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Stereoselective synthesis of vicinal aminodiols, diamines and diaminols by the use of enantiopure aldehydes in the three-component aromatic Mannich-type reaction

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Abstract—A short and stereoselective synthesis of vicinal aminodiols, diamines and diaminols obtained in good yields, through a three-component aromatic Mannich-type reaction, is reported. Enantiopure aldehydes containing stereogenic centres and functionalized with variously protected amino and hydroxy groups successfully afforded enantiopure aminoalkylnaphthols. Conformational analysis, compared with ^{1}H NMR data of the products obtained, allows the attribution of the absolute configuration, also confirmed by X-ray analysis.

1. Introduction

Enantiopure vicinal diamines and aminols are subunits often present in a large number of pharmaceutical compounds and bioactive natural products. They are important building blocks in organic synthesis and are privileged structural elements in the search for chiral ligands,[1] that can be efficiently applied in asymmetric catalysis, a field of great interest in modern organic chemistry.[2–6]

Chiral diamines and aminols are frequently prepared by stereoselective nucleophilic addition to readily available starting materials as aldimines or related compounds. For some time, we have been interested in the stereoselective synthesis of aminoalcohols by the reduction or alkylation of compounds containing the enaminonic unit (enamino ketones,[7] enamino esters[8–10] and imidoylphenols[11–14]). The Mannich reaction is one of the most important multicomponent reactions in organic synthesis. In this three-component aminoalkylation of aldehydes, C–N and C–C single bonds replace the C=O double bond.[15,16] We have found that a straightforward and stereoselective synthesis of aminoalkylnaphthols can be performed by a Mannich reaction using enantiopure amines and inexpensive reagents.[17,18] The aminoalkylnaphthols obtained by this methodology, in good yields and high enantiomeric purity, result in effective catalysts in the enantioselective alkylation of aldehydes.[11,17,19,20]

2. Results and discussion

Herein we report the results of the diastereoselective synthesis of enantiopure aminoalkylnaphthols from chiral aldehydes. In Table 1 are reported the results of the one-pot reaction of β-naphthol with several chiral aldehydes **1** and primary or secondary amines **2**. On the basis of our previous experience and of literature reports,[19,25] only electron-rich phenols can take part in this reaction to afford the desired adduct. We limited this research to 2-naphthol for practical reasons.

The reaction was performed at room temperature in solventless conditions for 12–36 h. The reaction mixture showed an increasing viscosity while the water produced by the condensation separates. The use of Lewis acid catalysts ($LiClO_4$, $BF_3{\cdot}OEt_2$) did not result in a better performance of the reaction.

Several enantiopure aldehydes **1** containing stereogenic centres, functionalized with variously protected amino and hydroxy groups (acetonide, NH-Boc, NH-Cbz),

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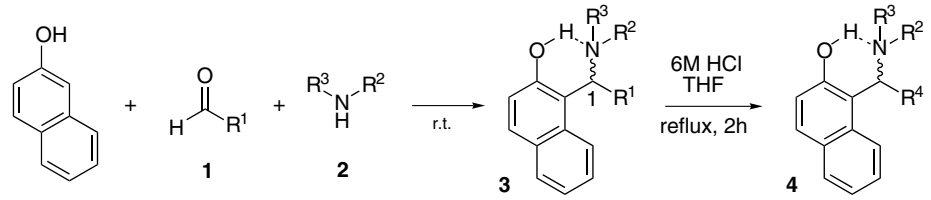
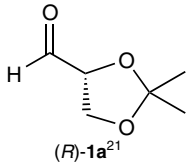
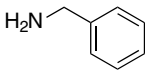
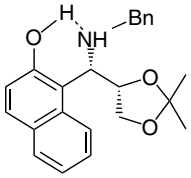
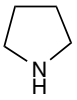
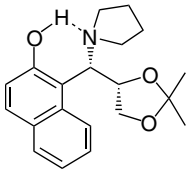
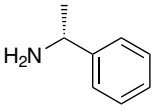
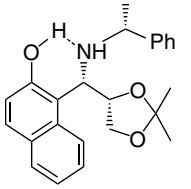
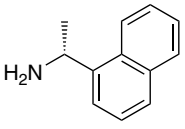
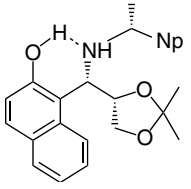
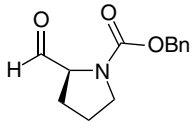
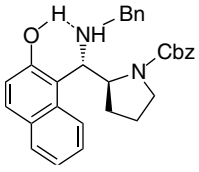
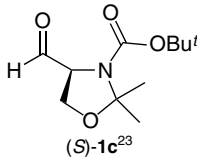
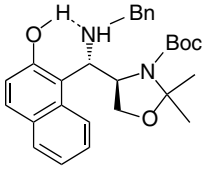
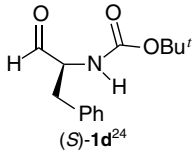
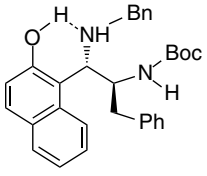
Table 1. Stereoselective synthesis of aminoalkylnaphthols **3a**–**g** by use of enantiopure aldehydes **1a**–**d**



