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Betti Reaction of Cyclic Imines with Naphthols and Phenols – Preparation of New Derivatives of Betti's Bases

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A large library of aminocycloalkylphenols and -naphthols is obtained by the Betti reaction between activated phenols and naphthols and five- and six-membered cyclic imines. Due to the formation of an intramolecular hydrogen bond in the transition state, the attack takes place regioselectively at the position adjacent to the hydroxy group of the aromatic compounds. X-ray crystallography and chirooptical methods (electronic circular dichroism) were used to ascertain the absolute configuration of two aminoalkylnaphthols obtained, after resolution of the corresponding racemates with (*R*,*R*)-tartaric acid. In addition, some aminoalkylnaphthols and -phenols were alkylated at the nitrogen atom to obtain *N*-methylated products in good yields.

Introduction

Carbon–carbon bond forming reactions play an important role in organic synthesis. The formation of new C–C bonds provides new opportunities in total synthesis, in medicinal chemistry, in chemical biology, and in nanotechnology. In particular, cross-coupling reactions between aromatic and aliphatic compounds have been largely studied. Usually this type of reactions takes place in the presence of catalysts such as transition metal complexes, for example palladium,[1,2] nickel,[2] or copper salts,[3] Lewis acids,[4] or a combination of them.[5]

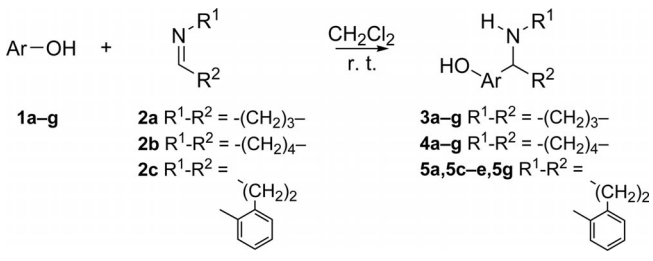
Among others, the reaction between 2-naphthol and a *N*-phenyltetraisoquinoline to form an aminoalkylnaphthol was studied by Li et al.[6] This approach requires the use of Cu^{I} salts, and the reaction is not selective, affording a relevant amount of BINOL as byproduct too. Subsequent studies of this group[7] show that analogues of this aminoalkylnaphthol can be obtained through an aza-Friedel–Crafts reaction, an approach that allows the preparation of these Betti base derivatives[8] in good yields, without metal catalysts and with 100% atom economy. Another group[9] studied the effect of microwaves on the solventless reaction of 3,4-dihydroisoquinoline with naphthols.

Aminoalkylphenols and -naphthols are interesting compounds, useful as chiral ligands in the enantioselective addition of diethylzinc to aldehydes.[10] Recently THIQNOL® and other derivatives have been objects of patents for this purpose.[11] Moreover, they can be used as chiral auxiliaries for the synthesis of α-aminophosphonic acids[12] and as chiral shift reagents for carboxylic acids.[13]

In this paper, the reaction of activated naphthols and phenols **1** with cyclic imines **2** is explored, and the synthesis of new aminocycloalkylphenols and -naphthols **3**, **4**, and **5** and *N*-methyl derivatives **6** is reported. The reaction is operationally simple, requests cheap reagents, does not need any metal or acid catalyst, and is performed under very mild conditions, providing the products in good yields and in short reaction times.

Results and Discussion

Activated naphthols and phenols **1a**–**g** react with imines **2a**–**c**, affording in 3–7 h products **3a**–**g**, **4a**–**g**, **5a**, **5c**–**e**, and **5g** with 37–84% yields (Scheme 1). The reaction is convenient, proceeds quickly, is operationally simple and does not request the use of microwave[9] or expensive starting materials. The products obtained and the corresponding yields are collected in Table 1.



Scheme 1. Synthesis of aminocycloalkylnaphthols **3**, **4**, and **5** by reaction of activated naphthols and phenols **1** with cyclic imines **2**.

