionally, a downfield shift caused by steric compression of especially the *o*-protons of the 2-phenyl substituent to the H-4$_{axial}$ proton is possible. The preferred angle around the C-4–C-*i* bond may also explain the relatively small changes in the chemical shifts of H-11b in the pairs **7/10** and **8/11** (+0.20 and +0.11 ppm, respectively). The much bigger change for the pair **9/12** (−0.73 ppm) is caused by another preferred rotational angle around the C-4–C-1′ bond in these compounds.

The steric compression of the axial moieties in position 1 to H-6$_{axial}$ in **10** and **11** with respect to their corresponding isomers **7** and **8** also leads to a downfield shift of H-6$_{axial}$ (+1.1 and +0.85 ppm, respectively), corroborating the flatter perhydrooxazine ring; the difference of the ^{1}H chemical shift of H-6$_{axial}$ is smaller (0.07 ppm) in **7** and **12**.

Table 4. Some measured (X-ray) and calculated torsional angles (in deg.) of **11**

	N5–C6–C7–C7a	C6–N5–C11b–C1	C6–N5–C4–O3
X-Ray	48.4	−73.4	63.3
Calculated	50.1	−76.7	68.3

2.3. X-ray measurements

In the solid state, the asymmetric unit of **11** is formed from the molecule shown in Figure 4. The bond parameters are as expected and the six-membered ring C1, C2, O3, C4, N5, C11b has a slightly distorted chair conformation, as seen from the torsional angles of this ring.

The solid-state structure is in very good agreement with the calculated structure regards the pyramidality of N5 and the ring conformations obtained. Table 4 gives as some selected torsional angles, found in X-ray structure and calculated in the theoretical study in this work. It is clearly seen that **11** occurs in the **B** form both in the solid state and in solution; the same result was obtained by studying the NMR spectra of this compound and corroborated the relevant results on the other compounds studied.

The solid-state conformation of **11** is in good agreement with the NOE enhancements observed in solution. A qualitative comparison of the NOE enhancements from the NOESY spectra of **11** corroborates the stereochemistry of **11** as obtained both in the solid state and calculated in the quantum-chemical study (Table 5).

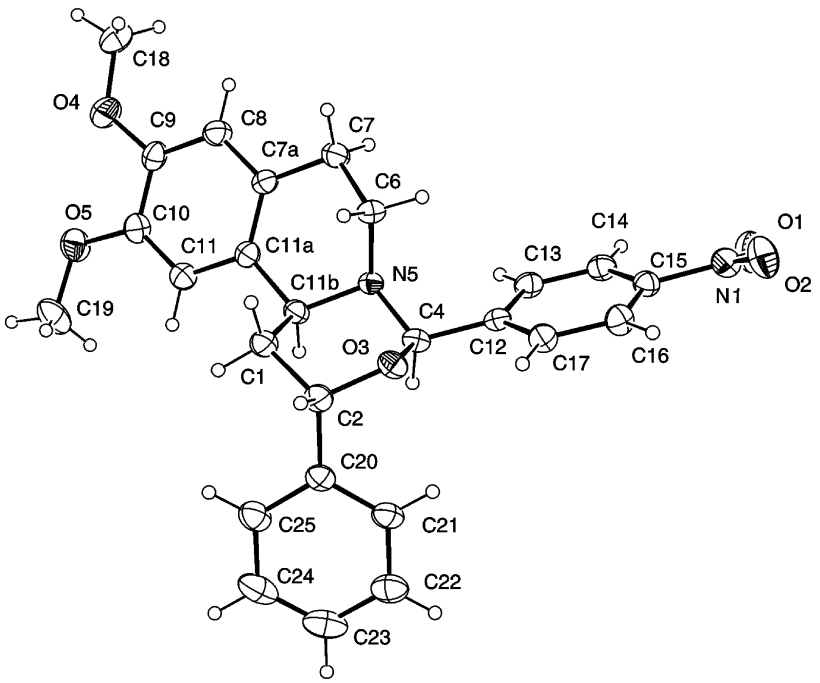


Figure 4. ORTEP perspective view of **11** showing the labelling system. Thermal ellipsoids are drawn at the 30% probability level.