Entry	1	2	3		Yields[a] (%)	dr[b]	$J_{H\text{-}1}$
1	 (*R*)-**1a**[21]	 **2a**		(*S*,*S*)-**3a** (1*R*,4*S*)-**3a**	52 18	75:25	3.4 9.9
2	(*R*)-**1a**	 **2b**		(*S*,*S*)-**3b** (1*R*,4*S*)-**3b**	40	73:27	2.8 7.3
3	(*R*)-**1a**	 (*R*)-**2c**		(1*S*,4*S*,1′*R*)-**3c** (1*R*,4*S*,1′*R*)-**3c**	62	89:11	2.9 9.5
4	(*R*)-**1a**	 (*R*)-**2d**		(1*S*,4*S*,1′*R*)-**3d** (1*R*,4*S*,1'*R*)-**3d**	54 8	86:14	3.3 9.5
5	 (*S*)-**1b**[22]	**2a**		(*S*,*S*)-**3e**[c]	32		8.8[c]
6	 (*S*)-**1c**[23]	**2a**		(1′*S*,4*R*)-**3f**[c]	24		5.1[c]
7	 (*S*)-**1d**[24]	**2a**		(*S*,*S*)-**3g**[c] (1*S*,2*R*)-**3g**[c]	44 28	62:38	3.7[c] 8.1[c]

[a] Yield of the pure isolated diastereomers.
[b] The dr values were determined by ^{1}H NMR of the crude reaction mixture.
[c] The absolute configuration was assigned on the basis of the $J_{H\text{-}1}$ values observed for the relative aminoalkyl naphthol **4**.

successfully afforded and with good stereoselectivities, condensation product **3**, as shown in Table 1.

The reaction works well with primary amines **2** but also with the secondary amines as pyrrolidine (Table 1, entry

2) and with the L-*N*-Boc 2-amino-3-phenylpropionaldehyde [(*S*)-**1d**, entry 7], in contrast to literature reports.[26]

The obtained aminoalkylnaphthol **3** was submitted to acid hydrolysis (HCl_{aq}/THF), to deprotect the protected amino and hydroxy groups in aldehydes **1**. The yields of the deprotected products **4** are reported in Table 2. The majority of product **4** can be obtained in enantiomerically pure form, by flash chromatography. Pure diastereomers are optically stable for a long time and do not show epimerization.

3. Absolute configuration attribution

The configuration of the new C-1 stereogenic centre, formed in the condensation reaction, was attributed on the basis of the $J_{H\text{-}1}$ values of ^{1}H NMR spectra, as reported

Table 2. Deprotection of aminoalkylnaphthols **3** to give enantiopure polyfunctional compound **4**

Entry	**3**	**4**	Yields[a] (%)	$J_{H\text{-}1}$
1	(*S*,*S*)-**3a**	(*S*,*S*)-**4a**	95	4.4
2	(*S*,*S*)-**3b**	(*S*,*S*)-**4b**	40	2.7
3	(1*S*,4*S*,1′*R*)-**3c**	(2*S*,3*S*,1′*R*)-**4c**	91	4.4
4	(*S*,*S*)-**3e**[b]	(*S*,*S*)-**4e**	78	8.8
5	(1′*S*,4*R*)-**3f**[b]	(1*S*,2*R*)-**4f**	88	5.1
6	(*S*,*S*)-**3g**[b]	(*S*,*S*)-**4g**	65	3.7
7	(1*R*,2*S*)-**3g**[b]	(1*R*,2*S*)-**4g**	51	8.1

[a] Yield of the pure isolated diastereomers.
[b] The absolute configuration was assigned on the basis of the $J_{H\text{-}1}$ values observed for the related aminoalkyl naphthol **4e**–**g**.

in Tables 1 and 2 and of the X-ray analysis[27] of product (*S*,*S*,*R*)-**3d** (see Fig. 1).

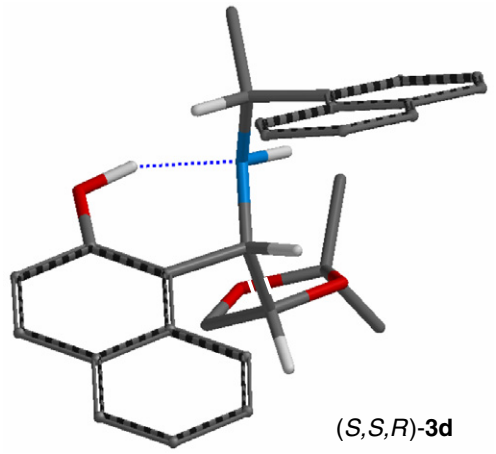


Figure 1. X-ray structure of the aminoalkyl naphthol (1*S*,4*S*,1′*R*)-**3d** major diastereomer.

The conformational analysis on all the possible diastereomers of products **3**, through stochastic methods (semiempirical PM3 minimizations),[28] showed that in diastereomers (1*S*)-**3a**–**d**,**f**,**g** and (1*R*)-**3e** the H-1 and H-2 protons are *gauche*, while in diastereomers (1*R*)-**3a**–**d**,**f**,**g** and (1*S*)-**3e** the same protons are *anti-periplanar*. In Figure 2 the more stable conformations for the (*S*,*S*)- and (*R*,*S*)-**3b** are reported.