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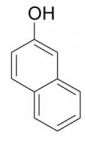
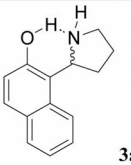
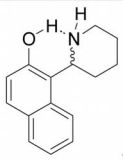
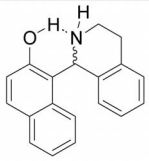
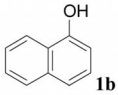
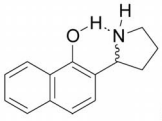
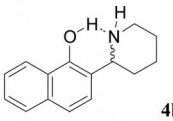
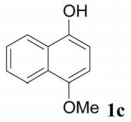
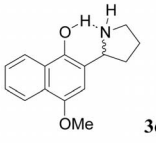
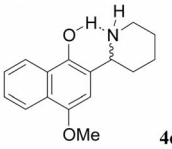
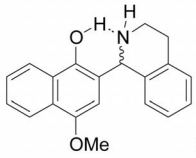
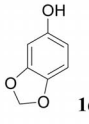
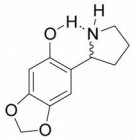
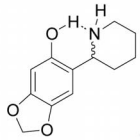
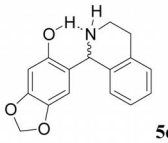
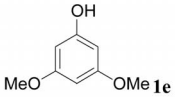
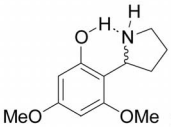
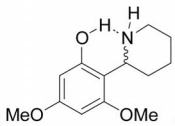
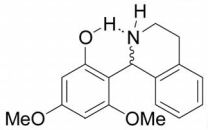
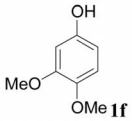
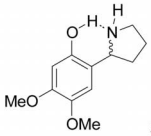
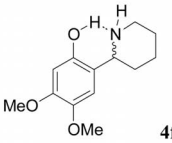
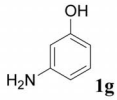
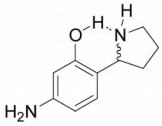
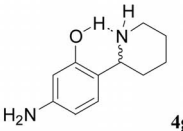
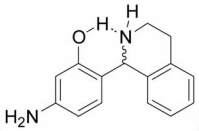
Table 1. Yields and structures of products **3**, **4**, and **5**.

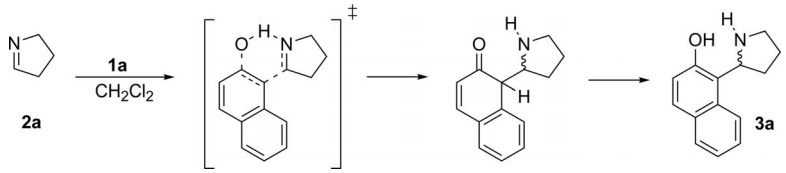
Entry	1	3 (Yield %)[a]	4 (Yield %)[a]	5 (Yield %)[a]
1	 **1a**	 **3a** (78)	 **4a** (81)	 **5a**[9] (66)
2	 **1b**	 **3b** (75)	 **4b** (79)	–
3	 **1c**	 **3c** (66)	 **4c** (58)	 **5c** (49)
4	 **1d**	 **3d** (67)	 **4d** (63)	 **5d** (73)
5	 **1e**	 **3e** (63)	 **4e** (86)	 **5e** (70)
6	 **1f**	 **3f** (66)	 **4f** (83)	–
7	 **1g**	 **3g** (84)	 **4g** (74)	 **5g** (37)

[a] Yield of the isolated product.

The new carbon–carbon bond is formed *ortho* to the hydroxy group. Probably regioselectivity is due to hydrogen-bond formation in the transition state, as depicted in Scheme 2 for the reaction of imine **2a** with β-naphthol (**1a**) to form product **3a**. This hypothesis is confirmed by the experimental observation that substitution of the hydroxy group by a methoxy group results in no reaction, as in 4-methoxyaniline, and that also aniline, indole, and *N*-methylindole, which cannot form any hydrogen bond with the imine, do not react under these conditions.

Moreover, when the amino and hydroxy functionalities are both present in the same molecule, as in 3-aminophenol (**1g**), only one product is recovered, which results from the reaction at position 6, *ortho* to the hydroxy group.

When the starting imine is substituted with a methyl group at position 2, the reaction does not take place: the reactions of **1a** with 5-methyl-3,4-dihydro-2*H*-pyrrole and 6-methyl-2,3,4,5-tetrahydropyridine resulted in the recovery of the unaltered starting materials.