Table 5. Qualitative NOE enhancements (s=strong, m=medium, w=weak) from the NOESY spectra, and the distances, extracted from the X-ray structure and ab initio calculated (both in Å), between some selected hydrogens of **11**

H positions	NOE strength	Distance (in Å)	
		By X-ray	Calculated
$6_{ax}-6_{eq}$	S	1.574	1.742
$1_{ax}-2$	M	2.214	2.318
$1_{eq}-2$		2.418	2.577
$1_{eq}-11b$	M	2.302	2.481
4–11b	M	2.306	2.264
11–11b	M	2.499	2.576
$1_{eq}-11$	W	2.632	2.576
$7_{eq}-8$	W	2.526	2.545
$7_{ax}-8$		2.868	2.995

Differences between H–H distances obtained by X-ray diffraction and calculated in ab initio calculations should essentially be due to uncertainties in determining hydrogen positions in the X-ray analysis.

2.4. Conclusions

It may be concluded that phenyl substituents significantly influence the conformation of the prepared 9,10-dimethoxy-1,6,7,11b-tetrahydro-2*H*,4*H*-1,3-oxazino[4,3-*a*]isoquinoline diastereomers. The 1-phenyl-substituted (**7**, **8**) and 2-phenyl-substituted (**10**, **11**) compounds could be characterized by different preferred conformations (**A** and **B**), while the 4-unsubstituted and 4-(*p*-nitrophenyl) derivatives proved to have the same predominant conformations. Phenyl substituents in positions 1 and 2 were axial, whereas the 4-(*p*-nitrophenyl) group both in **8** and in **11** was equatorial. An oxo group at position 4 caused a flattening of the 1,3-oxazine ring (**C**).

3. Experimental

3.1. General

Syntheses. Melting points were determined on a Kofler micro melting point apparatus and are not corrected.

NMR measurements. NMR spectra were recorded with an ARX 300 or an AVANCE DRX 400 (Bruker) spectrometer. Chemical shifts are given in δ (ppm) relative to TMS ($CDCl_3$) or TSP (D_2O) as internal standards. All of the oxazinoisoquinoline samples (**7**–**12**) were dissolved in $CDCl_3$ or, in the case of NOESY measurements, in acetone-D_6. The 2D spectra were acquired with the standard Bruker software. Typical parameters were for (i) gs-COSY-45: sweep width 2620 Hz, 1 k data points in F_2, 128 experiments in F_1 (20 scans, 4 dummy scans), relaxation delay 1.2 s; (ii) gs-HMQC: sweep width in F_1 10 kHz and in F_2 2620 Hz, 1 k data points in F_2, 128 experiments in F_1 (8 scans, 2 dummy scans), relaxation delay 1.2 s, zero filling to 2 k data points in F_2 and 256 data points in F_1, filter function square sine-bell in both dimensions. (iii) gs-HMBC: sweep width in F_1 10 kHz and in F_2 2620 Hz, 1 k data points in F_2, 128 experiments in F_1 (40 scans, 2 dummy scans), relaxation delay 1.2 s, delay for evolution of long-range couplings 50 ms, zero filling, 1 k data points in F_2 and 256 data points in F_1, filter function shifted square sine-bell in both dimensions. (iv) NOESY: sweep width 2670 Hz, 1 k data points in F_2, 128 experiments in F_1 (40 scans, 4 dummy scans), relaxation delay $\sim 5\times T_1$, mixing time $\sim T_1$. The pulse widths (90°) for all experiments were 12.5 μs (^{1}H), and 11.3 μs (^{13}C), respectively.

Quantum chemical calculations. Quantum chemical calculations were carried out using the ab initio program package GAUSSIAN 98 version A.7.[22] The different conformations of the compounds were optimized without any restrictions at the HF/6-31G* level of theory. The selected minimum energy conformations were analysed and the results were visualized with the modelling program Sybil 6.7.[23]

X-Ray diffraction studies. Data were collected on a Rigaku AFC5S diffractometer with graphite monochromated Mo K_α radiation (λ=0.71069 Å) in the $\omega-2\theta$ scan mode at room temperature. The data were corrected for Lorentz and polarization effects.

