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Stereocontrolled metalloenamine alkylations: application to the asymmetric synthesis of 4-alkyl-1,2,3,4-tetrahydroisoquinolines

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Abstract

A procedure for the asymmetric synthesis of 4-alkyl-1,2,3,4-tetrahydroisoquinolines is described. The key step in the synthetic route is a stereocontrolled metalloenamine alkylation using (*R*)-(+)-phenylglycinol methyl ether as the chiral auxiliary. Subsequent *N*-methylation, hydrogenolysis and cyclization afforded the target heterocycles with enantiomeric excesses higher than 99%.

1. Introduction

In recent years the stereoselective synthesis of isoquinoline alkaloids has been a field of increasing interest in synthetic organic chemistry.[1] Many methods have already been published for highly stereoselective syntheses of 1-substituted tetrahydroisoquinolines,[2] which are very useful intermediates for the preparation of a wide range of enantiopure alkaloids.[3] However, although chiral non racemic 4-substituted tetrahydroisoquinoline derivatives are of considerable interest due to their biological activity and as naturally occurring alkaloids,[4] the research towards their stereoselective synthesis is not as extensive as in the case of the 1-substituted tetrahydroisoquinolines. Some papers have appeared for the asymmetric synthesis of tetrahydroisoquinoline derivatives when the substituent at C-4 bears a hydroxy function,[5] but only a few reports can be found when the substitution at this position is not a heteroatom,[6] which occurs in nature quite often, e.g. in nomifemsine,[7] cherylline[8] and the spermidine alkaloids cyclocelabencine and isocyclocelabencine (Fig. 1).[9]

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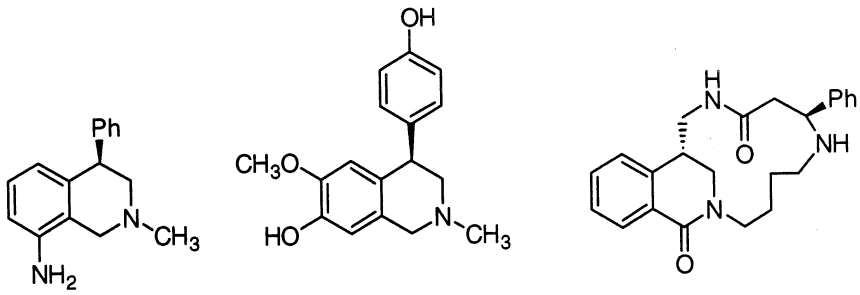
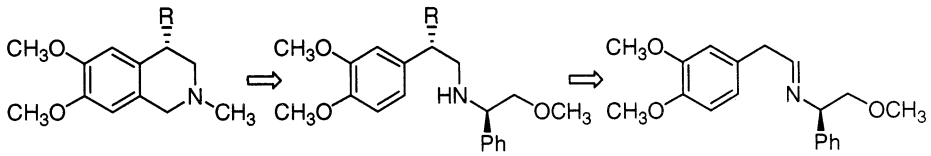


nomifemsine *cherylline* *cyclocelabencine*

Figure 1.

In this context, and in connection with our studies in the field of the asymmetric synthesis of isoquinoline alkaloids[5b,10] we have developed a suitable and general enantioselective synthetic method to obtain 4-alkyl-1,2,3,4-tetrahydroisoquinolines starting from chiral arylethylamine precursors (Scheme 1), which were prepared employing an asymmetric metalloenamine alkylation protocol starting from an imine derived from homoveratraldehyde and (*R*)-(+)-phenylglycinol methyl ether.[11] The developed protocol is interesting from a synthetic point of view taking into account the possibility of introducing any kind of alkyl chain at the 4-position of the isoquinoline core. This can lead to the synthesis of a wide range of naturally and unnaturally occurring isoquinoline derivatives.



Scheme 1.