Scheme 2. Hypothesis of hydrogen bond formation in the mechanism for the reaction between imine **2a** and β-naphthol (**1a**).

The reaction takes place with naphthols, also substituted with electron-donating substituents, and with electron-rich phenols, while substrates with electron-withdrawing substituents are unreactive under these conditions. This trend can be tentatively explained by observing that the HOMO orbital calculated for β-naphthol (**1a**) and the LUMO orbital for imine **2a** (optimized by using DFT at the B3LYP/6-31G level) result to be more developed at the site of attack of both molecules, as depicted in Figure 1. In the case of 3-aminophenol (**1g**), this observation is also in accord with the calculated local nucleophilicity index reported in the literature.[14]

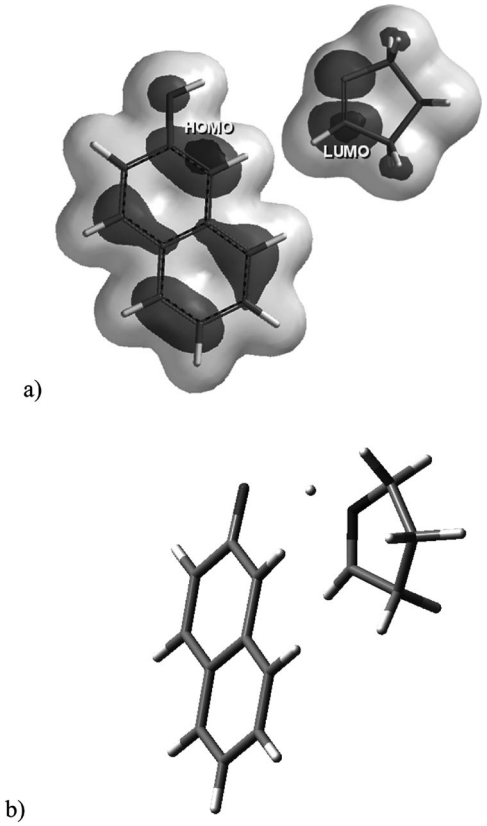


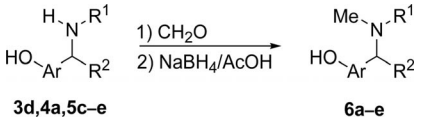
Figure 1. (a) Transparent potential surfaces of β-naphthol (**1a**) and imine **2a** and the respective HOMO and LUMO surfaces (optimized using DFT at the B3LYP/6-31G level). (b) Optimized structure for the six-membered transition structure (at the B3LYP/6-31G(d) level). The single imaginary frequency corresponds to the transfer of the hydrogen atom from the oxygen to the nitrogen atom.

The analysis of the reaction path by DFT calculations shows that the transition state[15] corresponds to the protonation of the imine by the phenolic hydrogen. IRC calculation[16] performed starting from this transition state indicated the formation of the sp^3 intermediate at the alpha position of naphthalene without any additional transition state. From this intermediate, the final product is generated by re-aromatization.

In order to obtain an enantiopure product, the racemates of aminoalkylnaphthols **3a** and **4a** were resolved by using (*R*,*R*)-tartaric acid. The racemate products were dissolved in acetone and added to an equimolecular amount of (*R*,*R*)-tartaric acid. The diastereomeric salt, which precipitated on standing, was filtered, and the (*R*,*R*)-tartaric acid was removed by treatment with a base (see Experimental Section). The resulting product was analyzed by ^{1}H NMR spectroscopy in the presence of (*S*)-(+)-*O*-acetyl mandelic acid.

The triplet at δ = 5.03 ppm in the ^{1}H NMR spectrum of product (±)-**3a**, attributed to the proton at the 2-position of the pyrrolidine ring, splits into two triplets at 5.07 and 5.00 ppm in the presence of an equimolecular amount of (*S*)-(+)-*O*-acetyl mandelic acid. In the resolved enantiomer, the ^{1}H NMR spectrum, registered after addition of (*S*)-(+)-*O*-acetyl mandelic acid, shows only one triplet.