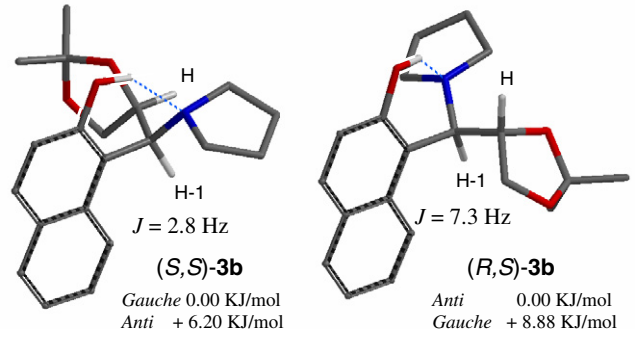


Figure 2. The more stable conformations for the *gauche*-(*S*,*S*)- and *anti*-(*R*,*S*)-**3b**.

This analysis allowed the assignment of the configuration on the basis of the observed ^{1}H NMR values of $J_{H\text{-}1}$ [$J = 2.8$–5.1 Hz (*gauche*), $J = 7.3$–9.9 Hz (*anti*) see Table 1]. This methodology was applied successfully to compounds **4**, allowing also in this case the assigned of the configuration, that corresponds to the one attributed to their precursors **3a**–**d**.

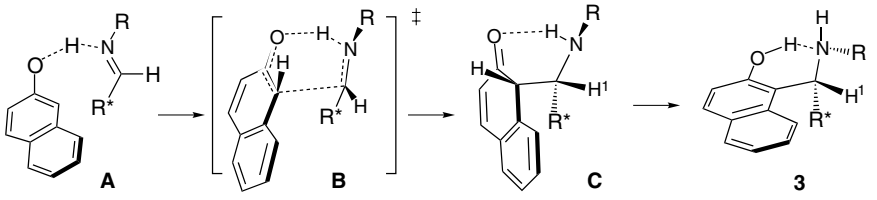
^{1}H NMR spectra analysis of products **3a**–**c** and **4a**–**c** revealed that no epimerization takes place during hydrolysis. In this way it is possible to assign the absolute configuration also to the newly formed stereogenic centres in products **3e**–**g**, that showed barely resolved ^{1}H NMR spectra (also at high temperatures (55 °C)), due to restricted rotation arising from the presence of voluminous protecting groups, that produces a mixture of different rotamers. With the ^{1}H NMR spectra of the deprotected isomer **4e**–**g** resolved, the attribution of the configurations of products **4e**–**g** allowed the assignment of the corresponding configurations to their precursors **3e**–**g**, as reported in Table 1.

A mechanistic hypothesis is depicted in Scheme 1. By mixing aldehydes **1** and amines **2** an immediate reaction takes place, which affords the corresponding imine, as illustrated by the formation of drops of water on the reaction flask. After this, it was assumed that an aldiminium-type complex (**A**) is formed through protonation of the C=N nitrogen by 2-naphthol, in which the reactivity of both the electrophilic iminium carbon atom and the nucleophilic α-position of β-naphthol are activated. Next the Friedel–Crafts reaction takes place, and in the first step, which is the rate-limiting one of the whole reaction, the arenium σ-complex **C** is formed through a six-membered transition state **B**, leading to the final 1-aminoalkyl-2-naphthols **3**, as shown in Scheme 1. The relative stabilities of the transition state **3a-*TS*** were calculated for all the possible diastereomers of product **3a**, at the semiempirical PM3 level, showing that the (*S*,*S*)-**3a-*TS*** is the more stable (Fig. 3). This is in agreement with the stereoselectivity observed in the products of this type of Mannich reaction.

The reaction between β-naphthol and benzaldehyde, in the absence of amine, did not result in the formation of the corresponding 1-hydroxyalkyl-2-naphthol. This evidence shows that the formation of the aldiminium complex **A** is a key step for the formation of the final 1-aminoalkyl-2-naphthols **3**, with the aldehyde not electrophilic enough to attack the aromatic ring without base catalysis.[29]

4. Conclusion

The introduction of chiral groups in the aldehyde moiety in this three-component aromatic Mannich-type reaction be-



Scheme 1. The mechanistic hypothesis for the Mannich-type diastereoselective aminoalkylation.

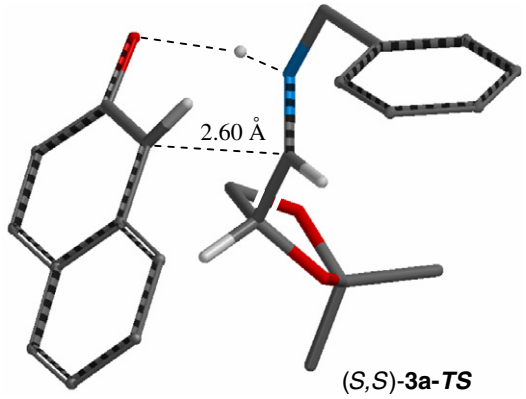


Figure 3. Molecular modelling representation of the more stable transition state for the formation of (*S*,*S*)-**3a**, optimized at the semiempirical PM3 level.

tween β-naphthol and several amines and aldehydes allows the stereoselective synthesis of vicinal aminodiols, diamines and diaminols in good yields and with high diastereoselectivity. Conformational analysis compared with ^{1}H NMR data and the X-ray analysis allowed the assignment of the absolute configuration of the obtained new products.