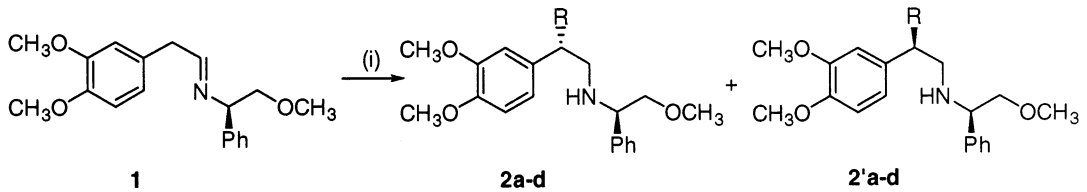
2. Results and discussion

The starting imine **1** was subjected to deprotonation with LDA at −78°C followed by alkylation with several alkyl halides at the same temperature and the crude reaction mixture was reduced in situ with $NaBH_4$ yielding the aminoethers **2a–d** in good yields and moderate to good diastereoselectivities. It was observed that when increasing the steric bulk of the incoming electrophile the **2**/**2′** ratio noticeably improved varying from 67/33 when R = Me to 93/7 when R = Bn (see Table 1). In all cases, it was possible to isolate and characterize each of the obtained diastereomers by flash column chromatography purification of the reaction crude. The stereochemistry of the newly created stereogenic center in the major isomers **2a–d** was provisionally assigned as (*S*) on the basis of the mechanism proposed by Meyers for a similar case (Scheme 2).[11g]

Table 1
Asymmetric alkylation-reduction of **1**

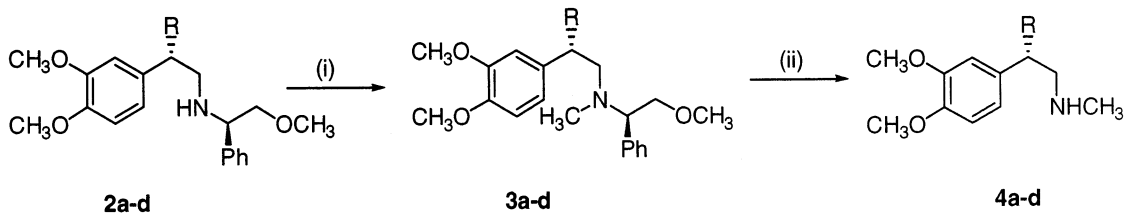
Product	R	Yield (%)[a]	**2**/**2′**[b]
2a	Me	66	67/33
2b	Et	88	86/14
2c	*i*-Pr	90	89/11
2d	Bn	78	93/7

[a] Global yield as mixture of diastereoisomers **2**/**2′**.
[b] Calculated by HPLC (Chiralcel OD column, UV detector, hexane/*i*-PrOH 95/5, flow rate 0.75 mL/min.



Scheme 2. *Reagents and conditions*: (i) LDA, THF, −78°C; (ii) RX, THF, −78°C; (iii) $NaBH_4$, MeOH, −20°C

Proceeding with the planned synthesis, the aminoethers **2a–d** were *N*-methylated under standard conditions[12] and the obtained products **3a–d** were subjected to a hydrogenolysis procedure to remove the benzylic part of the chiral appendage yielding the corresponding 2-substituted 2-arylethylamines **4a–d** in good yields. Their analysis by chiral HPLC under conditions optimized with the help of a racemic standard[13] showed that they were obtained as only one detectable enantiomer indicating that both processes, *N*-methylation and hydrogenolysis, proceeded without racemization in the previously formed stereogenic center (Scheme 3, Table 2).



Scheme 3. *Reagents and conditions*: (i) $HCHO_{aq}$, $NaBH_3CN$, CH_3CN, rt; (ii) H_2 (60 psi), Pd/C, 1 M HCl, EtOH

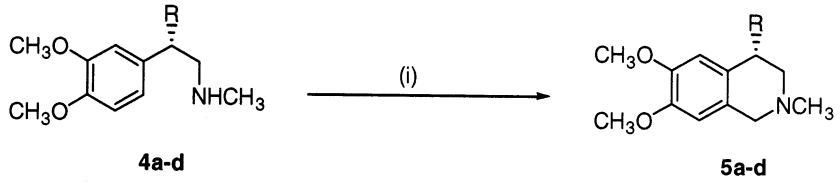
Table 2
N-Methylation/hydrogenolysis of aminoethers **2a–d**

Product	R	Yield (%)	Product	Yield (%)	E.e. (%)[a]
3a	Me	93	**4a**	83	>99
3b	Et	91	**4b**	84	>99
3c	*i*-Pr	93	**4c**	88	>99
3d	Bn	90	**4d**	87	>99

[a] Calculated by HPLC (Chiralcel OD column, UV detector, hexane/*i*-PrOH 90/10, flow rate 0.80 mL/min).

