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The first stereocontrolled synthesis of 12-methyl-hexahydrobenzo[*c*]phenanthridine alkaloids

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Abstract

12-Methyl B/C hexahydrobenzo[*c*]phenanthridines have been synthesized stereoselectively starting from chiral nonracemic 2-aryl-4-pentenoic acids prepared by asymmetric allylation of (+)-(*S*,*S*)-pseudoephedrine-based aryl-acetamide enolates. Subsequent transformations (Friedel–Crafts acylation, stereocontrolled reductive amination, Pictet–Spengler cyclization and PPA catalyzed cationic cyclization) led to the synthesis of enantiomerically enriched hexahydrobenzo[*c*]phenanthridines in which the sequential formation of all the new stereogenic centres was controlled by the starting chiral acids.

1. Introduction

The benzo[*c*]phenanthridine alkaloids, a group of isoquinoline alkaloids that occur naturally in papaveraceous and rutaceous plants,[1] are characterized by the basic skeleton **1** and can be mainly classified into two groups,[2] namely, fully aromatized and B/C hexahydro compounds (Fig. 1). Most of the members of the former group have shown interesting antitumour[3] and antileukaemic[4] properties as well as inhibiting HIV 1 and 2 reverse transcriptases,[5] however, toxicity problems have precluded their medical application.[6] As a result of this, there is a growing interest in determining structure–activity relationships and in developing structural analogues of these compounds with improved pharmacological properties.

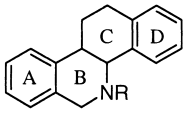

Figure 1.

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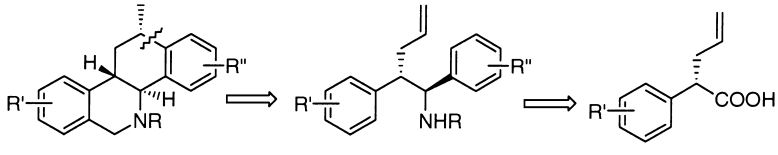
There are only a few reports on the synthesis of hexahydro derivatives of these compounds[4a,7] and amongst them, to date, none has focused on a stereocontrolled synthesis. In the case of these derivatives, where several stereogenic centres are present, the design of preparative procedures for a stereocontrolled synthesis is of interest to the organic chemist.

Recently, we have reported a general and efficient method for the asymmetric synthesis of 2-alkyl-1,2-diarylethylamines starting from chiral nonracemic α-substituted arylacetic acids obtained by diastereoselective alkylation of arylacetic acid derived pseudoephedrine amides.[8] As previous reports have shown that the aforementioned amines resulted to be appropriate precursors for the preparation of benzo[*c*]phenanthridine alkaloids,[9] we decided to explore the possibilities of a conveniently functionalized 2-substituted 1,2-diarylethylamines as valuables chiral synthons for the asymmetric synthesis of hexahydrobenzo[*c*]phenanthridines.

2. Results and discussion

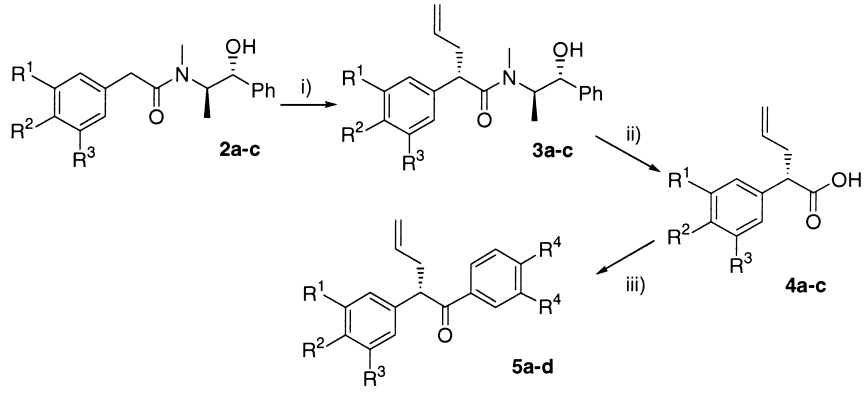
The designed synthetic pathway involves the introduction of an allyl group as a functionalized substituent in the 2-position of the starting arylacetic acid in an enantiocontrolled manner (Scheme 1). Subsequent acylation of the acid followed by reductive amination of the resulting ketone would lead to a key 1,2-diarylethylamine precursor in which the configuration of the newly created stereogenic centre should be controlled by the other stereogenic centre present in the starting acid. Next, the B ring closure should lead to a 4-functionalized 3-aryltetrahydroisoquinoline which on the last C ring formation step should give rise to the target heterocycles in which, again, a new stereogenic centre has been created during the cyclization, having a well defined stereochemistry controlled by other stereogenic centres present in the molecule.



Scheme 1.

Therefore, the starting arylacetic-based pseudoephedrine amides **2** were diastereoselectively alkylated with allyl bromide affording the corresponding 2-aryl-4-pentenoic pseudoephedrine-based amides in excellent yields and diastereoselectivities as could be assessed by ^{1}H-NMR spectroscopy (Scheme 2). The stereochemistry of the newly created stereogenic centre was assigned as *S* according to a previously reported mechanism[8] in which the adduct of the pseudoephedrine amide alkylation should arise from the attack to the preformed *Z* enolate from the less hindered *Si* face of an intermediate in an open staggered conformation which remains rigid by the help of bridging solvent or ^{i}PrNH (from LDA) molecules.

The resulting amides **3** were hydrolyzed to yield the corresponding enantiomerically enriched 2-aryl-4-pentenoic acids **4** after a standard acid–base work-up procedure from which pure (+)-(*S*,*S*)-pseudoephedrine in ca. 83% yield and with no racemization could be recovered from the basic aqueous layers which allows it to be recycled (Table 1). The acids **4** were subjected to Friedel–Crafts acylation either with 1,2-dimethoxybenzene (veratrole) or 1,2-methylenedioxybenzene yielding the corresponding aryl benzyl ketones **5** in excellent enantiomeric excesses as chiral HPLC analysis demonstrated. When methylenedioxy bridges were present, either in the starting arylacetic acid **4c** or in the alkoxybenzene moiety **5d**, the Friedel–Crafts acylation reaction had to be performed using $SnCl_4$ as the activating Lewis acid, as the use of $AlCl_3$ yielded mixtures of products in which the mentioned methylenedioxy bridge had



Scheme 2. Reagents and conditions: (i) 1. LDA, LiCl, THF −78°C; 2. CH_2=$CHCH_2Br$, THF, 0°C. (ii) 4 M H_2SO_4, dioxane, reflux. (iii) 1. $SOCl_2$, toluene, reflux; 2. 1,2-dialkoxybenzene, Lewis acid, CH_2Cl_2, −20°C

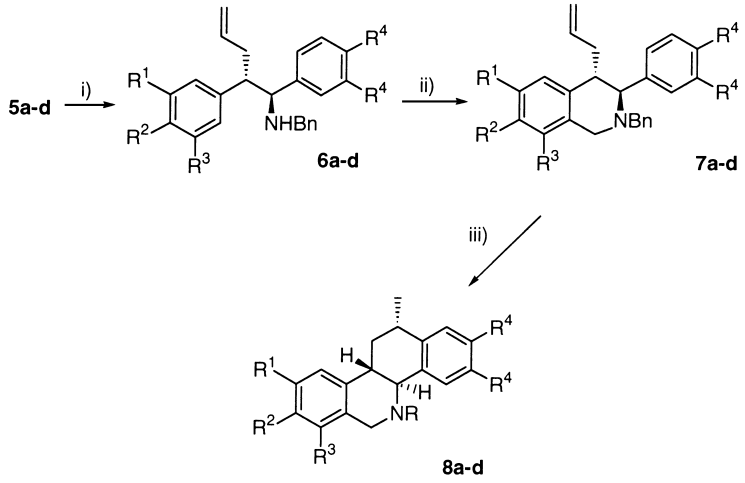
Table 1
Yields and enantioselectivities of the synthesis of the ketones **5**