5. Experimental

5.1. General methods

^{1}H and ^{13}C NMR spectra were recorded at 200 or 300 MHz and 50 or 75 MHz, respectively. Chemical shifts are given in parts per million downfield from Me_4Si in $CDCl_3$ solution. Coupling constants are given in Hertz. IR spectra were recorded using a FTIR apparatus. Optical rotations were measured in a 1 dm cell at 20 °C. All melting points are uncorrected. Where only the major diastereomer was obtained pure, the ^{1}H NMR signals for the minor diastereomer were deduced from the spectra of the crude reaction mixture or from enriched chromatographic fractions.

5.2. Materials and solvents

All reagents were commercially available, and purchased at the highest quality and were purified by distillation when necessary. THF and toluene were distilled and stored on sodium wires before use. Aldehydes **1a**–**d** were prepared following literature methods.[21–24]

5.3. General procedure for the preparation of aminoalkylnaphthols 3a–g

A mixture of 2-naphthol (0.72 g, 5.0 mmol), aldehydes **1a**–**d** (5.0 mmol) and amines **2a**–**d** (5.0 mmol) was stirred and left to stand under solventless conditions at room temperature for the time required (12–72 h). Aminoalkylnaphthols **3a**–**g** were purified by flash chromatography directly from the reaction mixture, without any work-up. The characterization of the newly prepared aminoalkylnaphthols **3a**–**g** is as follows.

5.3.1. 1-{(*S*)-Benzylamino[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}-2-naphthol, (*S*,*S*)-3a. Colourless oil; $[\alpha]_D^{20} = -26.2$ (*c* 0.38, $CHCl_3$); IR (liquid film): ν_{max} 3318, 3062, 2985, 1621, 1585, 1455, 1269 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (s, 3H), 1.51 (s, 3H), 2.85 (br s, 1H), 3.71 (d, 1H, $J = 13.1$ Hz), 3.80 (dd, 1H, $J = 9.2$, 7.0 Hz), 3.98 (d, 1H, $J = 12.8$ Hz), 4.35 (dd, 1H, $J = 9.2$, 6.4 Hz), 4.59 (dt, 1H, $J = 6.7$, 3.4 Hz), 5.04 (d, 1H, $J = 3.4$ Hz), 7.00–7.85 (m, 11H), 13.60 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.6, 26.5, 52.3, 59.2, 64.52, 77.0, 109.0, 109.2, 120.3, 120.7, 122.8, 127.0, 127.9, 128.6, 128.8, 128.9, 129.3, 130.3, 132.8, 137.9, 157.5. Anal. Calcd for $C_{23}H_{25}NO_3$ (363.45): C, 76.01; H, 6.93; N, 3.85. Found: C, 76.27; H, 7.22; N, 3.62.

5.3.2. 1-{(*R*)-Benzylamino[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}-2-naphthol, (1*R*,4*S*)-3a. Colourless crystals; mp 130–133 °C (hexane); $[\alpha]_D^{20} = -12.9$ (*c* 0.39, $CHCl_3$); IR (Nujol): ν_{max} 3339, 1621, 1598 1213 1168 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.33 (s, 3H), 1.39 (s, 3H), 3.00 (br s, 1H), 3.58 (d, 1H, $J = 13.6$ Hz), 3.61 (dd, 1H, $J = 9.2$, 5.9 Hz), 3.73 (dd, 1H, $J = 9.2$, 3.3 Hz), 3.91 (d, 1H, $J = 13.6$ Hz), 4.48 (ddd, 1H, $J = 9.9$, 5.9, 3.3 Hz), 4.67 (d, 1H, $J = 9.9$ Hz) 7.05–7.85 (m, 11H), 13.00 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 25.6, 27.7, 50.6, 58.8, 66.4, 76.9, 110.0, 111.1, 120.0, 121.4, 122.9, 127.1, 127.9, 128.9, 129.0, 129.1, 129.3, 130.6, 133.8, 138.2, 157.7. Anal. Calcd for $C_{23}H_{25}NO_3$ (363.45): C, 76.01; H, 6.93; N, 3.85. Found: C, 76.24; H, 7.19; N, 3.68.

5.3.3. 1-{(*S*)-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl](pyrrolidin-1-yl)methyl}-2-naphthol, (*S*,*S*)-3b. Colourless oil; $[\alpha]_D^{20} = +0.6$ (*c* 0.49, $CHCl_3$); IR (film): ν_{max} 3483, 3004, 2957, 2852, 2361, 1736 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (s, 3H), 1.31 (s, 3H), 1.80–1.95 (m, 4H), 2.70–2.94 (m, 4H), 3.78 (t, 1H, $J = 8.4$ Hz), 3.95 (dd, 1H, $J = 8.4$, 6.6 Hz), 4.48 (d, 1H, $J = 2.8$ Hz), 4.57 (ddd, 1H, $J = 8.4$, 6.6, 2.8 Hz), 7.05–7.85 (m, 6H), 11.70 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.5, 25.5, 26.1, 53.2, 64.4, 65.8, 77.8, 108.8, 112.3, 119.8, 121.1, 122.5, 124.2, 126.9, 129.3, 130.1, 133.0, 157.3. Anal. Calcd for $C_{20}H_{25}NO_3$ (327.42): C 73.37 H 7.70 N 4.28. Found: C, 73.55; H, 7.91; N, 4.02.