In the same way, the signal of the proton at the 2-position of the piperidine ring in product (±)-**4a** is a double doublet, which, in the presence of an equimolecular amount of (*S*)-(+)-*O*-acetyl mandelic acid, splits in two partially overlapping signals at δ = 4.66 and 4.63 ppm. Analogously, the ^{1}H NMR spectrum of the resolved enantiomer, regis-



Scheme 3. *N*-Alkylation of products **3d**, **4a**, and **5c**–**e**.

Table 2. Yields and structures of *N*-alkylated products **6a**–**e**.

Entry	Aminoalkyl-naphthol	**6** (Yield %)[a]
1	**3d**	**6a** (83)
2	**4a**	**6b** (85)
3	**5c**	**6c** (79)
4	**5d**	**6d** (49)
5	**5e**	**6e** (77)

[a] Yield of the isolated product.

tered after addition of (*S*)-(+)-*O*-acetyl mandelic acid in an equimolecular amount, indicates the presence of only one signal. In both cases the enantiomer is isolated with *ee* >96%.

Several examples[17] reported in the literature show that *N*-methylated aminoalkylnaphthols and -phenols perform better as catalysts with respect to the corresponding secondary amines.

Betti base derivatives **3d**, **4a**, **5c**, **5d**, and **5e** were methylated[10d] at the nitrogen atom by cyclization with formaldehyde to the corresponding oxazolidine, followed by reduction with sodium triacetoxyborohydride in THF, to form the corresponding products **6a**–**e** in yields of 49–85% (see Scheme 3 and Table 2). This procedure is a good alternative to the one reported in ref.,[7a] which involves the use of methyl iodide, because although both methyl iodide and formaldehyde are toxic reagents, the latter is used in aqueous solution, differently from the low-boiling methyl iodide, which is used without dilution. Moreover, the reduction of the naphthoxazine is performed in one pot, without isolating the intermediate, and thus avoiding any contact with formaldehyde.

Assignment of Absolute Configurations

The stereochemical assignment of compounds **3a** and **4a** has been carried out by means of X-ray crystallography and chirooptical techniques.

Compound **3a** lacks any atom sufficiently heavy to allow the determination of the absolute configuration (AC) by the X-ray anomalous dispersion method.[18] For this reason, crystals were grown as (*R*,*R*)-tartrate salts, where the enantiopure tartrate acts as the chirality reference. Single-crystal X-ray diffraction analysis showed that the configuration of the asymmetric carbon in compound **3a** is the same as that in the tartrate anion; therefore, the absolute configuration of **3a** is (*R*) too (see Figure 2).

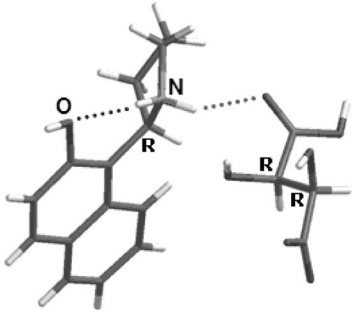


Figure 2. X-ray structure of the (*R*,*R*)-tartrate salt of compound **3a**. Dotted lines indicate intra- and intermolecular hydrogen bonds.

In the case of compound **4a**, we were unable to grow good crystals suitable for X-ray analysis. Having in hand the absolute configuration of compound **3a**, we approached the determination of the absolute configuration of compound **4a** by making use of chirooptical techniques. In particular, we made use of the simulation of electronic circular dichroism (ECD) spectra by TD-DFT calculations, because this technique has become highly reliable and has been successfully employed several times to assign the absolute configuration of complex organic molecules.[19] It has to be noted that in the present case the unambiguous knowledge of the AC of compound **3a** can be used as a reference to test the reliability of the ECD-based method. The X-ray structure of **3a**-(*R*,*R*)-tartrate shows the presence of an intramolecular hydrogen bond that links the amine hydrogen with the phenolic oxygen of the naphthalene ring. This hydrogen bond could be present also in compound **4a**, and it could greatly stabilize the ground state conformation.