Prod	R^1	R^2	R^3	R^4	Yield	d.e [a]	Prod	Yield	Prod	Yield	e.e.[b]
3a	OCH_3	OCH_3	H	OCH_3	88	>95	**4a**	96	**5a**	76	>99
3b	OCH_3	OCH_3	OCH_3	OCH_3	86	>95	**4b**	95	**5b**	82	>99
3c	OCH_2O		H	OCH_3	79	>95	**4c**	96	**5c**	71	>99
3d	OCH_3	OCH_3	H	OCH_2O	-	-	**4d**	-	**5d**	73	>99

[a] Determined by integration of the resonances due to the NCH_3 protons in the ^{1}NMR spectrum.
[b] Determined by Chiral HPLC (see experimental section)

been broken. The ketones **5** were subjected to a stereocontrolled reductive amination reaction (Scheme 3) yielding the desired 1,2-diarylethylamines **6** with an excellent degree of diastereoselectivity and, again, in excellent enantiomeric excesses. The reaction consisted of a modified procedure[9] which was achieved by a $TiCl_4$ catalyzed imine formation followed by hydride reduction of the C=N double bond. In this reaction, control of the temperature during the imine formation step was critical in that temperatures over −20°C allowed the imine–enamine tautomerism process to take place at a rate high enough to allow isomerization in the very racemization prone stereogenic carbon of the starting ketones **5**. Also, the temperature in the reduction step needed careful control because high temperatures led to a decrease of the degree of chirality control from the first stereogenic centre on the formation of the second one. The *trans* relationship between the two stereogenic centres of the amines **6** was assigned with the help of the coupling constants by comparison with data found in the literature for similar compounds[10] and it was unambiguously corroborated by NOE difference experiments on the subsequent tetrahydroisoquinolines **6** obtained by a standard Pictet–Spengler cyclization procedure (Table 2).[11]

The final cyclization step to obtain the desired benzo[*c*]phenanthridines, was performed using acidic reaction conditions that led to the formation of a carbocation at the alkene moiety followed by electrophilic aromatic substitution leading to the ring closure. In this way, treatment of the isoquinolines **6** with polyphosphoric acid (PPA) at 60°C for 24 h led to the desired final heterocycles being obtained in excellent yields and enantiomeric excesses, as chiral HPLC analysis demonstrated, which indicates that both Pictet–Spengler and PPA catalyzed cyclization proceeded without racemization or epimerization of any of the stereogenic centres present in the molecule. The last cyclization step proved to be highly



Scheme 3. Reagents and conditions: (i) 1. $TiCl_4$, $BnNH_2$, Et_3N, THF, −78°C; 2. $NaBH_4$, MeOH, −20°C. (ii) HCHO, 1 M HCl, 60°C. (iii) PPA, 60°C

Table 2
Yields and enantioselectivities of the synthesis of the benzo[*c*]phenanthridines **7**

Prod	R^1	R^2	R^3	R^4	Yield	e.e.[b]	Prod	Yield	Prod	Yield	e.e.[b]
6a	OCH_3	OCH_3	H	OCH_3	73	>99	**7a**	89	**8a**	86	>99
6b	OCH_3	OCH_3	OCH_3	OCH_3	81	>99	**7b**	91	**8b**	77	>99
6c	OCH_2O		H	OCH_3	66	>99	**7c**	89	**8c**	66	>99
6c	OCH_3	OCH_3	H	OCH_2O	66	>99	**7d**	84	**8d**	65	>99

[a] Determined by integration of the resonances due to the NCH_3 protons in the ^{1}NMR spectrum.
[b] Determined by Chiral HPLC (see experimental section)

diastereoselective as only one of the two possible epimers could be observed by ^{1}H-NMR. The stereochemistry of this newly created stereogenic centre was assigned as *S* by NOE difference experiments consistent with the final compound arising by first electrophilic attack of H^+ on the allyl moiety followed by the preferential attack of the resulting carbocation on the aryl ring from one of its faces.

In conclusion, a very efficient and highly stereoselective synthetic method has been developed for the synthesis of 12-methyl B/C hexahydrobenzo[*c*]phenanthridine alkaloids by sequential B and C ring closure by different cyclization procedures starting from the key 1,2-diaryl-4-pentenylamines **6**. For the stereocontrolled access to these key intermediates, an initial stereogenic centre is generated using an asymmetric enolate allylation procedure using (+)-(*S*,*S*)-pseudoephedrine as the chiral auxiliary. This stereogenic centre controls the subsequent creation of new asymmetric carbon atoms during the synthetic pathway.

3. Experimental[12]

3.1. Acylation of (+)-(S,S)-pseudoephedrine

3.1.1. Synthesis of (+)-[1′S,2′S]-N-(2′-hydroxy-1′-methyl-2′-phenylethyl)-2-(3,4-dimethoxyphenyl)-N-methylacetamide **2a**

$SOCl_2$ (13.94 mL, 111.13 mmol) was carefully added over a cooled (0°C) solution of (3,4-dimethoxyphenyl)acetic acid (15.00 g, 76.45 mmol) in dry toluene (200 mL). The reaction was refluxed for 3 h after which the volatiles were removed in vacuo. The resulting oil was dissolved in dry THF (150 mL) and was dropwise added within 45 min over a cooled (−10°C) solution of (+)-(*S*,*S*)-pseudoephedrine (12.71 g, 76.45 mmol) and triethylamine (12.77 mL, 91.75 mmol) in dry THF (300 mL). The reaction was stirred for 1 h and quenched with saturated ammonium chloride (100 mL). The mixture was extracted with CH_2Cl_2 (3×100 mL) and the combined organic fractions were collected, dried over Na_2SO_4, filtered and the solvent was removed in vacuo affording a yellowish oil which was purified by flash column chromatography (hexanes:ethyl acetate 2:8) after which pure **2a** was obtained as a yellowish solid. An analytically pure sample was obtained by crystallization in toluene. Yield: 87%. Mp: 110–112°C (toluene). $[\alpha]_D^{20}$=+82.0 (c=0.2, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$) (3:2 rotamer ratio; *denotes minor rotamer peaks): 0.63* (d, 3H, *J*=6.6 Hz); 0.88 (d, 3H, *J*=6.6 Hz); 2.68 (s, 3H); 2.75* (s, 3H); 3.47 (s, 2H); 3.67* (s, 3H); 3.69 (s, 3H); 3.70 (s, 3H); 3.90 (m, 1H); 4.49 (bs, 1H); 4.53 (m, 1H); 6.53–6.74 (m, 3H); 7.21–7.32 (m, 5H). ^{13}C-NMR ($CDCl_3$) (3:2 rotamer ratio; *denotes minor rotamer peaks): 13.7; 14.7*; 26.7; 31.7*; 40.4*; 40.7; 55.3; 55.7*; 56.6*; 58.3; 74.6*; 75.3; 110.8; 111.5*; 111.6; 120.3*; 126.1; 126.3*; 126.8; 127.0*; 127.4; 127.6*; 127.7*; 127.9; 141.6; 141.8; 147.1; 147.2*; 148.4*; 148.5; 172.0*; 172.5. IR (KBr): 3389; 1619. MS (EI) m/z (rel. int.): 343 (M^+, 1), 325 (M^+−18, 2), 310 (5), 236 (6), 178 (3), 151 (12), 107 (5), 106 (2), 91 (3), 79 (4), 77 (5), 58 (100), 51 (2). Anal. calcd for $C_{20}H_{25}NO_4$: C, 69.93; H, 7.34; N, 4.08. Found: C, 69.98; H, 7.28; N, 4.00.