5.3.4. 1-{(*R*)-[(4*S*)-2,2-Dimethyl-1,3-Dioxolan-4-yl](pyrrolidin-1-yl)methyl}-2-naphthol, (1*R*,4*S*)-3b. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 (s, 3H), 1.47 (s, 3H), 1.80–1.95 (m, 4H), 2.75–3.00 (m, 4H), 3.52 (d, 2 H, $J = 7.0$ Hz), 4.49 (d, 1H, $J = 7.3$ Hz), 4.88 (q, 1H, $J = 7.0$ Hz), 7.10–7.90 (m, 6H), 11.00 (br s, 1H).

5.3.5. 1-((*S*)-(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl{[(1*R*)-1-phenylethyl]amino}methyl)-2-naphthol, (1*S*,4*S*,1′*R*)-3c. Colourless crystals; mp 153–155 °C (hexane); $[\alpha]_D^{20} = -44.5$ (*c* 0.74, $CHCl_3$); IR (Nujol): ν_{max} 3301, 1620, 1519, 1270 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (s, 3H), 1.52 (d, 3H, $J = 7.0$ Hz), 1.58 (s, 3H), 2.87 (br s, 1H), 3.72–3.90 (m, 2H), 4.32–4.50 (m, 2H), 4.75 (d, 1H, $J = 2.9$ Hz), 7.05–7.85 (m, 11H), 13.80 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.4, 24.5, 26.6, 56.2, 56.7, 64.6, 76.9, 109.2, 109.7, 120.3, 120.7, 122.7, 126.8, 127.9, 128.8, 128.9, 129.0, 129.2, 130.2, 132.7, 142.7, 157.9. Anal.

Calcd for $C_{24}H_{27}NO_3$ (377.48): C, 76.36, H, 7.21, N, 3.71. Found: C, 76.54; H, 7.44; N, 3.56.

5.3.6. 1-((*R*)-(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl{[(1*R*)-1-phenylethyl]amino}methyl)-2-naphthol, (1*R*,4*S*,1′*R*)-3c. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (s, 3H), 1.52 (d, 3H, $J = 6.6$ Hz), 1.62 (s, 3H), 2.85 (br s, 1H), 3.64 (dd, 1H, $J = 8.8$, 6.2 Hz), 3.78 (dd, 1H, $J = 8.8$, 3.7 Hz), 3.80–3.90 (m, 1H), 4.48 (ddd, 1H, $J = 9.5$, 6.2, 3.7 Hz), 4.95 (d, 1H, $J = 9.5$ Hz), 6.95–8.03 (m, 11H), 13.80 (br s, 1H).

5.3.7. 1-{(*S*)-(1*R*)-1-(1-Naphthyl)ethan-1-amine[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}-2-naphthol, (1*S*,4*S*,1′*R*)-3d. Colourless crystals; mp 138–140 °C (hexane); $[\alpha]_D^{20} = -111.9$ (c 1.15, $CHCl_3$); IR (Nujol): ν_{max} 3311, 1621, 1599, 1582, 1520 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 3H), 1.55 (s, 3H), 1.64 (d, 3H, $J = 6.6$ Hz), 3.20 (br s, 1H), 3.79 (dd, 1H, $J = 8.1$, 6.6 Hz), 4.42 (dd, 1H, $J = 8.4$, 6.2 Hz), 4.50 (td, 1H, $J = 6.4$, 3.3 Hz), 4.79 (br q, 1H, $J = 6.6$ Hz), 4.90 (d, 1H, $J = 3.3$ Hz), 7.05–7.95 (m, 13H), 14.00 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.2, 24.4, 26.6, 51.5, 57.3, 64.6, 76.9, 109.3, 110.1, 120.3, 120.8, 122.7, 122.8, 125.8, 125.9, 126.4, 126.8, 128.2, 128.7, 129.1, 130.2, 131.5, 132.6, 134.1, 139.0, 157.8. Anal. Calcd for $C_{28}H_{29}NO_3$ (427.53): C, 78.66; H, 6.84; N, 3.28. Found: C, 78.47; H, 6.98; N, 3.07.

5.3.8. 1-{(*R*)-(1*R*)-1-(1-Naphthyl)ethan-1-amine[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}-2-naphthol, (1*R*,4*S*,1′*R*)-3d. Colourless oil; $[\alpha]_D^{20} = -22.6$ (c 0.46, $CHCl_3$); IR (liquid film): ν_{max} 3309, 3051, 2984, 1621, 1599, 1520 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.34 (s, 3H), 1.43 (s, 3H), 1.61 (d, 3H, $J = 6.6$ Hz), 3.10 (br s, 1H), 3.64 (dd, 1H, $J = 9.2$, 6.2 Hz), 3.76 (dd, 1H, $J = 9.2$, 3.7 Hz), 4.49 (ddd, 1H, $J = 9.5$, 6.2, 3.7 Hz), 4.71 (q, 1H, $J = 6.6$ Hz), 4.96 (d, 1H, $J = 9.5$ Hz), 7.00–8.00 (m, 13H), 14.00 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.9, 21.0, 24.5, 25.6, 27.7, 49.2, 49.3, 57.3, 66.4, 110.1, 120.1, 122.7, 122.9, 123.1, 125.5, 125.8, 126.3, 127.2, 128.1, 129.1, 130.4, 130.5, 132.6, 133.6, 134.1, 139.9, 157.6. Anal. Calcd for $C_{28}H_{29}NO_3$ (427.53): C, 78.66; H, 6.84; N, 3.28. Found: C, 78.53; H, 6.92; N, 3.39.