The fact that amine **4a** is a known product[6h] allowed us to establish unambiguously the absolute configuration of its stereogenic center by comparison of the obtained specific rotation value $\{[\alpha]_D^{20} = -16.3$, $(c = 1.75$, $CHCl_3)\}$ with that reported in the literature $\{[\alpha]_D^{20} = +13.0$, $(c = 1.75$, $CHCl_3)$ for the (R) enantiomer$\}$, thus confirming the previously assigned (S)-configuration for **4a** and by extension to the rest of amines **4** and all the obtained aminoethers **2a–d**, and **3a–d**.

Finally, the amines **4a–d** were converted into the target heterocycles by Pictet–Spengler heterocyclization reaction[14] by reacting them with aqueous formaldehyde and 1 M HCl at 60°C. The isoquinolines **5a–d** were obtained in excellent yields and again as only one detectable enantiomer as indicated by chiral HPLC analysis (Scheme 4, Table 3).



4a-d **5a-d**

Scheme 4. *Reagents and conditions*: (i) HCHO aq., 1 M HCl, 60°C

Table 3
Pictet–Spengler cyclization of amines **3a–d**

Product	R	Yield (%)	E.e. (%)[a]
5a	Me	96	>99
5b	Et	92	>99
5c	*i*-Pr	95	>99
5d	Bn	93	>99

In conclusion, we have developed a procedure to stereoselectively prepare 4-alkyl-1,2,3,4-tetrahydroisoquinolines employing a diastereoselective metalloenamine alkylation procedure of an imine derived from homoveratraldehyde and (R)-phenylglycinol methyl ether as the key step with respect to the stereochemical control. Although this key reaction proceeds with moderate to good stereoselectivities, the final diastereoisomers are easily separated by flash column chromatography which allows, after a series of simple transformations, the access to the target heterocycles in good yields and as enantiomerically pure compounds.

3. Experimental

3.1. General procedures

Melting points were determined in unsealed capillary tubes and are uncorrected. IR spectra were obtained on KBr pellets (solids) or $CHCl_3$ solution (oils). NMR spectra were recorded at 20–25°C, running at 250 MHz for ^1H and 62.8 MHz for ^{13}C in $CDCl_3$ solution and resonances

are reported in ppm relative to tetramethylsilane unless otherwise stated. Assignment of individual ^{13}C resonances are supported by DEPT experiments. ^{1}H–$\{^{1}H\}$ NOE experiments were carried out in the difference mode by irradiation of all the lines of a multiplet.[15] Mass spectra were recorded under electron impact at 70 eV. TLC was carried out with 0.2 mm thick silica gel plates (Merck Kiesegel GF_{254}). Visualization was accomplished by UV light or by spraying with Dragendorff's reagent.[16] Flash column chromatography[17] on silica gel was performed with Merck Kiesegel 60 (230–400 mesh). Determination of enantiomeric excesses was performed by chiral HPLC analysis of non crystallized samples using a Chiracel OD column with a UV detector with the eluents and flow rates as indicated in each case. All solvents used in reactions were dried and purified according to standard procedures.[18] *n*-BuLi was titrated with diphenylacetic acid periodically prior to use. All air- or moisture-sensitive reactions were performed under argon. The glassware was oven dried (140°C) overnight and purged with argon.

3.2. Synthesis of (1′R)-(−)-(3,4-dimethoxyphenyl)-N-(1′-phenyl-2′-methoxyethyl)ethylideneamine **1**

A dissolution of (*R*)-phenylglycinol methyl ether (0.16 g, 1.08 mmol) and homoveratraldehyde (0.16 g, 1.08 mmol) in Et_2O (10 mL) and in the presence of Na_2SO_4 was stirred for 5 min and was then filtered and the solvent was removed in vacuo affording imine **1**, which was directly employed in the alkylation reaction. Yield: 96%. ^{1}H NMR: 3.24 (s, 3H); 3.33 (m, 2H); 3.55 (d, 2H, $J=5.3$ Hz); 3.87 (s, 6H); 4.12 (m, 1H); 6.73–6.88 (m, 3H); 7.12–7.36 (m, 5H); 7.77 (t, 1H, $J=5.3$ Hz). ^{13}C NMR: 43.6, 55.5, 58.2, 59.3, 65.5, 76.8, 110.5, 112.8, 123.6, 127.4, 128.2, 129.1, 133.6, 138.2, 147.5, 148.9, 163.3. MS (EI) m/z (int. rel.): 313 (M^+, 13), 268 (92), 151 (100). IR ($CHCl_3$): 1631.