3.1.2. (+)-[1′S,2′S]-N-(2′-Hydroxy-1′-methyl-2′-phenylethyl)-N-methyl-2-(3,4,5-trimethoxyphenyl)-acetamide **2b**

Yield: 89%. Mp: 124–126°C (hexanes:ethyl acetate 1:1). $[\alpha]_D^{20}$=+81.3 (c=0.1, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$) (2:1 rotamer ratio; *denotes minor rotamer peaks): 0.78* (d, 3H, *J*=6.7 Hz); 1.02 (d, 3H, *J*=6.8 Hz); 2.81 (s, 3H); 2.89* (s, 3H); 3.61 (s, 2H); 3.77* (s, 3H); 3.78 (s, 3H); 3.80 (s, 6H); 4.05 (m, 1H); 4.21* (m, 1H); 4.49 (bs, 1H); 4.56 (m, 1H); 6.43 (s, 2H); 7.24–7.29 (m, 5H). ^{13}C-NMR ($CDCl_3$) (2:1 rotamer ratio; *denotes minor rotamer peaks): 14.0; 14.9*; 26.8; 31.9*; 41.2*; 41.5; 55.6*; 55.7; 58.4; 60.4; 74.8*; 75.7; 105.3; 105.5*; 126.2; 126.5*; 127.3; 127.7*; 128.0; 128.2*; 130.1; 131.0*; 136.1; 136.2*; 141.5*; 141.8; 152.8*; 152.9; 171.8*; 172.6. IR (KBr): 3389; 1619. MS (EI) m/z (rel. int.): 373 (M^+, 1), 355 (M^+−18, 24), 208 (100), 193 (21), 181 (62), 174 (5), 165 (3), 148 (26), 147 (98), 146 (36), 137 (5), 136 (5), 132 (9), 115 (8), 105 (4), 91 (15), 79 (5), 77 (7), 56 (27), 51 (3). Anal. calcd for $C_{21}H_{27}NO_5$: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.58; H, 7.22; N, 3.70.

3.1.3. (+)-[1′S,2′S]-N-(2′-Hydroxy-1′-methyl-2′-phenylethyl)-N-methyl-2-(3,4-methylenedioxyphenyl)-acetamide **2c**

Yield: 96%. Mp: 118–120°C (hexanes:ethyl acetate 2:8). $[\alpha]_D^{20}$=+134.2 (c=0.1, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$) (2:1 rotamer ratio; *denotes minor rotamer peaks): 0.81* (d, 3H, *J*=6.7 Hz); 1.08 (d, 3H, *J*=6.7 Hz); 2.80 (s, 3H); 2.90* (s, 3H); 3.36* (s, 2H); 3.56 (s, 2H); 3.71 (m, 1H); 4.03* (m, 1H); 4.42 (bs, 1H); 4.45* (d, 1H, *J*=7.1 Hz); 4.57 (d, 1H, *J*=7.1 Hz); 5.89* (s, 2H); 5.91 (s, 2H); 6.57–6.73 (m, 3H); 7.25–7.32 (m, 5H). ^{13}C-NMR ($CDCl_3$) (2:1 rotamer ratio; *denotes minor rotamer peaks): 14.0; 14.9*;

26.9; 32.4*; 40.5*; 40.9; 57.4*; 58.4; 74.9*; 75.6; 100.6*; 100.7; 107.9; 108.0*; 109.0; 109.1*; 121.5; 126.2; 126.6*; 127.3; 127.8*; 128.0; 128.3*; 129.0; 141.5*; 141.9; 146.0; 147.4; 147.5*; 172.1*; 172.7. IR (KBr): 3365; 1619. MS (EI) m/z (rel. int.): 327 (M^+, 1), 309 (M^+-18, 20), 176 (5), 174 (5), 162 (100), 148 (56), 147 (70), 146 (40), 135 (57), 132 (8), 131 (8), 115 (10), 105 (7), 91 (12), 79 (7), 77 (22), 56 (27), 51 (13). Anal. calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.77; H, 6.42; N, 4.28.

3.2. Typical procedure for the asymmetric allylation of the pseudoephedrine amides

*3.2.1. Synthesis of (+)-[2S,1′S,2′S]-*N*-(2′-hydroxy-1′-methyl-2′-phenylethyl)-*N*-methyl-2-(3,4-dimethoxyphenyl)-4-pentenamide* ***3a***

Over a cooled (−78°C) suspension of LiCl (738 mg, 17.42 mmol) and LDA (5.90 mmol) in dry THF (20 mL) was slowly added a cooled solution (0°C) of the amide (1.00 g, 2.90 mmol) in dry THF (10 mL). The mixture was stirred for 1 h at −78°C and 15 min at 0°C after which a solution of allyl bromide (1.00 mL, 11.61 mmol) in dry THF (5 mL) was added at once. The reaction was stirred for 2–3 h at 0°C and quenched with saturated Na_2CO_3 (20 mL). The mixture was extracted with CH_2Cl_2 (3×30 mL) and the combined organic fractions were collected, dried over Na_2SO_4, filtered and the solvent was removed in vacuo affording crude **2a** which was purified by flash column chromatography (hexanes:ethyl acetate 2:8). Yield: 88%. $[\alpha]_D^{20}$=+138.1 (c=0.2, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$) (3:1 rotamer ratio; *denotes minor rotamer peaks): 0.43* (d, 3H, *J*=6.7 Hz); 0.99 (d, 3H, *J*=6.7 Hz); 2.32 (m, 1H); 2.61 (s, 3H); 2.70 (m, 1H); 2.78* (s, 3H); 3.52 (t, 1H, *J*=7.9 Hz); 3.71* (s, 3H); 3.72* (s, 3H); 3.74 (s, 3H); 3.76 (s, 3H); 3.80 (m, 1H); 4.41 (m, 1H); 4.47 (bs, 1H); 4.88 (m, 2H); 5.60 (m, 1H); 6.65–6.71 (m, 3H); 7.16–7.26 (m, 5H). ^{13}C-NMR ($CDCl_3$) (3:1 rotamer ratio; *denotes minor rotamer peaks): 13.4; 14.1*; 27.0; 38.6*; 38.7; 48.2*; 48.8; 55.2*; 55.3; 57.1; 74.6*; 75.4; 110.0; 110.2*; 110.7; 115.5*; 115.6; 119.6*; 119.8; 125.9; 126.2*; 126.9; 127.4*; 127.6; 128.0*; 131.0*; 132.1; 135.9; 136.2*; 141.6; 141.7*; 147.1*; 147.4; 148.5*; 148.6; 173.1*; 174.0. IR ($CHCl_3$): 3430; 1619. MS (EI) m/z (rel. int.): 383 (M^+, 1), 276 (4), 234 (4), 191 (14), 160 (5), 145 (2), 121 (2), 117 (2), 105 (3), 91 (4), 79 (4), 77 (6), 58 (100), 51 (2). Anal. calcd for $C_{23}H_{29}NO_4$: C, 72.02; H, 7.63; N, 3.65. Found: C, 71.95; H, 7.70; N, 3.61.

*3.2.2. (+)-[2S,1′S,2′S]-*N*-(2′-Hydroxy-1′-methyl-2′-phenylethyl)-*N*-methyl-2-(3,4,5-trimethoxyphenyl)-4-pentenamide* ***3b***

Yield: 86%. $[\alpha]_D^{20}$=+101.7 (c=0.2, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$) (4:1 rotamer ratio; *denotes minor rotamer peaks): 0.49* (d, 3H, *J*=6.7 Hz); 1.05 (d, 3H, *J*=6.4 Hz); 2.36 (m, 1H); 2.70 (s, 3H); 2.77 (m, 1H); 2.86* (s, 3H); 3.57 (t, 1H, *J*=5.9 Hz); 3.75* (s, 3H); 3.76 (s, 3H); 3.80 (s, 6H); 3.81* (s, 6H); 3.78 (m, 1H); 4.11* (m, 1H); 4.41 (m, 1H); 4.51 (bs, 1H); 4.92 (m, 2H); 5.73 (m, 1H); 6.40* (s, 2H); 6.46 (s, 2H); 7.18–7.34 (m, 5H). ^{13}C-NMR ($CDCl_3$) (4:1 rotamer ratio; *denotes minor rotamer peaks): 13.3; 13.5*; 14.0*; 26.9; 38.4*; 38.7; 48.9*; 49.3; 55.4; 57.1; 60.0; 60.1*; 74.4; 75.3*; 104.1; 104.2*; 115.5*; 115.7; 125.8*; 126.1; 126.8; 127.3*; 127.5; 127.9*; 134.3*; 135.3; 135.8; 135.9*; 136.0; 136.1*; 141.5*; 141.7; 141.8*; 152.6; 173.4*; 173.6. IR ($CHCl_3$): 3389; 1625. MS (EI) m/z (rel. int.): 413 (M^+, 1), 395 (2), 354 (3), 306 (4), 304 (5), 249 (15), 248 (100), 233 (16), 221 (56), 208 (7), 195 (10), 191 (12), 190 (38), 189 (12), 186 (12), 175 (16), 174 (36), 159 (9), 148 (16), 147 (77), 146 (19), 131 (11), 117 (10), 115 (14), 105 (6), 103 (6), 91 (28), 79 (7), 77 (8), 58 (77), 56 (32), 51 (3). Anal. calcd for $C_{24}H_{31}NO_5$: C, 69.71; H, 7.56; N, 3.39. Found: C, 69.65; H, 7.59; N, 3.44.