5.3.9. Benzyl (*S*)-2-[(*S*)-benzylamino(2-hydroxy-1-naphthyl)methyl]pyrrolidine-1-carboxylate, (*S*,*S*)-3e. Colourless oil; $[\alpha]_D^{20} = -15.8$ (c 3.65, $CHCl_3$); IR (liquid film): ν_{max} 3290, 3030, 2956, 2888, 1891, 1694 cm^{-1}; ^{1}H NMR (50 °C) (400 MHz, $CDCl_3$): δ 1.50–1.75 (m, 5H), 3.16 (dd, 1H, $J = 10.4$, 5.2 Hz), 3.48 (br s, 1H), 3.58 (br d, 1H, $J = 9.2$ Hz), 3.77–3.88 (m, 1H), 4.53–4.62 (m, 1H), 4.72 (br s, 1H), 5.24 (br s, 2H), 7.05–7.80 (m, 16H), 14.50 (br s, 1H); ^{13}C NMR (50 °C) (100 MHz, $CDCl_3$): δ 24.3, 28.3, 47.0, 51.4, 60.5, 61.9, 67.6, 113.4, 120.2, 121.4, 122.6, 126.4, 127.6, 127.9, 128.1, 128.4, 128.6, 128.8, 128.9, 129.2, 130.1, 134.4, 136.9, 138.7, 157.6; Anal. Calcd for $C_{30}H_{30}N_2O_3$, MW 466.571: C, 77.23; H, 6.48; N, 6.00. Found: C, 77.45; H, 6.22; N, 6.23.

5.3.10. *tert*-Butyl (4*R*)-4-[(*S*)-benzylamino(2-hydroxy-1-naphthyl)methyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate, (1′*S*,4*R*)-3f. Colourless crystals; mp 123–126 °C (hexane); $[\alpha]_D^{20} = +3.5$ (c 1.44, $CHCl_3$); IR (Nujol): ν_{max} 2361, 1684, 1624, 1169 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.46 (s, 3H), 1.58 (s, 9H), 1.67 (br s, 3H), 2.68 (br s, 1H), 3.65 (d, 1H, $J = 13.3$ Hz), 3.79 (dd, 1H, $J = 10.0$, 7.8 Hz), 4.02 (d, 1H, $J = 13.2$ Hz), 4.38–4.45 (m, 2H), 5.25 (br s, 1H), 7.15–7.80 (m, 11H), 13.90 (br s, 1H); ^{13}C NMR (50 °C) (100 MHz, $CDCl_3$): δ 23.0, 27.4, 28.8, 52.8, 59.5, 60.6, 64.4, 81.3, 94.6, 110.7, 120.5, 122.0, 122.8, 126.9, 127.9, 128.7, 128.9, 129.0, 130.1, 133.3, 138.0, 153.0, 157.9; Anal. Calcd for $C_{28}H_{34}N_2O_4$, MW 462.581: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.91; H, 7.19; N, 6.29.

5.3.11. *tert*-Butyl-*N*-[(*S*,*S*)-1-benzyl-2-(benzylamino)-2-(2-hydroxy-1-naphthyl)ethyl]carbamate, (*S*,*S*)-3g. Colourless oil; $[\alpha]_D^{20} = +3.75$ (c 2.21, $CHCl_3$); IR (neat): ν_{max} 3311, 1697, 1622, 1496, 1471, 1455, 1367, 1266, 1164 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$ 50 °C): δ 1.40–1.60 (m, 9H), 2.81 (dd, 1H, $J = 14.6$, 11.7 Hz), 3.10 (dd, 1H, $J = 14.6$, 3.7 Hz), 3.15 (br s, 1H), 3.68 (d, 1H, $J = 13.0$ Hz), 4.02 (d, 1H, $J = 13.0$ Hz), 4.39 (ddd, 1H, $J = 11.7$, 7.0, 3.7 Hz), 5.25 (br s, 2H), 6.95–8.25 (m, 16H), 12.80 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.4, 30.2, 38.4, 56.4, 61.3, 82.6, 110.6, 119.9, 121.6, 122.7, 126.4, 126.8, 128.4, 128.6, 128.8, 128.9, 129.4, 129.5, 129.6, 130.2, 133.2, 137.4, 138.0, 156.2, 157.4; Anal. Calcd for $C_{31}H_{34}N_2O_3$ (482.613): C, 77.15; H, 7.10; N, 5.80. Found: C, 77.34; H, 7.29; N, 5.69.