The structure was solved by direct methods (SIR92)[24] and refined by full matrix least-squares techniques (SHELXL-97)[25] to an *R*1 value of 0.055 (*wR*2=0.101). The final *R* values were based on the reflections with $I>2\sigma(I)$. The heavy atoms were refined anisotropically. The hydrogen atoms were allowed to ride on their host atoms with a fixed distance and isotropic temperature factors (1.2 or 1.5 times B_{eq} of the carrying atom). Calculations were performed with teXsan for Windows[26] crystallographic software. The figures were drawn with ORTEP-3 for Windows.[27] (The final atomic coordinates and full lists of bond lengths and angles for **11** have been deposited with the Cambridge Crystallographic Data Centre (CCDC 198906).

3.1.1. (1*R,1′*R**)-1-(2′-Hydroxy-1′-phenylethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (3).** To a solution of 1-benzyl-6,7-dimethoxy-3,4-dihydroisoquinoline (**1**, 14.1 g, 0.05 mol) in MeOH (200 mL) paraformaldehyde (3.75 g, 0.125 mol) was added. Freshly prepared ethanolic NaOEt solution was added dropwise to the stirred suspension until a homogeneous solution was obtained (about 0.5 g Na in 25 mL EtOH was needed). After stirring for 5 h at room temperature, the mixture was evaporated at <40°C in vacuo and the residue was partitioned between cold water (150 mL) and $CHCl_3$ (150 mL). The separated aqueous layer was extracted with $CHCl_3$ (2×150 mL). The combined organic phases were dried (Na_2SO_4) and evaporated at <40°C to yield crude 1-(2′-hydroxy-1′-phenylethyl)-6,7-dimethoxy-3,4-dihydroisoquinoline as a yellowish-brown oil, which was dissolved in MeOH (250 mL). The solution was stirred and cooled in an ice bath, and $NaBH_4$ (5.67 g, 0.15 mol) was added in small portions. The mixture was stirred for 3 h with cooling and for 3 h without, then evaporated, and the residue was dissolved in 5% HCl (150 mL). The solution was made alkaline with 20% NaOH under ice cooling and extracted with $CHCl_3$ (3×150 mL). The combined organic solutions were dried (Na_2SO_4) and evaporated to give crude crystalline **3** with *de* >95%. The crystals were filtered off, washed with Et_2O and recrystallized from iPr$_2$O–EtOAc to obtain diastereomerically pure **3**.

Overall yield 9.77 g (62%), mp 134–135°C. ^{1}H NMR

(400 MHz, $CDCl_3$) δ 2.46–2.65 (H-4, m, 2H), 2.81 (H-3, m, 1H), 3.08 (H-3, dt, J=12.3, 4.8 Hz, 1H), 3.46 (H-1′, m, 1H), 3.72 (MeO, s, 3H), 3.83 (MeO, s, 3H), 4.12 (H-2′, H-1, m, 2H), 4.59 (H-2′, d, J=3.8 Hz, 1H), 6.51 (H-5, H-8, s, 2H), 7.16–7.28 (Ph, m, 5H). Analysis: calculated for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47; found: C, 72.59; H, 7.23; N, 4.38.

3.1.2. 1-(2′-Oxo-2′-phenylethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (5). Ethyl 3-oxo-3-phenylpropanoate (21.1 g, 0.11 mol) was added to a solution of NaOH (4.40 g, 0.11 mol) in water (110 mL) and the mixture was left to stand at room temperature with occasional shaking for 24 h. A solution of 6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride (22.8 g, 0.10 mol) in 50% aqueous MeOH (100 mL), conc. HCl (2.5 mL) were then added and the mixture was again left to stand at room temperature with occasional shaking for 6 h. The mixture was made alkaline with 10% Na_2CO_3 solution and extracted with CH_2Cl_2 (3×100 mL). The dried (Na_2SO_4) extracts were evaporated and the oily residue was converted to the crystalline hydrochloride salt by treatment of its methanolic solution with an excess of 22% ethanolic HCl and Et_2O. The crystalline hydrochloride was filtered off and recrystallized from MeOH–Et_2O.