3.2.3. (+)-[2S,1′S,2′S]-N-(2′-Hydroxy-1′-methyl-2′-phenylethyl)-N-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenamide ***3c***

Yield: 79%. $[\alpha]_D^{20}$=+84.5 (c=0.2, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$) (2:1 rotamer ratio; *denotes minor rotamer peaks): 0.58* (d, 3H, *J*=6.7 Hz); 1.06 (d, 3H, *J*=6.8 Hz); 2.35 (m, 1H); 2.68 (s, 3H); 2.70 (m, 1H); 2.84* (s, 3H); 3.54 (t, 1H, *J*=7.7 Hz); 3.81* (t, 1H, *J*=7.6 Hz); 4.08 (m, 1H); 4.39 (bs, 1H); 4.52 (m, 1H); 4.96 (m, 2H); 5.67 (m, 1H); 5.85* (s, 2H); 5.88 (s, 2H); 6.58–6.73 (m, 3H); 7.19–7.38 (m, 5H). ^{13}C-NMR ($CDCl_3$) (2:1 rotamer ratio; *denotes minor rotamer peaks): 13.5; 14.4*; 27.3; 38.7*; 38.8; 48.1*; 48.2; 57.1; 74.9*; 75.2; 95.7; 100.5; 107.5*; 107.7; 115.7*; 116.0; 120.6*; 120.7; 125.9; 126.3*; 126.9; 127.5*; 127.6; 128.1*; 132.3*; 133.4; 135.8; 136.1*; 141.7; 141.9*; 145.8*; 146.0; 147.4; 173.0*; 173.5. IR ($CHCl_3$): 3424; 1619. MS (EI) m/z (rel. int.): 367 (M^+, 1), 349 (6), 308 (2), 258 (2), 202 (100), 193 (2), 175 (16), 174 (8), 162 (5), 147 (64), 146 (21), 145 (15), 131 (6), 127 (4), 117 (73), 115 (22), 91 (17), 79 (3), 77 (8), 56 (31), 51 (3). Anal. calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.95; H, 7.89; N, 3.78.

3.3. General procedure for the hydrolysis of the pseudoephedrine amides

3.3.1. Synthesis of (+)-(S)-2-(3,4-dimethoxyphenyl)-4-pentenoic acid ***4a***

A solution of the amide (775 mg, 2.02 mmol) in dioxane (17 mL) was slowly added over a cooled (0°C) 4 M H_2SO_4 solution (17 mL). When the addition was complete the mixture was refluxed for 2 h. The reaction was quenched with water, carefully basified to pH=12 and washed with EtOAc (3×20 mL). The aqueous layer was carefully driven to pH=3 and extracted with CH_2Cl_2 (3×20 mL). After drying (Na_2SO_4), filtering and removing the solvent from the basic organic extracts it was possible to recover, after crystallization (hexanes:EtOAc), pure (+)-(*S*,*S*)-pseudoephedrine in 83% yield. The collected organic acidic fractions were dried over Na_2SO_4, filtered and the solvent was removed in vacuo yielding the arylacetic acid as a yellowish oil. Yield: 96%. $[\alpha]_D^{20}$=+65.9 (c=0.2, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$): 2.50 (m, 1H); 2.77 (m, 1H); 3.56 (t, 1H, *J*=7.7 Hz); 3.81 (s, 3H); 3.83 (s, 3H); 5.10 (m, 2H); 5.69 (m, 1H); 6.76–6.86 (m, 3H); 10.5–11.6 (bs, 1H). ^{13}C-NMR ($CDCl_3$): 36.9; 50.6; 55.6; 110.8; 110.9; 117.0; 120.0; 130; 134.7; 148.2; 148.7; 179.4. IR ($CHCl_3$): 3460; 1707. MS (EI) m/z (rel. int.): 237 (M^++1, 3), 236 (M^+, 17), 195 (100), 191 (5), 167 (19), 124 (10), 115 (10), 107 (7), 105 (6), 91 (11), 79 (11), 77 (21), 65 (15), 63 (10), 53 (12), 51 (17). Anal. calcd for $C_{13}H_{16}O_4$: C, 66.07; H, 6.83. Found: C, 65.98; H, 6.74.

3.3.2. (+)-(S)-2-(3,4,5-Trimethoxyphenyl)-4-pentenoic acid ***4b***

Yield: 95%. $[\alpha]_D^{20}$=+27.7 (c=0.2, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$): 2.43 (m, 1H); 2.73 (m, 1H); 3.52 (t, 1H, *J*=7.6 Hz); 3.76 (s, 3H); 3.78 (s, 6H); 5.06 (m, 2H); 5.63 (m, 1H); 6.50 (s, 2H); 10.5–11.6 (bs, 1H). ^{13}C-NMR ($CDCl_3$): 36.7; 50.9; 55.4; 60.1; 104.4; 116.6; 133.4; 134.4; 136.5; 152.6; 177.1. IR ($CHCl_3$): 3342; 1766. MS (EI) m/z (rel. int.): 267 (M^++1, 16), 266 (M^+, 100), 207 (81), 195 (15), 191 (34), 179 (22), 147 (29), 121 (22), 91 (43), 77 (36), 65 (31), 55 (17), 51 (19). Anal. calcd for $C_{14}H_{18}O_5$: C, 63.15; H, 6.81. Found: C, 63.22; H, 6.84.

3.3.3. (+)-(S)-2-(3,4-Methylenedioxyphenyl)-4-pentenoic acid ***4c***

Yield: 93%. $[\alpha]_D^{20}$=+55.6 (c=0.2, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$): 2.48 (m, 1H); 2.74 (m, 1H); 3.57 (t, 1H, *J*=7.5 Hz); 5.04 (m, 2H); 5.67 (m, 1H); 5.89 (s, 2H); 6.70–6.77 (m, 2H); 6.84 (s, 1H); 10.5–11.6 (bs, 1H). ^{13}C-NMR ($CDCl_3$): 36.9; 50.6; 100.9; 107.8; 108.1; 117.0; 121.3; 131.4; 134.7; 146.7; 147.6; 178.8. IR ($CHCl_3$): 3436; 1707. MS (EI) m/z (rel. int.): 221 (M^++1, 3), 220 (M^+, 25), 179 (100), 149

(40), 117 (13), 93 (22), 65 (18), 63 (6), 51 (10). Anal. calcd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 65.39; H, 5.53.

3.4. General procedure for the Friedel–Crafts acylation of the acids ***4***

*3.4.1. Synthesis of (+)-(*S*)-1,2-bis(3,4-dimethoxyphenyl)-4-penten-1-one* ***5a***