5.3.12. *tert*-Butyl-*N*-[(1*S*,2*R*)-1-benzyl-2-(benzylamino)-2-(2-hydroxy-1-naphthyl)ethyl]carbamate, (1*S*,2*R*)-3g. Crystals; mp 98–101 °C (hexane); $[\alpha]_D^{20} = -0.3$ (c 2.98, $CHCl_3$); IR (Nujol): ν_{max} 3307, 1695, 1629, 1495, 1468, 1364, 1264, 1165 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.35 (m, 9H), 2.53 (dd, 1H, $J = 13.9$, 4.2 Hz), 2.84 (br t, 1H, $J = 11.4$ Hz), 3.61 (d, 1H, $J = 13.2$ Hz), 3.91 (d, 1H, $J = 13.2$ Hz), 4.08 (br s, 1H, $J_{1/2} = 24.3$ Hz), 4.55 (br d, 1H, $J = 7.0$ Hz), 5.05 (br s, 2H), 6.90–7.87 (m, 16H), 12.80 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.4, 30.4, 37.4, 57.2, 59.2, 80.0, 112.5, 120.1, 112.0, 122.8, 126.5, 126.8, 128.5, 128.96, 129.01, 129.2, 129.4, 129.5, 129.6, 130.3, 134.0, 137.9, 138.4, 156.0, 157.0; Anal. Calcd for $C_{31}H_{34}N_2O_3$ (482.613): C, 77.15; H, 7.10; N, 5.80. Found: C, 76.92; H, 7.32; N, 5.61.

5.4. General procedure for the preparation of aminoalkylnaphthols 4a–c,e–g

A solution of aminoalkylnaphthols **3a–c**,**e–g** (5.0 mmol) in 6 M HCl (5 mL) and THF (5 mL) was stirred and heated under reflux for 2 h. Then, the mixture was extracted with H_2O/CH_2Cl_2 and the aqueous phase alkalyzed with 10% aqueous NaOH. Extraction with CH_2Cl_2, drying over Na_2SO_4, evaporation of the solvent gives crude aminoalkylnaphthols **4a–c**,**e–g**, which were purified by crystallization or filtration on a thin pad of silica gel, with *n*-hexane/ethyl acetate (60:40) as eluent. Spectral data of products **4a–c**,**e–g** follow.

5.4.1. (*S*,*S*)-3-(Benzylamino)-3-(2-hydroxy-1-naphthyl)propane-1,2-diol, (*S*,*S*)-4a. Colourless oil; $[\alpha]_D^{20} = -0.9$ (c 0.64, $CHCl_3$); IR (neat): ν_{max} 3316, 3055, 2926, 2852, 1622, 1599,1584, 1520 cm^{-1}; ^{1}H NMR: δ 3.57–3.67 (m, 1H), 3.65 (d, 1H, $J = 12.8$ Hz), 3.82 (dt, 1H,

$J = 11.4,7.3$, Hz), 3.92 (d, 1H, $J = 12.8$ Hz), 4.17 (m, 1H), 5.02 (d, 1H, $J = 4.4$ Hz), 5.55 (br s, 4H), 7.05–7.80 (m, 11H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 52.3, 61.2, 62.6, 73.3, 120.0, 122.9, 127.0, 127.1, 128.0, 128.1, 128.9, 128.97, 129.0, 129.3, 130.5, 133.0, 137.2, 157.4. Anal. Calcd for $C_{20}H_{21}NO_3$ (323.386): C, 74.28; H, 6.55; N, 4.33. Found: C, 74.45; H, 6.61; N, 4.20.

5.4.2. (*S*,*S*)-3-(2-Hydroxy-1-naphthyl)-3-pyrrolidin-1-yl-propane-1,2-diol, (*S*,*S*)-4b. Colourless oil; $[\alpha]_D^{20} = -0.8$ (*c* 0.91, $CHCl_3$); IR: ν_{max} 3055, 2985, 1622, 1600, 1517 cm^{-1}; ^{1}H NMR: δ 1.78–1.93 (m, 4H), 2.76–2.96 (m, 4H), 3.22–3.30 (m, 1H), 3.58 (ddd, 1H, $J = 10.9$, 4.3, 2.0 Hz), 4.28–4.33 (m, 1H), 4.41 (d, 1H, $J = 5.0$ Hz), 6.40 (br s 3H), 7.10–8.00 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.0, 23.1, 24.3, 30.9, 44.9, 51.9, 120.8 123.0, 128.7, 129.1, 129.3, 130.4, 131.1, 149.1, 153.5. Anal. Calcd for $C_{17}H_{21}NO_3$ (287.354): C, 71.06; H, 7.37; N, 4.87. Found: C, 70.76; H, 7.64; N, 5.10.

5.4.3. (2*S*,3*S*)-3-(2-Hydroxy-1-naphthyl)-3-{[(1′*R*)-1′-phenylethyl]amino}propane-1,2-diol, (2*S*,3*S*,1′*R*)-4c. Colourless oil; $[\alpha]_D^{20} = -0.8$ (*c* 1.5, $CHCl_3$); IR: ν_{max} 3327, 3055, 2968, 1622, 1600, 1519 cm^{-1}; ^{1}H NMR: δ 1.47 (d, 3H, $J = 7.0$ Hz), 3.51–3.84 (m, 3H), 3.97 (m, 1H), 4.64 (d, 1H, $J = 4.4$ Hz), 4.95 (br s, 4H), 7.05–7.75 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.4, 56.0, 58.5, 62.6, 73.2, 110.5, 119.9, 120.8, 122.7, 126.8, 126.9, 127.9, 128.7, 128.9, 129.1, 130.1, 132.8, 142.6, 157.8. Anal. Calcd for $C_{21}H_{23}NO_3$ (337.412): C, 74.75; H, 6.87; N, 4.15. Found: C, 74.50; H, 6.91; N, 4.29.