Yield 25.73 g (74%), mp 189–190°C. ^{1}H NMR (400 MHz, D_2O) δ 3.04–3.20 (H-4, m, 2H), 3.50 (H-3, m, 1H), 3.63 (H-3, m, 1H), 3.77 (MeO, s, 3H), 3.87 (MeO, s, 3H), 3.91 (H-1′, dd, J=19.2, 3.5 Hz, 1H), 4.03 (H-1′, dd, J=19.2, 8.4 Hz, 1H), 5.15 (H-1, m, 1H), 6.84 (H-5, s, 1H), 6.95 (H-8, s, 1H), 7.60 (*m*-Ph, t, J=7.8 Hz, 2H), 7.75 (*p*-Ph, t, J=7.7 Hz, 1H), 8.04 (*o*-Ph, d, J=7.9 Hz, 2H). Analysis: calculated for $C_{19}H_{22}ClNO_3$: C, 65.61; H, 6.37; N, 4.03; found: C, 65.80; H, 6.49; N, 3.95.

3.1.3. (1*R,2′*R**)-1-(2′-Hydroxy-2′-phenylethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (6).** Compound **5** (17.39 g, 0.05 mol) was suspended in methanol (200 mL). The suspension was stirred and cooled in an ice bath. $NaHCO_3$ (4.20 g, 0.05 mol) and then small portions of $NaBH_4$ (5.67 g, 0.15 mol) were added. Stirring was continued until the mixture had warmed up to room temperature (about 3 h). It was then stirred for a further 3 h and processed in the usual way to give a yellowish-brown oil containing an approximately 2:1 mixture of the (1*R**,2′*R**) and (1*R**,2′*S**) diasteromers. The oily product was crystallized on treatment with Et_2O. The crystals were filtered off and washed with Et_2O. Recrystallization from iPr_2O–EtOAc gave diastereomerically pure **6**.

Yield 7.32 g (47%), mp 134–136°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.03 (H-1′, ddd, J=14.8, 7.7, 2.9 Hz, 1H), 2.38 (H-1′, ddd, J=14.8, 7.4, 2.8 Hz, 1H), 2.63 (H-4, dt, J=15.5, 5.0 Hz, 1H), 2.85–2.94 (H-4, m, 1H), 3.01 (H-3, ddd, J=12.2, 7.9, 4.3 Hz, 1H), 3.27 (H-3, dt, J=12.4, 5.7 Hz, 1H), 3.82 (MeO, s, 3H), 3.86 (MeO, s, 3H), 4.27 (H-1, dd, J=6.8, 2.0 Hz, 1H), 4.87 (H-2′, dd, J=7.7, 2.6 Hz, 1H), 6.46 (H-5, s, 1H), 6.59 (H-8, s, 1H), 7.21–7.27 and 7.32–7.40 (Ph, 2×m, 5H). The ^{1}H NMR spectrum of **6** is in accordance with literature[17] data on the (1*R*,2′*R*) isomer. Analysis: calculated for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47; found: C, 72.74; H, 7.22; N, 4.37.

3.1.4. (1*R,11b*R**)-9,10-Dimethoxy-1-phenyl-1,6,7,11b-tetrahydro-2*H*,4*H*-1,3-oxazino[4,3-*a*]isoquinoline (7).** Amino alcohol **3** (0.94 g, 3 mmol) was added to a stirred mixture of 37% formaldehyde solution (10 mL) and H_2O (10 mL). Crystals of **10** started to separate from the solution after the slow dissolution of amino alcohol **6**. Stirring was continued for 1 h, and the crystalline product was then filtered off, washed with cold water, dried and recrystallized from iPr_2O.