3.3. General procedure for the alkylation-reduction of metalloenamine **1**

A solution of **1** (0.20 mmol) was slowly added over a cold (−78°C) LDA solution (0.20 mmol) in dry THF (15 mL). The mixture was stirred for 1 h at this temperature and then a solution of RX (0.20 mmol) in dry THF (10 mL) was dropwise added within 40 min. The reaction was stirred for a further 2 h and a solution of $NaBH_4$ (0.40 mmol) in MeOH (10 mL) was added at once. The mixture was allowed to reach to rt and was stirred for 30 min after which it was quenched with a saturated solution of NH_4Cl. The mixture was extracted with CH_2Cl_2 (3×15 mL) and the combined organic fractions were dried over Na_2SO_4, filtered and the solvent was removed in vacuo. The amines **2** and **2′** were obtained separately by flash column chromatography separation (hexane/AcOEt 1/1).

3.3.1. (1R,2′S)-(−)-N-[2′-(3,4-Dimethoxyphenyl)propyl]-2-methoxy-1-phenylethylamine **2a**

Yield: 44%. Mp 52–54°C (Et_2O/pentane 1/1). $[\alpha]_D^{20}=-29.7$ ($c=1.4$, CH_2Cl_2). ^{1}H NMR: 1.21 (d, 3H, $J=6.9$ Hz); 2.07 (sa, 1H); 2.58 (d, 2H, $J=7.4$ Hz); 2.83 (m, 1H); 3.26 (s, 3H); 3.35 (m, 2H); 3.79 (m, 1H); 3.84 (s, 3H); 3.85 (s, 3H); 6.71–6.82 (m, 3H); 7.22–7.39 (m, 5H). ^{13}C NMR: 20.2, 39.7, 55.0, 55.7, 55.8, 58.5, 62.8, 77.7, 110.4, 111.2, 118.7, 127.3, 127.5, 128.2, 138.1, 140.8, 147.2, 148.9. MS (EI) m/z (rel. int.): 329 (M^+, 1), 135 (100). IR (KBr): 3425. Anal. calcd for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26; N, 4.25. Found: C, 73.00; H, 8.23; N, 4.28.

*3.3.2. (1*R,*2′*S*)-(−)-*N*-[2′-(3,4-Dimethoxyphenyl)butyl]-2-methoxy-1-phenylethylamine* ***2b***

Yield: 75%. Mp 63–65°C (Et_2O/pentane 1/1). $[\alpha]_D^{20}=-32.2$ ($c=1.2$, CH_2Cl_2). ^1H NMR: 0.75 (t, 3H, $J=7.3$ Hz); 1.44 (m, 1H); 1.72 (m, 1H); 2.00 (sa, 1H); 2.66 (m, 3H); 3.21 (s, 3H); 3.31 (m, 2H); 3.77 (m, 1H); 3.83 (s, 3H); 3.84 (s, 3H); 6.66–6.81 (m, 3H); 7.19–7.36 (m, 5H). ^{13}C NMR: 11.8, 27.3, 47.7, 53.5, 55.6, 58.3, 62.9, 77.6, 110.8, 111.0, 119.5, 127.1, 127.4, 128.1, 136.3, 140.7, 147.2, 148.7. MS (EI) m/z (rel. int.): 343 (M^+, 1), 135 (100). IR (KBr): 3436. Anal. calcd for $C_{21}H_{29}NO_3$: C, 73.44; H, 8.51; N, 4.08. Found C, 73.48; H, 8.49; N, 4.03.