Over a cooled (0°C) solution of the starting acid (263 mg, 1.11 mmol) in dry toluene (15 mL) was slowly added $SOCl_2$ (0.17 mL, 2.53 mmol). The mixture was stirred for 15 min at 0°C and refluxed for 4 h. The volatiles were removed in vacuo and the resulting red oil was dissolved in dry CH_2Cl_2 (10 mL) and was dropwise added within 40 min over a stirred suspension of $AlCl_3$ (358 mg, 2.46 mmol) and 1,2-dimethoxybenzene (0.16 mL, 1.21 mmol) in dry CH_2Cl_2 (20 mL) at −20°C. The reaction was stirred at this temperature for 2 h and quenched with 4 M HCl (10 mL). The mixture was extracted with CH_2Cl_2 (3×20 mL) and the combined organic fractions were collected, dried over Na_2SO_4, filtered and the solvent was removed in vacuo yielding the pure ketone **5a** after flash column chromatography purification (hexanes:ethyl acetate 1:1). The *ee* of the ketones **5** was >99% calculated by chiral HPLC analysis (Chiralcel OD, UV detector, hexanes:isopropanol 93:7, flow rate 1.00 mL/min). An analytically pure sample was obtained by crystallization in MeOH. Yield: 76%. Mp: 82–84°C (MeOH). $[\alpha]_D^{20}$=+64.7 (c=0.2, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$): 2.51 (m, 1H); 2.87 (m, 1H); 3.78 (s, 3H); 3.82 (s, 3H); 3.85 (s, 6H); 4.51 (t, 1H, *J*=7.4 Hz); 4.99 (m, 2H); 5.73 (m, 1H); 6.73–6.84 (m, 4H); 7.51 (d, 1H, *J*=1.9 Hz); 7.63 (dd, 1H, *J*=1.9, 9.5 Hz). ^{13}C-NMR ($CDCl_3$): 38.1; 52.4; 55.6; 55.7; 55.8; 109.7; 110.4; 110.6; 111.1; 116.3; 120.3; 123.1; 129.6; 131.9; 136.0; 147.8; 148.7; 149.0; 152.9; 197.7. IR (KBr): 1670. MS (EI) m/z (rel. int.): 356 (M^+, 1), 191 (18), 165 (100), 137 (8), 79 (12), 77 (16), 53 (4). Anal. calcd for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79. Found: C, 70.80; H, 6.85.

*3.4.2. (+)-(*S*)-1-(3,4-Dimethoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-4-penten-1-one* ***5b***

Yield: 82%. $[\alpha]_D^{20}$=+66.7 (c=0.2, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$): 2.52 (m, 1H); 2.87 (m, 1H); 3.75 (s, 3H); 3.76 (s, 3H); 3.79 (s, 3H); 3.86 (s, 6H); 4.48 (t, 1H, *J*=7.3 Hz); 5.01 (m, 2H); 5.71 (m, 1H); 6.48 (s, 2H); 6.54 (d, 1H); 7.52 (d, 1H, *J*=1.9 Hz); 7.60 (dd, 1H, *J*=1.9, 9.5 Hz). ^{13}C-NMR ($CDCl_3$): 38.2; 53.0; 55.7; 55.8; 56.0; 60.6; 104.7; 109.8; 110.6; 116.4; 123.2; 129.6; 135.1; 135.9; 136.8; 148.8; 153.0; 153.3; 197.5. IR ($CHCl_3$): 1666. MS (EI) m/z (rel. int.): 386 (M^+, 2), 221 (25), 190 (12), 165 (100), 137 (8), 91 (5), 79 (9), 77 (12), 65 (3), 53 (4). Anal. calcd for $C_{22}H_{26}O_6$: C, 68.38; H, 6.78. Found: C, 68.44; H, 6.82.

*3.4.3. (+)-(*S*)-1-(3,4-Dimethoxyphenyl)-2-(3,4-methylenedioxyphenyl)-4-penten-1-one* ***5c***

The same procedure as indicated above was employed but $SnCl_4$ was employed as Lewis acid and the acylation step was performed for 6 h. Yield: 71%. Mp: 93–95°C (MeOH). $[\alpha]_D^{20}$=+58.9 (c=0.2, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$): 2.44 (m, 1H); 2.84 (m, 1H); 3.78 (s, 3H); 3.86 (s, 3H); 4.50 (t, 1H, *J*=7.3 Hz); 5.01 (m, 2H); 5.71 (m, 1H); 5.85 (d, 2H, *J*=13.0 Hz); 6.67–6.80 (m, 4H); 7.52 (d, 1H, *J*=1.8 Hz); 7.61 (dd, 1H, *J*=1.8, 9.5 Hz). ^{13}C-NMR ($CDCl_3$): 37.9; 52.3; 55.6; 55.8; 100.8; 108.0; 108.3; 109.7; 110.5; 116.4; 121.2; 123.1; 129.4; 131.1; 135.8; 146.4; 147.8; 148.7; 152.9; 197.5. IR (KBr): 1675. MS (EI) m/z (rel. int.): 340 (M^+, 5), 165 (100), 137 (9), 117 (9), 91 (3), 79 (5), 77 (6), 65 (2), 51 (3). Anal. calcd for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92. Found: C, 70.55; H, 5.93.

*3.4.4. (+)-(*S*)-2-(3,4-Dimethoxyphenyl)-1-(3,4-methylenedioxyphenyl)-4-penten-1-one* ***5d***

The same procedure as indicated above was employed but $SnCl_4$ was employed as Lewis acid and the acylation step was performed for 6 h. Yield: 73%. Mp: 98–100°C (MeOH). $[\alpha]_D^{20}$=+49.0 (c=0.3,

CH_2Cl_2). ^{1}H-NMR ($CDCl_3$): 2.51 (m, 1H); 2.89 (m, 1H); 3.79 (s, 3H); 3.83 (s, 3H); 4.45 (t, 1H, *J*=7.3 Hz); 4.96 (m, 2H); 5.70 (m, 1H); 5.94 (s, 2H); 6.72–6.83 (m, 4H); 7.41 (d, 1H, *J*=1.6 Hz); 7.58 (dd, 1H, *J*=1.6, 9.3 Hz). ^{13}C-NMR ($CDCl_3$): 38.1; 52.7; 55.6; 55.7; 101.7; 107.7; 108.3; 110.4; 111.1; 116.4; 120.4; 124.7; 131.3; 131.6; 136.0; 147.9; 148.0; 149.0; 151.4; 197.3. IR (KBr): 1670. MS (EI) m/z (rel. int.): 340 (M^+, 1), 191 (63), 160 (15), 149 (100), 121 (17), 91 (9), 77 (7), 65 (20). Anal. calcd for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92. Found: C, 70.59; H, 6.03.

*3.5. General procedure for the reductive amination of the ketones **5***

*3.5.1. Synthesis of (−)-(1S,2S)-N-benzyl-1,2-bis(3,4-dimethoxyphenyl)-4-pentenylamine **6a***

Over a stirred solution of the ketone **5a** (1.96 g, 5.00 mmol), Et_3N (2.08 mL, 15.00 mmol) and benzylamine (0.60 mL, 5.50 mmol) in THF (30 mL) at −78°C was slowly added a 1 M CH_2Cl_2 solution of $TiCl_4$ (5.00 mL, 5.00 mmol). The mixture was stirred for 5 min at −78°C and for 1 h at −20°C after which a MeOH (20 mL) solution of $NaBH_4$ (851 mg, 22.5 mmol) was dropwise added within 30 min. The reaction was stirred for 2 h at −20°C and quenched with saturated Na_2CO_3 (20 mL). The mixture was extracted with CH_2Cl_2 (3×15 mL) and the combined organic fractions were collected, dried over Na_2SO_4, filtered and the solvent was removed in vacuo yielding the separated pure amine **6a** after flash column chromatography purification (hexanes:ethyl acetate 1:1). The *ee* of the amines **6** was >99% calculated by chiral HPLC analysis (Chiralcel OD, UV detector, hexanes:isopropanol 90:10, flow rate 0.80 mL/min.). An analytically pure sample was obtained by crystallization in MeOH. Yield: 73%. Mp: 102–105 (MeOH). $[\alpha]_D^{20}$=−88.2 (c=0.2, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$): 1.62 (bs, 1H); 2.05 (m, 2H); 2.75 (m, 1H); 3.27 (d, 1H, *J*=13.8 Hz); 3.54 (d, 1H, *J*=9.2 Hz); 3.57 (d, 1H, *J*=13.8 Hz); 3.81 (s, 3H); 3.89 (s, 3H); 3.91 (s, 6H); 4.70 (m, 2H); 5.39 (m, 1H); 6.59 (d, 1H, *J*=1.6 Hz); 6.72 (dd, 1H, *J*=1.6, 8.0 Hz); 6.80–6.97 (m, 4H); 7.19–7.27 (m, 5H). ^{13}C-NMR ($CDCl_3$): 37.4; 50.6; 52.7; 55.5; 55.6; 55.7; 65.8; 110.4; 110.8; 111.1; 115.4; 120.7; 120.9; 123.6; 126.4; 127.8; 127.9; 133.7; 134.3; 136.2; 139.9; 147.4; 147.8; 148.6; 148.8. IR (KBr): 3350. MS (EI) m/z (rel. int.): 447 (M^+, 1), 257 (18), 256 (87), 91 (100), 65 (5). Anal. calcd for $C_{28}H_{33}NO_4$: C, 75.13; H, 7.44; N, 3.13. Found: C, 75.22; H, 7.40; N, 3.19.