A preliminary conformational search was carried out by using systematic search together with the MMFF94 molecular mechanics force field.[20] All the conformations within a 3 kcal/mol window were then optimized by using DFT at the B3LYP/6-31G(d) level,[21] and the harmonic vibrational frequencies of each conformation were calculated at the same level to confirm their stability (no imaginary frequencies were observed) and to evaluate the free energy of each conformation by ZPE correction. After DFT minimization, the lowest energy conformation was found to be much more stable with respect to any other (see Figure 3). This conformation is stabilized by an intramolecular hydrogen bond in which the nitrogen acts as the acceptor. This hydrogen bond, although reversed in polarity, corresponds to that already observed in the X-ray structure of **3aa**-(*R*,*R*)-tartrate. The six-membered ring of **3ab** has a chair conformation, which is further stabilized by the hydrogen bond, and the naphthalene ring occupies the equatorial position.

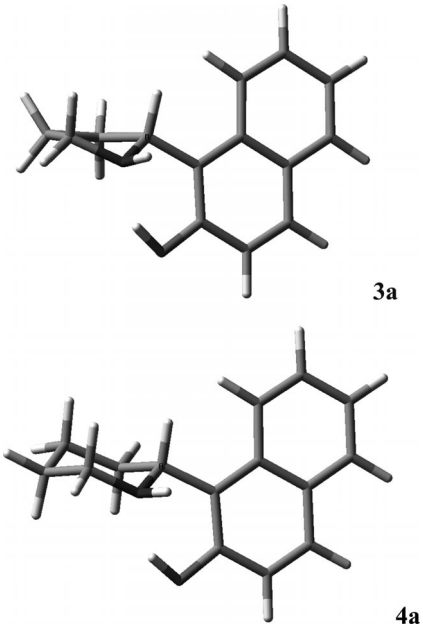


Figure 3. The lowest energy conformations obtained for **3a** and **4a** by molecular mechanics (MM) conformational search followed by DFT optimization.

As a further indication that the actual theoretical level is suitable to handle these molecules, the same procedure (i.e. MM search followed by DFT minimization) has been ap-

plied to compound **3aa** as free base, and the best conformation has a structure almost identical to that of the X-ray structure, the only difference being the disposition of the phenolic hydrogen. In the free base, this is indeed involved in the hydrogen bond with the nitrogen.

The results of the calculations indicate that these molecules are conformationally rigid, and this feature will be helpful for the simulation of the ECD spectrum of **4a**. The electronic excitation energies and rotational strengths were calculated with TD-DFT at the B3LYP/6-311++G(2d,p) level by using the optimized geometries and assuming the (*R*) absolute configuration for both **3a** and **4a**; the results are shown in Figure 4a. The calculated curves for (*R*)-**3a** and (*R*)-**4a** have a similar pattern: this suggests that the ECD spectrum is not heavily influenced by the size of the ring containing the chiral center.

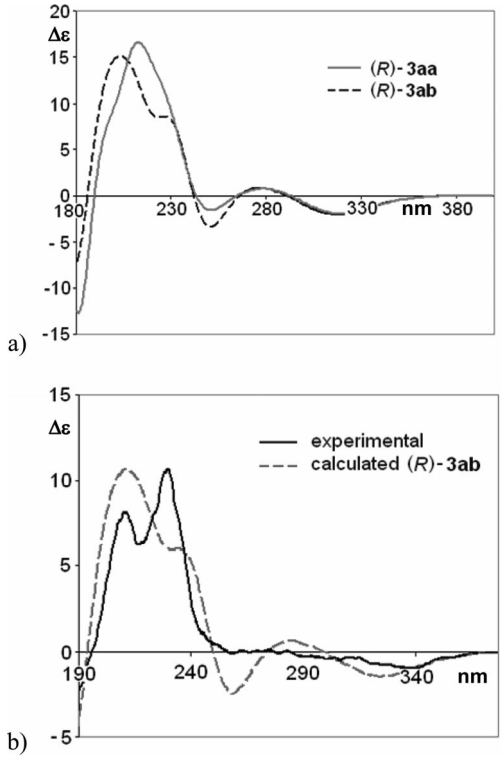


Figure 4. (a) ECD spectra calculated for (*R*)-**3a** and (*R*)-**4a**. Calculations at the TD-DFT B3LYP/6-311++G(2d,p) level. (b) Experimental (solid line) and calculated ECD spectra (dashed line) of **4a**. The experimental ECD spectrum was obtained in acetonitrile solution (1×10^{-4} M) with a 0.2 cm cell. Molecular CD ($\Delta\varepsilon$) values are expressed in $L\,mol^{-1}\,cm^{-1}$. The simulated spectrum was scaled and redshifted by 8 nm for comparison with the experimental trace.