*3.3.3. (1*R,*2′*S*)-(−)-*N*-[2′-(3,4-Dimethoxyphenyl)-3-methylbutyl]-2-methoxy-1-phenylethylamine* ***2c***

Yield: 79%. Mp 74–76°C (Et_2O/pentane 1/1). $[\alpha]_D^{20}=-25.7$ ($c=1.1$, CH_2Cl_2). ^1H NMR: 0.75 (d, 3H, $J=6.8$ Hz); 0.98 (d, 3H, $J=6.8$ Hz); 1.44 (m, 1H); 2.03 (sa, 1H); 2.62 (m, 3H); 3.23 (s, 3H); 3.32 (m, 2H); 3.75 (m, 1H); 3.82 (s, 3H); 3.85 (s, 3H); 6.71–6.89 (m, 3H); 7.12–7.29 (m, 5H). ^{13}C NMR (δ, ppm): 9.7, 11.5, 27.8, 47.5, 53.4, 55.5, 58.3, 62.7, 77.5, 110.8, 111.2, 119.4, 127.2, 127.6, 128.1, 136.2, 140.5, 147.1, 148.4. MS (EI) m/z (rel. int.): 357 (M^+, 1), 135 (100). IR (KBr): 3433. Anal. calcd for $C_{22}H_{31}NO_3$: C, 73.91; H, 8.74; N, 3.92. Found C, 73.99; H, 8.77; N, 3.87.

*3.3.4. (1*R,*2′*S*)-(+)-*N*-[2′-(3,4-Dimethoxyphenyl)-3′-phenylpropyl]-2-methoxy-1-phenylethylamine* ***2d***

Yield 73%. Mp 57–59°C (Et_2O/pentane 1/1). $[\alpha]_D^{20}=+84.8$ ($c=0.8$, CH_2Cl_2). ^1H NMR: 1.35 (sa, 1H); 2.04 (m, 3H); 2.22 (m, 2H); 3.27 (s, 3H); 3.55 (m, 2H); 3.78 (s, 3H); 3.81 (m, 1H); 3.86 (s, 3H); 6.64 (d, 1H, $J=1.6$ Hz); 6.56 (dd, 1H, $J=1.2$, 8.2 Hz); 6.77 (s, 1H); 6.98 (dd, 2H, $J=1.6$, 7.6 Hz); 7.05 (m, 3H); 7.27 (m, 5H). ^{13}C NMR: 41.2, 47.8, 52.7, 55.6, 58.4, 62.8, 77.5, 110.8, 111.0, 119.4, 125.5, 127.2, 127.4, 127.8, 127.9, 128.2, 128.9, 135.4, 140.1, 140.7, 147.2, 148.4. MS (EI) m/z (rel. int.): 405 (M^+, 1), 135 (100). IR (KBr): 3436. Anal. calcd for $C_{26}H_{31}NO_3$: C, 77.01; H, 7.71; N, 3.45. Found C, 77.02; H, 7.69; N, 3.40.

3.4. General procedure for the N*-methylation of aminoethers* ***2a–d***

Aqueous formaldehyde (0.50 mmol) $NaBH_3CN$ (0.20 mmol) was added over a solution of amine **2a–d** (0.10 mmol) in acetonitrile (20 mL). The mixture was stirred at rt for 6 h, quenched with water and extracted with CH_2Cl_2 (3×15 mL). The combined organic fractions were dried over Na_2SO_4, filtered and the solvent was removed in vacuo. Yielding the amines **3a–d** after flash column chromatography purification (hexane/AcOEt 1/1).

*3.4.1. (1*R,*2′*S*)-(−)-*N*-[2′-(3,4-Dimethoxyphenyl)propyl]-2-methoxy-*N*-methyl-1-phenylethylamine* ***3a***

Yield: 93%. Mp 65–67°C (Et_2O). $[\alpha]_D^{20}=-36.5$ ($c=0.5$, CH_2Cl_2). ^1H NMR: 1.19 (d, 3H, $J=7.0$ Hz); 2.43 (s, 3H); 2.55 (d, 2H, $J=7.4$ Hz); 2.80 (m, 1H); 3.31 (s, 3H); 3.43 (m, 2H); 3.68 (m, 1H); 3.83 (s, 3H); 3.85 (s, 3H); 6.77–6.93 (m, 3H); 7.15–7.28 (m, 5H). ^{13}C NMR: 20.0; 39.6; 45.5; 55.1; 55.7; 55.9; 58.4; 62.9; 77.3; 110.6, 111.2, 118.9, 127.4, 127.5, 128.4; 138.5, 140.7; 147.3, 149.4. MS (EI) m/z (rel. int.): 343 (M^+, 12), 151 (100).