5.4.4. 1-{(*S*)-(Benzylamino)[(2*S*)pyrrolidin-2-yl]methyl}-2-naphthol, (*S*,*S*)-4e. Oil; $[\alpha]_D^{20} = +2.7$ (*c* 1.3, $CHCl_3$); IR: ν_{max} 3288, 3056, 3030, 2977, 2931, 2886, 1621, 1600, 1584, 1521 cm^{-1}; ^{1}H NMR: δ 1.36–1.92 (m, 4H), 2.87 (dt, 1H, $J = 11.0$, 6.8 Hz), 2.99 (ddd, 1H, $J = 11.0$, 7.4, 5.8 Hz), 3.61 (d, 1H, $J = 13.3$ Hz), 3.70 (ddd, 1H, $J = 9.8$, 8.0, 5.1 Hz), 3.82 (d, 1H, $J = 13.3$ Hz), 4.35 (d, 1H, $J = 9.8$ Hz), 7.00–7.80 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.3, 29.2, 46.7, 51.1, 59.9, 61.5, 114.4, 120.0, 120.6, 121.6, 122.4, 126.4, 127.5, 128.7, 128.8, 129.1, 129.6, 134.2, 139.0, 157.1. Anal. Calcd for $C_{22}H_{24}N_2O$ (332.439): C, 79.48; H, 7.28; N, 8.43. Found: C, 79.66; H, 7.14; N, 8.36.

5.4.5. 1-[(1*S*,2*R*)-2-Amino-1-(benzylamino)-3-hydroxypropyl]-2-naphthol, (1*S*,2*R*)-4f. Oil; $[\alpha]_D^{20} = +1.1$ (*c* 0.46, $CHCl_3$); IR (neat): ν_{max} 3350, 1621, 1238, 1027 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.45 (q, 1H, $J = 5.5$ Hz), 3.58 (d, 1H, $J = 13.3$ Hz), 3.60–3.65 (m, 1H), 3.70–3.80 (m, 1H), 3.80 (br s, 5H), 3.87 (d, 1H, $J = 12.9$ Hz), 4.68 (d, 1H, $J = 5.1$ Hz), 7.05–7.80 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.2, 55.8, 60.9, 63.3, 111.7, 120.1, 121.1, 122.7, 126.5, 126.8, 127.8, 128.9, 129.3, 129.8, 130.1, 133.4, 138.2, 157.4; Anal. Calcd for $C_{20}H_{22}N_2O_2$ (322.401): C, 74.51; H, 6.88; N, 8.69. Anal. Calcd for $C_{20}H_{22}N_2O_2$ (322.401): C, 74.51; H, 6.88; N, 8.69. Found: C, 74.70; H, 6.72; N, 8.74.

5.4.6. 1-[(*S*,*S*)-2-Amino-1-(benzylamino)-3-phenylpropyl]-2-naphthol, (*S*,*S*)-4g. Colourless oil; $[\alpha]_D^{20} = +1.9$ (*c* 1.2, $CHCl_3$); IR (neat): ν_{max} 3350, 3275, 1620, 1600, 1492, 1408, 1270, 824 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.70 (br s, 4H), 2.66 (dd, 1H, $J = 13.5$, 11.0 Hz), 2.92 (dd, 1H, $J = 13.5$, 3.0 Hz), 3.64 (d, 1H, $J = 12.8$ Hz), 3.69 (ddd, 1H, $J = 11.0$, 3.7, 3.0 Hz), 3.97 (d, 1H, $J = 12.8$ Hz), 4.73 (d, 1H, $J = 3.7$ Hz), 6.95–7.85 (m, 16H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 36.8, 52.6, 55.7, 62.8, 111.6, 120.3, 121.0, 122.5, 126.5, 126.7, 128.2, 128.5, 128.7, 128.8, 129.6, 129.2, 129.3, 129.9, 133.3, 138.4, 139.2, 157.6. Anal. Calcd for $C_{26}H_{26}N_2O$ (382.498): C, 81.64; H, 6.85; N, 7.32. Found: C, 81.77; H, 7.01; N, 7.30.

5.4.7. 1-[(1*R*,2*S*)-2-Amino-1-(benzylamino)-3-phenylpropyl]-2-naphthol, (1*R*,2*S*)-4g. Colourless oil; $[\alpha]_D^{20} = -0.5$ (*c* 1.44, $CHCl_3$); IR (neat): ν_{max} 3348, 3280, 1622, 1596, 1498, 1411, 1267, 828 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.32 (dd, 1H, $J = 13.6$, 10.2 Hz), 2.63 (dd, 1H, $J = 13.6$, 4.0 Hz), 3.36 (ddd, 1H, $J = 10.3$, 8.0, 4.0 Hz), 3.60 (d, 1H, $J = 13.2$ Hz), 3.92 (d, 1H, $J = 13.2$ Hz), 4.45 (d, 1H, $J = 8.0$ Hz), 4.85 (br s, 3H), 6.85–7.80 (m, 16H), 12.80 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 43.0, 51.3, 56.7, 61.2, 113.8, 120.3, 121.7, 122.5, 126.5, 126.6, 127.7, 128.7, 128.8, 129.0, 129.27, 129.29, 133.4, 134.1, 135.5, 138.8, 139.1, 157.2; Anal. Calcd for $C_{26}H_{26}N_2O$ (382.498): C, 81.64; H, 6.85; N, 7.32. Found: C, 81.37; H, 6.88; N, 7.25.

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