The rotational strengths were calculated in the length and velocity representations. The resulting values are very similar, and errors due to basis set incompleteness are therefore very small or negligible.[22] The final simulated ECD spectrum was obtained by taking into account that only one conformation was calculated to be populated. The agreement between the calculated spectrum of **4a** and the experimental spectrum is very good, and the CD simulation thus supports the conclusion that the absolute configuration of **4a** is (*R*). This result is also in agreement with the unambiguously determined (*R*) configuration of **3a**.

As correctly suggested by some authors,[23] the use of more than one chirooptic method is always desirable. In the present study, both compounds **3a** and **4a** exhibit large values of $[\alpha]_D$ (+249 and +135° for **3a** and **4a**, respectively), which are well outside the "uncertainty zone" suggested by some authors.[24] For this reason, the calculation of the $[\alpha]_D$ can independently confirm the absolute configuration of **4a**. As a benchmark, the $[\alpha]_D$ was previously calculated for compound **3a**, yielding a value of +209, in good agreement with the experimental value. The same calculation obtained for (*R*)-**4a** provided a value of +173.2, again in agreement with the experimental value.[25]

Conclusions

A large number of compounds is obtained by the Betti reaction of activated phenols and naphthols **1a**–**g** with cyclic imines **2a**–**c**. The reaction is operationally simple and is carried out under mild conditions, affording good yields of the desired product in short reaction times. Due to the formation of an intramolecular hydrogen bond in the transition state, the attack takes place regioselectively at the *ortho* position of the aromatic compounds. The absolute configuration of products **3a** and **4a** was ascertained by X-ray analysis and chirooptical methods (ECD), after resolution of the corresponding racemates with (*R*,*R*)-tartaric acid. In addition, aminoalkylnaphthols and -phenols **3d**, **4a**, **5c**, **5d**, and **5e** were alkylated at the nitrogen atom to obtain *N*-methylated products **6a**–**e** in good yields.

Experimental Section

General Remarks: Imines **2a**–**c** were prepared according to literature[26] methods. Products **5** were prepared according to literature[7b] methods. ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz respectively, with $CDCl_3$ as solvent at ambient temperature and were calibrated by using residual undeuteriated solvents as the internal reference. Coupling constants (*J*) are given in Hertz. IR spectra were recorded by using FTIR apparatus. Optical rotations were measured in a 1 dm cell at 20 °C. All reagents are commercially available and of the highest quality; they were purified by distillation when necessary.

General Procedure for the Synthesis of Aminocycloalkylnaphthols and -phenols 3, 4, and 5: 3,4-dihydro-2*H*-pyrrole **2a** (2 mmol, 0.138 g) or 2,3,4,5-tetrahydropyridine **2b** (2 mmol, 0.166 g) or 3,4-dihydroisoquinoline **2c** (2 mmol, 0.262 g) was dissolved in dichloromethane (4 mL) in a round-bottomed flask equipped with magnetic stirring. Then, naphthols or phenols **1a**–**g** (2 mmol) were added at room temperature. The reaction was monitored by TLC, with *n*-hexane/ethyl acetate (1:1) as eluent, until the starting materials were consumed. The solvent was evaporated under reduced pressure. The raw mixture obtained was purified by column chromatography on silica gel, by using cyclohexane/ethyl acetate (1:1) as the eluent. Purified aminocycloalkylnaphthols and -phenols **3**, **4**, and **5** were crystallized from a cyclohexane/ethyl acetate mixture. Spectral characterization of products **3a** and **4a** follow. Spectral characterization of compound **5a** is in accord with that reported in ref.[9]