*3.4.2. (1*R,*2′*S*)-(−)-*N*-[2′-(3,4-Dimethoxyphenyl)butyl]-2-methoxy*-N*-methyl-1-phenylethylamine* ***3b***

Yield: 91%. $[\alpha]_D^{20} = -40.2$ ($c = 0.1$, CH_2Cl_2). ^{1}H NMR: 0.73 (t, 3H, $J = 7.1$ Hz); 1.41 (m, 1H); 1.68 (m, 1H); 2.45 (s, 3H); 2.60 (m, 3H); 3.11 (s, 3H); 3.28 (m, 2H); 3.76 (m, 1H); 3.83 (s, 3H); 3.85 (s, 3H); 6.68–6.79 (m, 3H); 7.06–7.28 (m, 5H). ^{13}C NMR: 11.9, 27.0, 45.1, 47.9, 53.2, 55.6, 58.5, 70.4, 77.9, 110.6, 111.0, 119.4, 127.3, 127.4, 128.5, 136.0, 140.7, 147.5, 148.6. MS (EI) m/z (rel. int.): 357 (M^+, 1), 151 (100).

*3.4.3. (1*R,*2′*S*)-(−)-*N*-[2′-(3,4-Dimethoxyphenyl)-3-methylbutyl]-2-methoxy*-N*-methyl-1-phenyl ethylamine* ***3c***

Yield: 93%. $[\alpha]_D^{20} = -43.6$ ($c = 0.3$, CH_2Cl_2). ^{1}H NMR: 0.74 (d, 3H, $J = 6.8$ Hz); 1.02 (d, 3H, $J = 6.9$ Hz); 1.41 (m, 1H); 2.41 (s, 3H); 2.65 (m, 3H); 3.21 (s, 3H); 3.30 (m, 2H); 3.77 (m, 1H); 3.82 (s, 3H); 3.84 (s, 3H); 6.76–6.99 (m, 3H); 7.15–7.31 (m, 5H). ^{13}C NMR: 9.3, 11.2, 27.6, 45.0, 47.3, 53.9, 55.5, 58.6, 62.0, 77.7, 110.9, 111.4, 119.4, 127.6, 127.9, 128.6, 136.7, 140.3, 147.4, 148.2. MS (EI) m/z (rel. int.): 371 (M^+, 1), 151 (100).

*3.4.4. (1*R,*2′*S*)-(+)-*N*-[2′-(3,4-Dimethoxyphenyl)-3′-phenylpropyl]-2-methoxy*-N*-methyl-1-phenyl-ethylamine* ***3d***

Yield 90%. $[\alpha]_D^{20} = +77.6$ ($c = 0.1$, CH_2Cl_2). ^{1}H NMR: 2.07 (m, 3H); 2.19 (m, 2H); 3.26 (s, 3H); 2.47 (s, 3H); 3.50 (m, 2H); 3.78 (s, 3H); 3.86 (m, 1H); 3.91 (s, 3H); 6.58 (d, 1H, $J = 1.4$ Hz); 6.44 (dd, 1H, $J = 1.4$, 8.2 Hz); 6.77 (s, 1H); 7.03 (dd, 2H, $J = 1.4$, 7.6 Hz); 7.08 (m, 3H); 7.33 (m, 5H). ^{13}C NMR: 41.9, 45.2, 47.6, 52.7, 55.6, 58.3, 62.9, 77.1, 110.4, 111.0, 119.8, 125.3, 127.7, 127.9, 128.2, 128.3, 128.6, 128.9, 135.6, 140.7, 140.9, 147.2, 148.6. MS (EI) m/z (rel. int.): 419 (M^+, 7), 151 (100).

3.5. General procedure for the hydrogenolysis of amines ***3a–d***

A solution of **3a–d** (0.10 mmol) in EtOH was stirred in the presence of Pd/C (0.5 g) and 10% HCl (2 mL) under 2 atm H_2 pressure. When the reaction was finished (tlc), the catalyst was filtered and water (20 mL) was added. Amines **4a–d** were obtained pure by NMR after a standard acid–base work-up. An analytically pure sample was obtained by crystallization in Et_2O of the corresponding HCl salt.