*3.5.2. (−)-(1S,2S)-N-Benzyl-1-(3,4-dimethoxyphenyl)-2-(1,2,3-trimethoxyphenyl)-4-pentenylamine **6b***

Yield: 81%. $[\alpha]_D^{20}$=−37.5 (c=0.2, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$): 1.84 (bs, 1H); 2.24 (m, 2H); 2.72 (m, 1H); 3.22 (d, 1H, *J*=13.8 Hz); 3.50 (d, 1H, *J*=9.2 Hz); 3.68 (d, 1H, *J*=13.8 Hz); 3.82 (s, 6H); 3.89 (s, 3H); 3.92 (s, 3H); 3.94 (s, 3H); 4.63 (m, 2H); 5.32 (m, 1H); 6.32 (s, 2H, *J*=1.6 Hz); 6.40 (s, 1H); 6.82–6.91 (m, 2H); 7.19–7.27 (m, 5H). ^{13}C-NMR ($CDCl_3$): 35.4; 51.2; 52.0; 55.6; 55.7; 55.8; 60.7; 65.8; 106.0; 110.2; 111.0; 116.1; 120.5; 126.7; 127.8; 128.1; 133.1; 136.2; 136.4; 137.0; 140.4; 147.7; 148.1; 152.3. IR ($CHCl_3$): 3389. MS (EI) m/z (rel. int.): 477 (M^+, 1), 257 (10), 256 (58), 91 (100), 65 (6). Anal. calcd for $C_{29}H_{35}NO_5$: C, 72.92; H, 7.39; N, 2.93. Found: C, 72.99; H, 7.40; N, 3.01.

*3.5.3. (−)-(1S,2S)-N-Benzyl-1-(3,4-dimethoxyphenyl)-2-(3,4-methylenedioxyphenyl)-4-pentenylamine **6c***

Yield: 86%. Mp: 123–125 (MeOH). $[\alpha]_D^{20}$=−39.4 (c=0.3, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$): 1.57 (bs, 1H); 2.14 (m, 2H); 2.87 (m, 1H); 3.37 (d, 1H, *J*=13.8 Hz); 3.53 (d, 1H, *J*=9.2 Hz); 3.59 (d, 1H, *J*=13.8 Hz); 3.85 (s, 3H); 3.87 (s, 3H); 4.81 (m, 2H); 5.47 (m, 1H); 6.02 (d, 2H, *J*=2.7 Hz); 6.57 (d, 1H, *J*=1.6 Hz); 6.75 (dd, 1H, *J*=1.6, 8.0 Hz); 6.82–7.02 (m, 4H); 7.27–7.41 (m, 5H). ^{13}C-NMR ($CDCl_3$): 37.5; 50.5; 52.5; 55.4; 55.5; 66.0; 100.6; 107.8; 110.2; 110.8; 115.5; 120.4; 120.9; 121.7; 126.4; 127.8; 127.9; 133.6; 134.2; 136.2; 139.9; 146.0; 147.0; 147.6; 147.9. IR (KBr): 3340. MS (EI) m/z (rel. int.): 431 (M^+,

1), 368 (100), 277 (65), 256 (56), 247 (12), 205 (80), 174 (19), 144 (6), 115 (16), 91 (76), 65 (10). Anal. calcd for $C_{27}H_{29}NO_4$: C, 75.15; H, 6.77; N, 3.25. Found: C, 75.20; H, 6.70; N, 3.22.

*3.5.4. (−)-(1*S*,2*S*)-*N*-Benzyl-2-(3,4-dimethoxyphenyl)-1-(3,4-methylenedioxyphenyl)-4-pentenylamine* ***6d***

Yield: 66%. Mp: 127–129 (MeOH). $[\alpha]_D^{20}$=−41.3 (c=0.5, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$): 1.64 (bs, 1H); 2.25 (m, 2H); 2.79 (m, 1H); 3.35 (d, 1H, *J*=13.8 Hz); 3.56 (d, 1H, *J*=9.2 Hz); 3.61 (d, 1H, *J*=13.8 Hz); 3.84 (s, 3H); 3.89 (s, 3H); 4.89 (m, 2H); 5.36 (m, 1H); 6.09 (s, 2H); 6.59 (d, 1H, *J*=1.6 Hz); 6.73 (dd, 1H, *J*=1.6, 8.0 Hz); 6.85–7.05 (m, 4H); 7.29–7.54 (m, 5H). ^{13}C-NMR ($CDCl_3$): 37.4; 50.6; 52.3; 55.7; 55.8; 66.5; 100.2; 107.8; 110.1; 110.3; 115.6; 120.0; 120.3; 120.9; 125.2; 127.4; 127.6; 133.5; 134.2; 136.3; 139.8; 146.0; 147.1; 147.7; 147.9. IR (KBr): 3342. MS (EI) m/z (rel. int.): 431 (M^+, 4), 267 (15), 237 (11), 176 (100), 149 (10), 91 (39), 65 (7). Anal. calcd for $C_{27}H_{29}NO_4$: C, 75.15; H, 6.77; N, 3.25. Found: C, 75.23; H, 6.79; N, 3.31.

3.6. General procedure for the Pictet–Spengler cyclization

*3.6.1. Synthesis of (+)-(3*S*,4*S*)-*N*-benzyl-3-(3,4-dimethoxyphenyl)-6,7-dimethoxy-4-(2-propenyl)-1,2,3,4-tetrahydroisoquinoline* ***7a***

A solution of the amine **6a** (107 mg, 0.24 mmol) and formaldehyde (0.12 mL, 1.42 mmol) in 1 M HCl (10 mL) was stirred for 16 h at 60°C. Saturated Na_2CO_3 (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3×15 mL). The combined organic fractions were collected, dried over Na_2SO_4, filtered and the solvent was removed in vacuo yielding the pure heterocycle after flash column chromatography purification (hexanes:ethyl acetate 1:1). An analytically pure sample was obtained by crystallization in MeOH. Yield: 89%. Mp: (as HCl salt) 198–200°C (MeOH). $[\alpha]_D^{20}$=+38.7 (c=0.1, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$): 2.38 (m, 1H); 2.75 (m, 1H); 3.00 (m, 1H); 3.12 (d, 1H, *J*=13.1 Hz); 3.33 (d, 1H, *J*=14.7 Hz); 3.42 (d, 1H, *J*=14.6 Hz); 3.59 (d, 1H, *J*=13.2 Hz); 3.71 (s, 3H); 3.74 (d, *J*=3.7 Hz); 3.81 (s, 3H); 3.86 (s, 6H); 5.02 (m, 2H); 5.80 (m, 1H); 6.47 (s, 1H); 6.65–6.79 (m, 4H); 7.21–7.39 (m, 5H). ^{13}C-NMR ($CDCl_3$): 40.5; 44.3; 51.6; 55.6; 55.8; 56.0; 59.5; 64.5; 108.7; 110.6; 111.2; 111.6; 116.7; 121.4; 121.9; 123.2; 123.8; 126.9; 127.1; 129.8; 137.1; 139.4; 147.2; 147.7; 148.1; 148.6. MS (EI) m/z (rel. int.): 459 (M^+, 6), 310 (16), 234 (28), 219 (43), 206 (23), 203 (17), 191 (12), 188 (14), 177 (3), 91 (100), 65 (11). Anal. calcd for $C_{29}H_{34}ClNO_4$: C, 70.22; H, 6.91; N, 2.82. Found: C, 70.16; H, 7.00; N, 2.96.