1-Pyrrolidin-2-yl-naphthalen-2-ol (3a): Yield 78% (0.333 g), white crystals, m.p. 85–88 °C. $\tilde{\nu}_{max}$ (solid) = 3306, 2571, 1620, 1335, 956, 816, 743 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.81 (dq, J = 12.5, 8.6 Hz, 1 H, 3′-H_a), 1.91–2.05 (m, 2 H, 4′-H), 2.42–2.50 (m, 1 H, 3′-H_b), 2.56 (br. s, 1 H, NH), 3.11 (q, J = 8.1 Hz, 1 H, 5′-H_a), 3.28 (dt, J = 10.3, 6.6 Hz, 1 H, 5′-H_b), 5.03 (t, J = 8.1 Hz, 1 H, 2′-H), 7.07 (d, J = 9.0 Hz, 1 H, Ar), 7.28 (t, J = 7.5 Hz, 1 H, Ar), 7.43 (t, J = 7.7 Hz, 1 H, Ar), 7.64 (d, J = 8.5 Hz, 1 H, Ar), 7.74 (t, J = 7.0 Hz, 2 H, Ar), 14.00 (br. s, 1 H, OH) ppm. ^{13}C NMR ($CDCl_3$): δ = 25.5, 33.2, 45.8, 58.9, 115.6, 120.5, 121.3, 122.3, 126.4, 128.4, 128.9, 129.0, 132.4, 156.6 ppm. $C_{14}H_{15}NO$ (213.275): calcd. C 78.84, H 7.09, N 6.57; found C 79.10, H 7.01, N 6.29.

2-Piperidin-2-yl-naphthalen-2-ol (4a): Yield 81% (0.368 g), white crystals, m.p. 124–129 °C. $\tilde{\nu}_{max}$ (solid) = 3280, 2853, 2536, 1621, 1266, 1099, 820 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.54 (qt, J = 12.6, 3.7 Hz, 1 H, 3′-H_a), 1.65 (qt, J = 12.6, 3.7 Hz, 1 H, 3′-H_b), 1.72–1.94 (m, 4 H, 4′-H, 5′-H), 2.38 (br. s, 1 H, NH), 2.81 (td, J = 11.6, 2.8 Hz, 1 H, 6′-H_a), 3.30 (dq, J = 11.6, 1.9 Hz, 1 H, 6′-H_b), 4.62 (dd, J = 11.1, 6.8 Hz, 1 H, 2′-H), 7.11 (d, J = 9.1 Hz, 1 H, Ar), 7.27–7.31 (m, 1 H, Ar), 7.42–7.46 (m, 1 H, Ar), 7.67 (d, J = 8.5 Hz, 1 H, Ar), 7.76 (dd, J = 8.1, 1.3 Hz, 1 H, Ar), 7.85 (d, J = 9.0 Hz 1 H, Ar), 12.37 (br. s, 1 H, OH) ppm. ^{13}C NMR ($CDCl_3$): δ = 24.8, 25.3, 30.5, 46.9, 56.3, 118.4, 120.1, 120.9, 122.6, 126.5, 128.6, 129.0, 129.2, 131.6, 155.8 ppm. $C_{15}H_{17}NO$ (227.302): calcd. C 79.26, H 7.54, N 6.16; found C 79.19, H 7.62, N 6.24.

Resolution of (±)3a and (±)4a: Product **3a** or **4a** (3 mmol) was dissolved in acetone (3 mL) and added to a solution of (*R*,*R*)-tartaric acid (3 mmol, 0.450 g) in acetone (3 mL). The mixture was allowed to stand overnight and then filtered. The precipitate obtained was dried under vacuum and then dispersed in dichloromethane. After the addition of saturated sodium carbonate solution until basic pH was reached, the solution was extracted with CH_2Cl_2 (2 × 20 mL) The extract was dried with anhydrous sodium sulfate, and the solvent was evaporated under vacuum to afford a white solid in both cases. The optical purity of the isolated enantiomers of products **3a** and **4a** was ascertained by ^1H NMR spectroscopy in the presence of (*S*)-(+)-*O*-acetyl mandelic acid as chiral solvating agent, yielding a result of 96% *ee*.

(*R*)-(+)-1-Pyrrolidin-2-yl-naphthalen-2-ol [(*R*)-(+)-3a]: $[\alpha]_D^{20}$ = +249.1 (c = 0.47, $CHCl_3$).

(*R*)-(+)-2-Piperidin-2-yl-naphthalen-2-ol [(*R*)-(+)-4a]: $[\alpha]_D^{20}$ = +135 (c = 0.47, $CHCl_3$).