Yield 0.67 g (69%), mp 143–144°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.40 (H-6$_{ax}$, m, 1H), 2.59 (H-7, m, 1H), 2.97 (H-6$_{eq}$, H-7, m, 2H), 3.24 (H-1, br, 1H), 3.75 (MeO-9, MeO-10, s, 6H), 3.93 (H-11b, d, J=3.3 Hz, 1H), 4.10 (H-2$_{ax}$, dd, J=11.2, 3.3 Hz, 1H), 4.11 (H-4$_{ax}$, d, J=7.9 Hz, 1H), 4.28 (H-2$_{eq}$, d, J=11.3 Hz, 1H), 4.70 (H-4$_{eq}$, d, J=7.9 Hz, 1H), 6.44 (H-8, s, 2H), 6.58 (H-11, s, 1H), 7.08 (*m*-Ph, *p*-Ph, m, 3H), 7.53 (*o*-Ph, d, J=8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 28.5 (C-7), 43.6 (C-1), 46.3 (C-6), 55.5 (MeO-10), 55.8 (MeO-9), 63.6 (C-11b), 73.6 (C-2), 87.5 (C-4), 108.6 (C-11), 111.1 (C-8), 125.8 (C-4′-Ph), 127.1 (C-11a), 127.1 (C-7a), 127.4 (C-3′-Ph), 130.1 (C-2′-Ph), 141.2 (C-1′-Ph), 146.8 (C-10), 147.0 (C-9). Analysis: calculated for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30; found: C, 73.69; H, 6.95; N, 4.12. IR ν_{max} 2834, 1517, 1263, 1142, 1103 cm^{-1}. EIMS *m*/*z* (%): M+1 326 (20), 314 (100).

3.1.5. (2*R,11b*R**)-9,10-Dimethoxy-2-phenyl-1,6,7,11b-tetrahydro-2*H*,4*H*-1,3-oxazino[4,3-*a*]isoquinoline (10).** To a solution of amino alcohol **6** (0.94 g, 3 mmol) in MeOH (10 mL), 37% formaldehyde solution (0.5 mL) was added. The mixture was allowed to stand at room temperature for 1 h. It was then poured into H_2O (50 mL) and extracted with $CHCl_3$ (3×25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. The oily product crystallized on treatment with Et_2O. The crystals were filtered off and recrystallized from *n*-hexane.

Yield 0.75 g (77%), mp 100–102°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.31 (H-1$_{eq}$, ddd, J=14.3, 3.1, 3.1 Hz, 1H), 2.58 (H-1$_{ax}$, ddd, J=13.3, 11.0, 5.5 Hz, 1H), 2.81 (H-7, m, 2H), 2.87 (H-6$_{ax}$, m, 1H), 3.50 (H-6$_{eq}$, m, 1H), 3.86 (MeO-9, s, 3H), 3.89 (MeO-10, s, 3H), 4.13 (H-11b, dd, J=10.9, 3.2 Hz, 1H), 4.39 (H-4$_{eq}$, d, J=10.1 Hz, 1H), 4.65 (H-4$_{ax}$, d, J=10.1 Hz, 1H), 5.11 (H-2, br, 1H), 6.58 (H-11, s, 1H), 6.62 (H-8, s, 1H), 7.32 (*p*-Ph, t, J=7.2 Hz, 1H), 7.45 (*m*-Ph, t, J=7.3 Hz, 2H), 7.54 (*o*-Ph, d, J=7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 28.3 (C-7), 30.5 (C-1), 43.8 (C-6), 52.8 (C-11b), 55.8 (MeO-9), 56.2 (MeO-10), 73.1 (C-2), 79.9 (C-4), 109.1 (C-11), 111.7 (C-8), 126.3 (C-7a), 126.7 (C-2′-Ph), 127.2 (C-4′-Ph), 128.7 (C-3′-Ph), 129.6 (C-11a), 140.2 (C-1′-Ph), 147.4 (C-9), 147.8 (C-10). Analysis: calculated for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30; found: C, 73.99; H, 7.27; N, 4.16. IR ν_{max} 2916, 2866, 1518, 1243, 1229, 1139 cm^{-1}. EIMS *m*/*z* (%): [M$^+$] 325 (2), 314 (100).