*3.6.2. (+)-(3*S*,4*S*)-*N*-Benzyl-3-(3,4-dimethoxyphenyl)-6,7,8-trimethoxy-4-(2-propenyl)-1,2,3,4-tetrahydroisoquinoline* ***7b***

Yield: 91%. Mp: (as HCl salt) 210–218°C (MeOH). $[\alpha]_D^{20}$=+43.2 (c=0.1, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$): 2.41 (m, 1H); 2.72 (m, 1H); 2.95 (m, 1H); 3.28 (d, 1H, *J*=13.2 Hz); 3.34 (d, 1H, *J*=14.5 Hz); 3.51 (d, 1H, *J*=14.4 Hz); 3.62 (s, 3H); 3.64 (d, 1H, *J*=13.2 Hz); 3.70 (s, 3H); 3.76 (d, *J*=3.2 Hz); 3.81 (s, 3H); 3.88 (s, 6H); 5.12 (m, 2H); 5.86 (m, 1H); 6.61–6.72 (m, 4H); 7.23–7.32 (m, 5H). ^{13}C-NMR ($CDCl_3$): 40.2; 44.1; 46.2; 54.8; 55.1; 55.3; 58.6; 59.8; 60.2; 106.5; 109.8; 110.8; 116.0; 120.5; 120.8; 126.2; 127.5; 128.1; 131.2; 133.1; 136.1; 138.6; 139.2; 147.3; 147.8; 148.7; 151.3. MS (EI) m/z (rel. int.): 489 (M^+, 2), 310 (16), 234 (28), 219 (43), 206 (23), 203 (17), 191 (12), 188 (12), 91 (100), 65 (11). Anal. calcd for $C_{30}H_{36}ClNO_5$: C, 68.54; H, 6.91; N, 2.67. Found: C, 68.49; H, 7.01; N, 2.72.

*3.6.3. (+)-(3S,4S)-*N*-Benzyl-3-(3,4-dimethoxyphenyl)-6,7-methylenedioxy-4-(2-propenyl)-1,2,3,4-tetrahydroisoquinoline* ***7c***

Yield: 89%. Mp: 119–121°C (MeOH). $[\alpha]_D^{20}$=+39.9 (c=0.1, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$): 2.40 (m, 1H); 2.69 (m, 1H); 2.98 (m, 1H); 3.36 (d, 1H, *J*=13.1 Hz); 3.42 (d, 1H, *J*=14.7 Hz); 3.54 (d, 1H, *J*=14.6 Hz); 3.61 (d, 1H, *J*=13.2 Hz); 3.75 (s, 3H); 3.79 (d, *J*=3.7 Hz); 3.86 (s, 3H); 5.03 (m, 2H); 5.73 (m, 1H); 5.90 (d, 2H, *J*=1.0 Hz); 6.49 (s, 1H); 6.67–6.81 (m, 4H); 7.23–7.42 (m, 5H). ^{13}C-NMR ($CDCl_3$): 40.6; 44.6; 51.9; 55.6; 55.7; 59.3; 64.1; 100.6; 105.9; 108.0; 110.4; 111.5; 116.8; 121.0; 126.9; 128.0; 128.2; 128.7; 130.8; 132.0; 136.8; 139.2; 145.6; 146.2; 148.0; 148.5. MS (EI) m/z (rel. int.): 443 (M^+, 6), 370 (16), 281 (38), 265 (10), 219 (10), 209 (11), 207 (100), 193 (14), 142 (11), 134 (10), 119 (12), 105 (10), 91 (15), 83 (16), 77 (15), 64 (25) 51 (35). Anal. calcd for $C_{28}H_{29}NO_4$: C, 75.82; H, 6.59; N, 3.16. Found: C, 75.87; H, 6.61; N, 3.14.

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

Yield: 84%. Mp: 126–128°C (MeOH). $[\alpha]_D^{20}$=+25.7 (c=0.1, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$): 2.43 (m, 1H); 2.74 (m, 1H); 2.98 (m, 1H); 3.34 (d, 1H, *J*=13.1 Hz); 3.45 (d, 1H, *J*=14.7 Hz); 3.52 (d, 1H, *J*=14.6 Hz); 3.63 (d, 1H, *J*=13.2 Hz); 3.73 (s, 3H); 3.75 (d, *J*=3.7 Hz); 3.84 (s, 3H); 5.00 (m, 2H); 5.77 (m, 1H); 5.94 (s, 2H); 6.45 (s, 1H); 6.59–6.77 (m, 4H); 7.24–7.39 (m, 5H). ^{13}C-NMR ($CDCl_3$): 40.9; 44.2; 51.1; 55.7; 55.9; 59.4; 64.1; 100.8; 107.7; 108.7; 109.9; 111.2; 116.7; 122.3; 123.5; 126.9; 128.2; 128.9; 129.5; 133.4; 137.0; 139.3; 145.4; 146.5; 147.1; 147.6. MS (EI) m/z (rel. int.): 443 (M^+, 4), 401 (25), 280 (24), 204 (67), 189 (86), 176 (47), 173 (26), 161 (11), 158 (14), 129 (10), 117 (12), 91 (100), 77 (9), 65 (18). Anal. calcd for $C_{28}H_{29}NO_4$: C, 75.82; H, 6.59; N, 3.16. Found: C, 75.89; H, 6.44; N, 3.09.

3.7. General procedure for the acid catalyzed cyclization

*3.7.1. Synthesis of (−)-(4b*S*,10b*S*,12*S*)-*N*-benzyl-2,3,8,9-tetramethoxy-12-methyl-4b,5,6,10b,11,12-hexahydrobenzo[*c*]phenanthridine* ***8a***

A mixture of the isoquinoline **7a** (100 mg, 0.22 mmol) and PPA (2 mL) was heated at 60°C with stirring for 12 h. The reaction was quenched with 4 M NaOH and extracted with CH_2Cl_2 (3×15 mL). The combined organic fractions were collected, dried over Na_2SO_4, filtered and the solvent was removed in vacuo yielding the pure heterocycle after flash column chromatography purification (hexanes:ethyl acetate 1:1). The *ee* of the heterocycles **8** was >99% calculated by chiral HPLC analysis (Chiralcel OD, UV detector, hexanes:isopropanol 90:10, flow rate 1.00 mL/min). An analytically pure sample was obtained by crystallization in MeOH. Yield: 86%. Mp: 171–172°C (MeOH). $[\alpha]_D^{20}$=−32.3 (c=0.1, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$): 1.33 (d, 3H, *J*=6.7 Hz); 1.37 (m, 1H); 2.73 (m, 1H); 2.97 (m, 1H); 3.12 (m, 1H); 3.30 (d, 1H, *J*=14.4 Hz); 3.59 (d, 1H, *J*=14.4 Hz); 3.66 (d, 1H, *J*=16.7); 3.74 (s, 6H); 3.80 (s, 3H); 3.82 (s, 3H); 4.05 (d, 1H, *J*=11.1 Hz); 4.17 (d, 1H, *J*=16.7 Hz); 6.43 (s, 1H); 6.75 (s, 1H); 6.89 (s, 1H); 7.10–7.40 (m, 5H); 7.43 (s, 1H). ^{13}C-NMR ($CDCl_3$): 22.6; 32.2; 33.5; 37.4; 49.2; 52.6; 55.6; 55.8; 55.9; 56.0; 64.1; 108.7; 108.9; 110.1; 110.2; 126.6; 128.0; 128.2; 129.7; 129.9; 134.1; 140.2; 140.3; 147.6; 147.9. MS (EI) m/z (rel. int.): 459 (M^+, 3), (22), 337 (8), 177 (9), 146 (9), 91 (100), 77 (7), 65 (14). Anal. calcd for $C_{29}H_{33}NO_4$: C, 75.79; H, 7.24; N, 3.05. Found: C, 75.65; H, 7.29; N, 3.18.