*3.5.1. (2*S*)-(−)-2-(3,4-Dimethoxyphenyl)*-N*-methylpropylamine* ***4a***

Yield 83%. Mp (as HCl salt): 188–191°C (Et_2O). $[\alpha]_D^{20} = -16.3$ ($c = 1.75$, $CHCl_3$). ^{1}H NMR: 1.21 (d, 3H, $J = 6.9$ Hz); 2.35 (s, 3H); 2.71 (m, 2H); 2.88 (m, 1H); 3.83 (s, 3H); 3.86 (s, 3H); 6.74–6.88 (m, 3H). ^{13}C NMR: 20.3, 36.5, 39.7, 55.8, 56.0, 60.1, 110.6, 111.4, 118.9, 137.8, 147.5, 149.0. MS (EI) m/z (rel. int.): 209 (M^+, 21), 151 (100). IR ($CHCl_3$): 3440. Anal. calcd for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69. Found C, 68.93; H, 9.02; N, 6.58.

*3.5.2. (2*S*)-(−)-2-(3,4-Dimethoxyphenyl)*-N*-methylbutylamine* ***4b***

Yield: 84%. $[\alpha]_D^{20} = -18.4$ ($c = 1.0$, CH_2Cl_2). ^{1}H NMR: 0.68 (t, 3H, $J = 7.1$ Hz); 1.43 (m, 1H); 1.59 (m, 1H); 2.37 (s, 3H); 2.68 (m, 2H); 2.79 (m, 1H); 3.84 (s, 3H); 3.88 (s, 3H); 6.65–6.77 (m, 3H). ^{13}C NMR: 12.0, 25.4, 36.2, 39.4, 55.8, 56.1, 60.3, 110.2, 111.4, 118.7, 137.6, 147.9, 149.5. IR ($CHCl_3$): 3443. MS (EI) m/z (rel. int.): 223 (M^+,15), 151 (100). Anal. calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found C, 69.99; H, 9.45; N, 6.30.

3.5.3. (2S)-(−)-N,3-Dimethyl-2-(3,4-dimethoxyphenyl)butylamine ***4c***

Yield 88%. $[\alpha]_D^{20} = -21.3$ ($c = 1.0$, CH_2Cl_2). ^1H NMR: 0.71 (d, 3H, $J = 6.8$ Hz); 0.94 (d, 3H, $J = 6.8$ Hz); 1.37 (m, 1H); 2.35 (s, 3H); 2.65 (m, 2H); 2.84 (m, 1H); 3.82 (s, 3H); 3.86 (s, 3H); 6.79–7.03 (m, 3H). ^{13}C NMR: 9.3, 11.5, 27.3, 36.5, 39.9, 55.8, 56.3, 60.4, 110.3, 111.4, 118.5, 137.4, 147.8, 149.7. IR ($CHCl_3$): 3440. MS (EI) m/z (rel. int.): 237 (M^+, 23), 151 (100). Anal. calcd for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90. Found C, 70.92; H, 9.84; N, 6.03.

3.5.4. (2S)-(−)-2-(3,4-Dimethoxyphenyl)-N-methyl-l3-phenylpropylamine ***4d***

Yield 87%. $[\alpha]_D^{20} = -75.4$ ($c = 0.5$, CH_2Cl_2). ^1H NMR: 1.88 (dd, 1H, $J = 6.6$, 10.4 Hz); 2.02 (dd, 1H, $J = 4.8$, 10.4 Hz); 2.28 (m, 2H); 2.31 (s, 3H); 2.89 (m, 1H); 3.79 (s, 3H); 3.82 (s, 3H); 6.69–6.85 (m, 3H); 7.08–7.24 (m, 5H). ^{13}C NMR: 36.1, 39.7; 40.4; 55.6; 56.1; 60.9; 110.3, 111.1, 111.4, 112.3, 117,4, 118.5; 137.4, 138.6; 147.5, 149.3. IR ($CHCl_3$): 3445. MS (EI) m/z (rel. int.): 285 (M^+, 18), 91 (100). Anal. calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found C, 75.68; H, 8.04; N, 5.00.

3.6. General procedure for the Pictet–Spengler cyclization

A solution of amine **4a**–**d** (0.10 mmol) and aqueous formaldehyde (0.60 mmol) in 1 M HCl (5 mL) was stirred for 16 h at 60°C. A solution of saturated Na_2CO_3 (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo yielding isoquinolines **5a**–**d** after flash column chromatography purification (hexane/AcOEt 1/1).