3.1.6. (1*R,4*S**,11b*R**)-9,10-Dimethoxy-1-phenyl-4-(*p*-nitrophenyl)-1,6,7,11b-tetrahydro-2*H*,4*H*-1,3-oxazino-[4,3-*a*]isoquinoline (8) and (2*R**,4*S**,11b*R**)-9,10-dimethoxy-2-phenyl-4-(*p*-nitrophenyl)-1,6,7,11b-tetrahydro-2*H*,4*H*-1,3-oxazino[4,3-*a*]isoquinoline (11).** Amino alcohol **3** or **6** (0.94 g, 3 mmol) was refluxed with an equimolar amount of *p*-nitrobenzaldehyde (0.45 g) in dry toluene

(30 mL). When no more starting material could be detected on TLC (6 h for **8** and 8 h for **11**), the solvent was evaporated off and the residual oil crystallized on treatment with Et_2O. The crystalline product was filtered off and recrystallized from iPr_2O–EtOAc.

8: Yield 0.97 g (72%), mp 181–182°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.22 (H-6$_{ax}$, ddd, J=11.0, 10.9, 3.8 Hz, 1H), 2.46 (H-7$_{ax}$, d, J=14.7 Hz, 1H), 2.60 (H-6$_{eq}$, m, 1H), 2.80 (H-7$_{eq}$, m, 1H), 3.45 (H-1, br, 1H), 3.74 (MeO-9, s, 3H), 3.77 (MeO-10, s, 3H), 4.24 (H-11b, br, 1H), 4.34 (H-2, m, 2H), 4.95 (H-4, s, 1H), 6.44 (H-8, s, 2H), 6.61 (H-11, s, 1H), 7.11 (*p*-Ph, t, J=7.3 Hz, 1H), 7.18 (*m*-Ph, t, J=6.9 Hz, 2H), 7.64 (*o*-Ph, d, J=7.1 Hz, 2H), 7.78 (H-2″-*p*-O_2N-C_6H_4, d, J=8.6 Hz, 2H), 8.28 (H-3″-*p*-O_2N-C_6H_4, d, J=8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 28.5 (C-7), 43.5 (C-1), 45.5 (C-6), 55.6 (MeO-10), 55.9 (MeO-9), 64.4 (C-11b), 73.7 (C-2), 95.9 (C-4), 108.7 (C-11), 111.0 (C-8), 123.8 (C-3″-*p*-O_2N-C_6H_4), 126.1 (C-4″-Ph), 127.0 (C-11a), 127.2 (C-7a), 127.8 (C-3′-Ph),129.0 (C-2″-*p*-O_2N-C_6H_4), 130.1 (C-2′-Ph), 140.8 (C-1′-Ph), 146.5 (C-1″-*p*-O_2N-C_6H_4),147.0 (C-9), 147.3 (C-10), 148.3 (C-4″-*p*-O_2N-C_6H_4). Analysis: calculated for $C_{26}H_{26}N_2O_5$: C, 69.94; H, 5.87; N, 6.27; found: C, 69.75; H, 5.60; N, 6.18. IR ν_{max} 2915, 2841, 1523, 1346, 1100 cm^{-1}. EIMS *m*/*z* (%): 446 [M]$^+$ (3), 314 (100).

11: Yield 0.92 g (69%), mp 166–168°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37–2.77 (H-1, H-7, m, 4H), 2.48 (H-6$_{eq}$, ddd, J=11.7, 5.7, 3.1 Hz, 1H), 3.07 (H-6$_{ax}$, ddd, J=11.5, 10.5, 4.3 Hz, 1H), 3.86 (MeO-9, s, 3H), 3.93 (MeO-10, s, 3H), 4.35 (H-11b, d, J=10.5 Hz, 1H), 5.47 (H-2, d, J=5.8 Hz, 1H), 5.61 (H-4, s, 1H), 6.62 (H-8, H-11, s, 2H), 7.33 (*p*-Ph, t, J=7.2 Hz, 1H), 7.45 (*m*-Ph, t, J=7.7 Hz, 2H), 7.56 (*o*-Ph, d, J=7.7 Hz, 2H), 7.77 (H-2′-*p*-O_2N-C_6H_4, d, J=8.5 Hz, 2H), 8.24 (H-3″-*p*-O_2N-C_6H_4, d, J=8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 28.7 (C-1), 28.8 (C-7), 37.1 (C-6), 54.7 (C-11b), 55.8 (MeO-9), 56.2 (MeO-10), 73.8 (C-2), 85.5 (C-4), 109.2 (C-11), 111.6 (C-8), 123.4 (C-3″-*p*-O_2N-C_6H_4), 126.4 (C-2′-Ph), 126.4 (C-7a), 127.4 (C-4′-Ph), 127.7 (C-2″-*p*-O_2N-C_6H_4), 128.9 (C-3′-Ph), 130.0 (C-11a), 139.8 (C-1′-Ph), 146.4 (C-1″-*p*-O_2N-C_6H_4), 147.4 (C-10), 147.5 (C-4″-*p*-O_2N-C_6H_4), 147.9 (C-9). Analysis: calculated for $C_{26}H_{26}N_2O_5$: C, 69.94; H, 5.87; N, 6.27; found: C, 70.16; H, 5.58; N, 6.13. IR ν_{max} 2958, 2830, 1522, 1347, 1272 cm^{-1}. EIMS *m*/*z* (%): M+1 447 (7), 314 (100).