Synthesis of Products 6a–e: The methylation of products **3d**, **4a**, and **5c**–**e** was performed by cyclization to the corresponding oxazine with formaldehyde and subsequent reductive ring opening with sodium borohydride/acetic acid in THF, according to the literature.[22]

1-(1-Methyl-piperidin-2y-l)-naphthalen-2-ol (6b): Yield 85% (0.410 g), white crystals, m.p. 95–97 °C. $\tilde{\nu}_{max}$ (solid) = 2937, 2586, 1620, 1471, 1249, 1106, 810, 745 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.45 (qt, J = 12.0, 4.0 Hz, 1 H, 4′-H_a), 1.68–1.96 (m, 5 H, 4′-H_b, 3′-H, 5′-H), 2.24 (td, J = 11.6, 3.6 Hz, 1 H, 6′-H_a), 2.25 (s, 3 H, NCH_3), 3.19 (d, J = 11.6 Hz, 1 H, 6′-H_b), 3.92 (dd, J = 11.3, 3.2 Hz, 1 H, 2′-H), 7.10 (d, J = 8.5 Hz, 1 H, Ar), 7.26–7.31 (m, 1 H, Ar), 7.41–7.46 (m, 1 H, Ar), 7.67 (d, J = 9.0 Hz, 1 H, Ar), 7.77 (d, J = 8.1 Hz, 1 H, Ar), 7.86 (d, J = 9.0 Hz, 1 H, Ar), 12.43 (br. s, 1 H, OH) ppm. ^{13}C NMR ($CDCl_3$): δ = 24.4, 25.9, 31.2, 44.1, 56.5, 64.3, 117.6, 119.5, 120.9, 122.5, 126.4, 128.8, 129.0, 129.1, 132.1, 155.0 ppm. $C_{16}H_{19}NO$ (241.147): calcd. C 79.63, H 7.94, N 5.80; found C 79.41, H 7.79, N 5.58.

X-ray Crystallography: Crystals of product **3a** suitable for X-ray diffraction were obtained from wet acetone solution and analyzed with a Bruker APEX II diffractometer equipped with a CCD area detector using Mo-K_α radiation. Molecular formula: $C_{36}H_{44}N_2O_{15}$, M_r = 744.73, monoclinic, space group C_2 (No. 5), a = 26.963(4) Å, b = 7.4562(10) Å, c = 8.8922(12) Å, β = 93.613(3)°, V = 1784.2(4) $Å^3$, T = 298(2) K, Z = 2, ρ_c = 1.386 $g\,cm^{-3}$, $F(000)$ = 788, μ(Mo-K_α) = 0.109 mm^{-1}, 2400 frames, exposure time 10 s, 2.29 ≤ θ ≤ 27.50, –34 ≤ h ≤ 34, –9 ≤ k ≤ 9, –11 ≤ l ≤ 11, 10192 reflections collected, 2196 independent (R_{int} = 0.0237), solution by direct methods (SHELXS-97)[27] and subsequent Fourier syntheses, full-matrix least-squares on F_o^2 (SHELXL-97),[27] hydrogen atoms refined with a riding model, data/restraints/parameters = 2196/1/261, $S(F^2)$ = 1.051, $R(F)$ = 0.0320 and $wR(F^2)$ = 0.0846 on all data, $R(F)$ = 0.0315 and $wR(F^2)$ = 0.0839 for 2153 reflections with $F_0 > 4\sigma(F_0)$, weighting scheme $w = 1/[\sigma^2(F_o^2) + (0.0611P)^2 + 0.2845P]$, where $P = (F_o^2 + 2F_c^2)/3$, largest difference between peak and hole was 0.152 and –0.254 e $Å^{-3}$. The unit cell contains one molecule of water. CCDC-798179 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Complete characterization of products **3b**–**g**, **4b**–**g**, **5c**–**e**, **5g** and **6a**, **6c**–**e**; ^1H and ^{13}C NMR spectra of compounds **3a**–**d**, **4a**–**g**, **5c**–**e**, **5g** and **6a**–**e**. Equilibrium conformers of compounds **3a** and **4a** and the number of states calculated for the calculated CD spectra are also included.

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