3.6.1. (4S)-(+)-6,7-Dimethoxy-N,4-dimethyl-1,2,3,4-tetrahydroisoquinoline ***5a***

Yield 96%. $[\alpha]_D^{20} = +6.3$ ($c = 0.3$, CH_2Cl_2). ^1H NMR: 1.48 (d, 3H, $J = 6.9$ Hz); 2.19 (s, 3H); 2.55 (dd, 1H, $J = 4.2$, 11.4 Hz); 3.08 (m, 1H); 3.24 (dd, 1H, $J = 3.0$, 11.4 Hz); 3.53 (d, 1H, $J = 13.3$ Hz); 3.62 (d, 1H, $J = 13.3$ Hz); 3.81 (s, 3H); 3.85 (s, 3H); 6.62 (s, 1H); 6.94 (s, 1H). ^{13}C NMR: 20.6, 33.4, 36.3, 49.5, 55.8, 56.2, 58.9, 110.5, 111.0, 129.3, 131.4, 147.7, 148.4. MS (EI) m/z (rel. int.): 221 (M^+, 15), 56 (100).

3.6.2. (4S)-(+)-6,7-Dimethoxy-4-ethyl-N-methyl-1,2,3,4-tetrahydroisoquinoline ***5b***

Yield 92%. $[\alpha]_D^{20} = +7.5$ ($c = 0.5$, CH_2Cl_2). ^1H NMR: 0.90 (t, 3H, $J = 7.4$ Hz); 1.65 (m, 1H); 1.88 (m, 1H); 2.28 (s, 3H); 2.61 (dd, 1H, $J = 4.6$, 11.2 Hz); 2.81 (dd, 1H, $J = 2.8$, 11.2 Hz); 2.98 (m, 1H); 3.21 (d, 1H, $J = 13.3$ Hz); 3.58 (d, 1H, $J = 13.3$ Hz); 3.79 (s, 3H); 3.82 (s, 3H); 6.35 (s, 1H); 6.86 (s, 1H). ^{13}C NMR: 11.2, 26.4, 33.6, 36.5, 50.4, 55.7, 56.0, 59.4, 110.3, 111.5, 129.4, 131.2, 147.8, 148.9. MS (EI) m/z (rel. int.): 235 (M^+, 18), 56 (100).

3.6.3. (4S)-(+)-6,7-Dimethoxy-N-methyl-4-(2-methylethyl)-1,2,3,4-tetrahydroisoquinoline ***5c***

Yield 95%. $[\alpha]_D^{20} = +8.4$ ($c = 0.5$, CH_2Cl_2). ^1H NMR: 0.97 (d, 3H, $J = 7.5$ Hz); 1.02 (d, 3H, $J = 7.3$ Hz); 2.03 (m, 1H); 2.28 (s, 3H); 2.65 (dd, 1H, $J = 4.3$, 11.4 Hz); 2.79 (dd, 1H, $J = 2.7$, 11.4 Hz); 3.04 (m, 1H); 3.26 (d, 1H, $J = 13.3$ Hz); 3.66 (d, 1H, $J = 13.3$ Hz); 3.79 (s, 3H); 3.81 (s, 3H); 6.21 (s, 1H); 6.89 (s, 1H). ^{13}C NMR: 11.3, 12.4, 27.1, 33.2, 36.7, 49.9, 55.6, 56.0, 58.7, 110.4, 111.0, 129.5, 131.7, 147.9, 148.2. MS (EI) m/z (rel. int.): 249 (M^+, 21), 56 (100).

3.6.4. (4S)-(+)-4-Benzyl-6,7-dimethoxy-N-methyl-1,2,3,4-tetrahydroisoquinoline ***5d***

Yield 93%. $[\alpha]_D^{20} = +31.6$ ($c = 0.7$, CH_2Cl_2). ^1H NMR: 2.31 (s, 3H); 2.59 (dd, 1H, $J = 4.6$, 11.2 Hz); 2.77 (dd, 1H, $J = 2.8$, 11.2 Hz); 3.05–3.54 (m, 5H); 3.81 (s, 3H); 3.84 (s, 3H); 6.23 (s, 1H); 6.88 (s, 1H); 7.03–7.16 (m, 5H). ^{13}C NMR: 33.2, 36.7, 42.6, 50.9, 55.5, 56.8, 58.9, 110.3, 111.4, 112.6, 116.5, 117.3, 128.6, 129.3, 131.0, 147.7, 148.2. MS (EI) m/z (rel. int.): 297 (M^+, 31), 91 (100).

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