3.2. Crystal data for 11

$C_{26}H_{26}N_2O_5$, M_r=446.49, orthorhombic, space group *Pbca* (No 60), lattice parameters: a=16.550(5), b=29.566(3), c=9.156(3) Å, Z=8, V=4480.5(18) Å^3, D_c=1.324 g/cm^3, μ(Mo K$_\alpha$)=0.092 mm^{-1}, F(000)=1888, T=294 K; pale-yellow prism, crystal dimensions 0.32×0.36×0.38 mm^3.

3.2.1. (1*R* *,11b*R* *)-9,10-Dimethoxy-1-phenyl-1,6,7,11b-tetrahydro-2*H*,4*H*-1,3-oxazino[4,3-*a*]isoquinolin-4-one (9). To a stirred mixture of amino alcohol **3** (0.94 g, 3 mmol), toluene (25 mL), $NaHCO_3$ (0.38 g, 4.5 mmol) and H_2O (25 mL), ethyl chloroformate (0.35 g, 3.2 mmol) was added and the mixture was stirred at room temperature for 1 h. The organic layer was separated and the aqueous layer was extracted with EtOAc (3×30 mL). The combined extracts were dried (Na_2SO_4) and evaporated to yield 1.11 g (96%) of ethyl (1*R* *,1′*R* *)-1-(2′-hydroxy-1′-phenylethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2-carboxylate as a crystalline product (mp 160–161°C), which was used in the next step without further purification.

The previous urethane derivative (1.11 g, 2.9 mmol) was thoroughly mixed with NaOMe (0.15 g, 2.8 mmol) and the mixture was kept under N_2 at 160–165°C for 45 min. The melt was extracted with hot EtOAc (5×30 mL), and the combined organic phases were washed with 5% HCl (2×30 mL) and H_2O (2×30 mL), dried (Na_2SO_4) and evaporated. The oily residue crystallized on treatment with Et_2O. The crystals were filtered off and recrystallized from iPr_2O–EtOAc.

Yield 0.52 g (53%), mp 150–152°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.18 (H-7$_{ax}$, ddd, J=16.4, 12.3, 4.6 Hz, 1H), 2.38 (H-7$_{eq}$, ddd, J=15.6, 2.5, 2.5 Hz, 1H), 2.94 (H-6$_{ax}$, ddd, J=12.5, 12.5, 3.1 Hz, 1H), 3.59 (H-1, dd, J=3.6, 3.9 Hz, 1H), 3.80 (MeO-9, s, 3H), 3.84 (MeO-10, s, 3H), 4.53 (H-6$_{eq}$, m, 1H), 4.57 (H-2$_{eq}$, d, J=11.0 Hz, 1H), 4.82 (H-2$_{ax}$, dd, J=11.1, 4.1 Hz, 1H), 5.20 (H-11b, d, J=3.9 Hz, 1H), 6.42 (H-8, s, 1H), 6.64 (H-11, s, 1H), 6.89 (*o*-Ph, d, J=7.7 Hz, 2H), 7.10 (*m*/*p*-Ph, m, 3H); ^{13}C NMR ($CDCl_3$) δ 28.0 (C-7), 41.3 (C-6), 43.9 (C-1), 55.7 (MeO-9), 56.1 (MeO-10), 57.6 (C-11b), 70.8 (C-2), 109.0 (C-11), 111.1 (C-8), 124.6 (C-7a), 127.1 (C-4′-Ph), 128.1 (C-2′-Ph), 128.5 (C-11a), 128.5 (C-3′-Ph), 136.8 (C-1′-Ph), 147.8 (C-9/C-10), 153.2 (C-4). Analysis: calculated for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13; found: C, 70.91; H, 6.08; N, 4.19. IR ν_{max} 2994, 2835, 1691, 1430, 1253, 1106 cm^{-1}. EIMS *m*/*z* (%): M+1 340 (100).