*3.7.2. (−)-(4b*S*,10b*S*,12*S*)-*N*-Benzyl-2,3,7,8,9-pentamethoxy-12-methyl-4b,5,6,10b,11,12-hexahydro-benzo[*c*]phenanthridine* ***8b***

Yield: 77%. Mp: 160–162°C (MeOH). $[\alpha]_D^{20}$=−28.6 (c=0.1, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$): 1.40 (d, 3H, *J*=6.7 Hz); 1.52 (m, 1H); 2.70 (m, 1H); 2.96 (m, 1H); 3.15 (m, 1H); 3.30 (d, 1H, *J*=14.7 Hz); 3.61

(d, 1H, *J*=14.7 Hz); 3.68 (d, 1H, *J*=16.5); 3.75 (s, 3H); 3.82 (s, 3H); 3.87 (s, 3H); 3.88 (s, 3H); 3.89 (s, 3H); 4.07 (d, 1H, *J*=11.2 Hz); 4.13 (d, 1H, *J*=16.5 Hz); 6.79 (s, 1H); 6.82 (s, 1H); 7.19–7.43 (m, 5H); 7.52 (s, 1H). ^{13}C-NMR ($CDCl_3$): 22.7; 29.7; 32.2; 33.6; 47.9; 49.5; 55.7; 55.9; 56.1; 60.4; 60.8; 63.7; 104.8; 108.8; 110.0; 126.6; 128.0; 128.1; 128.3; 129.8; 133.5; 134.1; 140.2; 147.7; 148.2; 148.3; 151.0; 151.1. MS (EI) m/z (rel. int.): 489 (M^+, 18), 447 (13), 367 (45), 336 (15), 207 (17), 176 (13), 106 (25), 91 (100), 79 (10), 77 (11), 65 (12). Anal. calcd for $C_{30}H_{35}NO_5$: C, 73.58; H, 7.21; N, 2.86. Found: C, 73.65; H, 7.29; N, 3.05.

*3.7.3. (−)-(4b*S*,10b*S*,12*S*)*-N*-Benzyl-2,3-dimethoxy-12-methyl-8,9-methylenedioxy-4b,5,6,10b,11,12-hexahydrobenzo[*c*]phenanthridine* ***8c***

Yield: 66%. Mp: 197–199°C (MeOH). $[\alpha]_D^{20}$=−44.1 (c=0.2, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$): 1.31 (d, 3H, *J*=6.7 Hz); 1.35 (m, 1H); 2.69 (m, 1H); 2.81 (m, 1H); 3.15 (m, 1H); 3.29 (d, 1H, *J*=14.4 Hz); 3.63 (d, 1H, *J*=14.4 Hz); 3.70 (d, 1H, *J*=16.7); 3.80 (s, 3H); 3.82 (s, 3H); 4.00 (d, 1H, *J*=11.1 Hz); 4.12 (d, 1H, *J*=16.7 Hz); 5.92 (d, 2H, *J*=1.4 Hz); 6.41 (s, 1H); 6.77 (s, 1H); 6.85 (s, 1H); 7.11–7.43 (m, 5H); 7.49 (s, 1H). ^{13}C-NMR ($CDCl_3$): 22.5; 32.1; 33.1; 37.6; 49.5; 52.6; 55.6; 55.9; 64.2; 100.2; 108.6; 108.8; 110.0; 110.3; 126.6; 128.0; 128.3; 129.9; 130.1; 134.2; 140.2; 140.3; 147.5; 147.8; 147.9; 150.6. MS (EI) m/z (rel. int.): 443 (M^+, 1), 428 (10), 412 (31), 368 (11), 325 (12), 175 (25), 165 (10), 146 (10), 131 (2), 91 (100), 65 (22). Anal. calcd for $C_{28}H_{29}NO_4$: C, 75.82; H, 6.59; N, 3.16. Found: C, 75.88; H, 7.49; N, 3.16.

*3.7.4. (−)-(4b*S*,10b*S*,12*S*)*-N*-Benzyl-8,9-dimethoxy-12-methyl-2,3-methylenedioxy-4b,5,6,10b,11,12-hexahydrobenzo[*c*]phenanthridine* ***8d***

Yield: 65%. Mp: 203–206°C (MeOH). $[\alpha]_D^{20}$=−47.6 (c=0.2, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$): 1.33 (d, 3H, *J*=6.6 Hz); 1.39 (m, 1H); 2.54 (m, 1H); 2.92 (m, 1H); 3.12 (m, 1H); 3.36 (d, 1H, *J*=14.4 Hz); 3.59 (d, 1H, *J*=14.4 Hz); 3.70 (d, 1H, *J*=16.7); 3.81 (s, 3H); 3.84 (s, 3H); 4.02 (d, 1H, *J*=11.1 Hz); 4.19 (d, 1H, *J*=16.7 Hz); 6.04 (s, 2H); 6.43 (s, 1H); 6.74 (s, 1H); 6.82 (s, 1H); 7.12–7.47 (m, 5H); 7.54 (s, 1H). ^{13}C-NMR ($CDCl_3$): 22.4; 32.6; 33.4; 37.9; 49.4; 52.5; 55.6; 55.7; 64.5; 100.0; 108.6; 108.7; 110.0; 110.4; 126.5; 128.2; 128.9; 129.8; 130.2; 134.2; 140.7; 140.9; 147.5; 147.7; 147.9; 148.5. MS (EI) m/z (rel. int.): 443 (M^+, 4), 412 (23), 355 (15), 325 (24), 280 (18), 175 (33), 146 (37), 115 (24), 91 (100), 65 (33). Anal. calcd for $C_{28}H_{29}NO_4$: C, 75.82; H, 6.59; N, 3.16. Found: C, 75.84; H, 7.44; N, 3.05.

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References

1. (a) Krane, B. D.; Fagbule, M. O.; Shamma, M.; Gözler, B. *J. Nat. Prod.* **1984**, *47*, 1. (b) Ninomiya, I.; Naito, T. *Recent Developments in the Chemistry of Natural Carbon Compounds*; Bognár, R.; Szántay, Cs., Eds.; Akadémiai Kiadó: Budapest, 1984; Vol. 10.
2. Simánek, V. *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1985; Vol. 26, p. 185.
3. (a) Cushman, M.; Mohan, P.; Smith, E. C. R. *J. Med. Chem.* **1984**, *27*, 544. (b) Hanaoka, M.; Motegi, A.; Yokumoto, Y. A.; Takahashi, K. JP Patent 02243629, Jpn. Kokai Tokkyo Koho; *Chem. Abstr*. **1991**, *115*, 780. (c) Hanaoka, M.; Ekimoto,

H.; Kobayashi, F.; Irie, Y.; Takahashi, K. EP Patent 432630, Eur. Pat. Appl.; *Chem. Abstr.* **1992**, *116*, 718. (d) Janin, Y. L.; Croisy, A.; Riou, J.-F.; Bisagni, E. *J. Med. Chem.* **1993**, *36*, 3686.

4. (a) Cushman, M.; Choong, T.-C.; Valko, J. T.; Koleck, M. P. *J. Org. Chem.* **1980**, *45*, 5067. (b) Cheng, R. K. Y.; Cheng, C. C. *J. Med. Chem.* **1978**, *21*, 199. (c) Cordell, G. A.; Farnsworth, N. R. *Heterocycles* **1976**, *4*, 393.
5. Tan, G. T.; Miller, J. F.; Kinghorn, A. D.; Hughes, S. H.; Pezzuto, J. M. *Biochem. Biophys. Res. Commun.* **1992**, *185*, 370.
6. Cushman, M.; Moham, P. *J. Med. Chem*. **1985**, *28*, 1031.
7. (a) Ninomiya, I.; Yamamoto, O.; Naito, T. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2165. (b) Cushman, M.; Abbaspour, A.; Gupta, Y. P. *J. Am. Chem. Soc.* **1983**, *105*, 2873. (c) Cushman, M.; Choong, T.-C.; Valko, J. T.; Koleck, M. P. *Tetrahedron Lett.* **1980**, *21*, 3845. (d) Shamma, M.; Tomlinson, H. H. *J. Org. Chem.* **1978**, *43*, 2852. (e) Oppolzer, W. *Heterocycles* **1980**, *14*, 1615. (f) Iida, H.; Endo, I.; Narimiya, M.; Kikuchi, T. *Heterocycles* **1980**, *14*, 1325.
8. Vicario, J. L.; Badía, D.; Domínguez, E.; Carrillo, L. *J. Org. Chem.* **1999**, in press.
9. Sotomayor, N.; Vicente, T.; Domínguez, E.; Lete, E.; Villa, M.-J. *Tetrahedron* **1994**, *50*, 2207.
10. Spassov, S. L. *Tetrahedron* **1971**, *27*, 1323.
11. For a review on the Pictet–Spengler cyclization see Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797.
12. For general experimental procedures see Ref. 8.