3.2.2. (2*R* *,11b*R* *)-9,10-Dimethoxy-2-phenyl-1,6,7,11b-tetrahydro-2*H*,4*H*-1,3-oxazino[4,3-*a*]isoquinolin-4-one (12). Di-*tert*-butyl dicarbonate (1.09 g, 5 mmol) was added in small portions to a solution of **6** (0.94 g, 3 mmol) in EtOAc (30 mL) at 0°C. The mixture was stirred at room temperature for 16 h, then washed with 1 M HCl (25 mL), saturated aqueous $NaHCO_3$ (25 mL) and H_2O (25 mL), dried (Na_2SO_4) and concentrated in vacuo. Treatment of the oily residue with Et_2O gave crystalline *tert*-butyl (1*R* *,2′*R* *)-1-(2′-hydroxy-2′-phenylethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (1.02 g, 82%, mp 119–120°C), which was used in the next step without further purification.

KO*t*Bu (0.34 g, 3 mmol) was added in one portion to a stirred solution of the previous *N*-Boc derivative (1.02 g, 2.5 mmol) in freshly distilled THF (40 mL) at 0°C. After 30 min, saturated aqueous NH_4Cl solution (40 mL) and EtOAc (40 mL) were added to the mixture and the organic layer was separated. The aqueous layer was extracted with EtOAc (2×40 mL). The combined organic phases were washed with H_2O (30 mL), dried (Na_2SO_4) and evaporated. The oily residue crystallized on treatment with Et_2O. The crystals were filtered off and recrystallized from iPr_2O–EtOAc.

Yield 0.68 g (81%), mp 128–131°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (H-1$_{ax}$, ddd, J=14.0, 9.0, 4.2 Hz, 1H), 2.63 (H-7$_{eq}$, m, 1H), 2.69 (H-1$_{eq}$, ddd, J=14.0, 4.9, 4.9 Hz, 1H), 2.98 (H-7$_{ax}$, m, 1H), 3.01 (H-6$_{ax}$, m, 1H), 3.84 (MeO-10, s,

3H), 3.86 (MeO-9, s, 3H), 4.47 (H-11b, dd, J=8.8, 5.0 Hz, 1H), 4.63 (H-6_{eq}, m, 1H), 5.46 (H-2, t, J=4.2 Hz, 1H), 6.51 (H-11, s, 1H), 6.64 (H-8, s, 1H), 7.35–7.43 (Ph, m, 5H); ^{13}C NMR ($CDCl_3$) δ 28.3 (C-7), 35.3 (C-1), 42.5 (C-6), 50.9 (C-11b), 55.8 (MeO-9), 56.2 (MeO-10), 75.2 (C-2), 107.6 (C-11), 111.9 (C-8), 125.0 (C-2′-Ph), 127.2 (C-7a), 127.5 (C-11a), 128.0 (C-4′-Ph), 128.8 (C-3′-Ph), 139.1 (C-1′-Ph), 147.8 (C-10), 148.1 (C-9), 152.9 (C-4). Analysis: calculated for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13; found: C, 70.52; H, 5.97; N, 4.06. IR ν_{max} 3854, 3752, 1686, 1509, 1267, 1245 cm^{-1}. EIMS *m/z* (%): M+1 340 (35), 399 (100).

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