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Stereocontrolled synthesis of 2-aryl tetralones. Application in the synthesis of B/C hexahydrobenzo[*c*]phenanthridine alkaloids[1]

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Abstract

Hexahydrobenzo[*c*]phenanthridines possessing a B/C *cis* ring junction have been synthesized in a stereoselective way starting from chiral non-racemic 2-aryl-tetralones prepared by asymmetric alkylation of (+)-(*S*,*S*)-pseudoephedrine based arylacetamide enolates with appropriately functionalized 2-aryl-1-iodoethane electrophiles. Subsequent transformations (intramolecular Friedel–Crafts acylation, stereocontrolled reductive amination and Pictet–Spengler cyclization) yielded the target heterocycles in good overall yields and in excellent stereoselectivities. © 2000 Elsevier Science Ltd. All rights reserved.

1. Introduction

The hexahydrobenzo[*c*]phenanthridine alkaloids are a small class of isoquinoline alkaloids that are characterized by the basic skeleton shown in Fig. 1 and they are structurally divided into two classes,[2] one is the chelidonine group of alkaloids and the other is the corynoline group with an additional 10b-methyl group at the ring junction. Most of the synthetic studies on benzo[*c*]-phenanthridines have been focused on fully aromatized derivatives because most of them have shown interesting antitumor[3] and antileukemic[4] properties as well as inhibiting HIV 1 and 2 reverse transcriptases[5] and DNA topoisomerases I and II.[6] However, only limited efforts towards the synthesis of B/C hexahydrobenzo[*c*]phenanthridines have been reported[4a,7] and are mainly focused towards basic studies with only a few being directed towards stereocontrolled procedures.[8] As a result of the interesting potential biological activities shown by this group of alkaloids there is a growing interest in determining structure–activity relationships and in developing new structural analogues of these compounds with improved pharmacological properties. Additionally, in the case of the hexahydro-derivatives, where several stereogenic centers are present, the design of preparative procedures for stereocontrolled synthesis becomes a field of interest for organic chemists.

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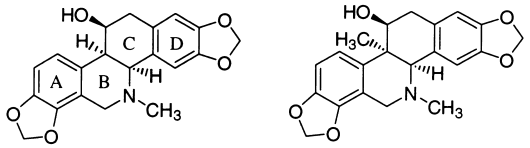


Figure 1.

On the other hand, 2-aryl tetralones have been reported to be extremely versatile synthons for the preparation of benzophenanthridine alkaloids[9] although the latter are always in fully aromatized form. In relation it should be pointed out that if the 2-aryl tetralone moiety is prepared in an enantioselective fashion it should offer access to chiral non-racemic hexahydrobenzo[*c*]phenanthridines by careful control of the stereochemical course of the reactions along the synthetic pathway.

Recently we have reported a general and efficient method for the stereocontrolled synthesis of 2-alkyl-substituted aryl benzyl ketones starting from chiral non-racemic α-substituted arylacetic acids obtained by diastereoselective alkylation of (+)-(*S*,*S*)-pseudoephedrine based arylacetamides.[10] In this context and in connection with our research efforts in the field of the asymmetric synthesis of isoquinoline alkaloids[8c,10,11] we decided to survey the possibilities of conveniently functionalized 2-substituted arylacetic acids as valuable precursors for the synthesis of enantiopure 2-aryl tetralones and thus develop synthetic methodology for access to chiral hexahydrobenzo-[*c*]phenanthridines (Fig. 2).

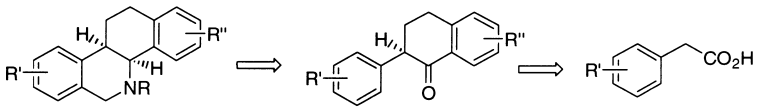
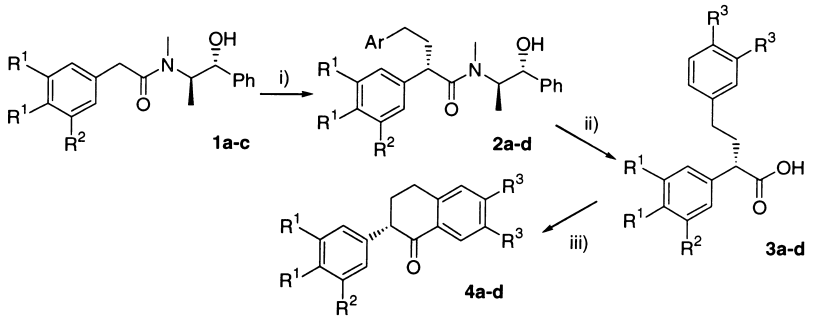


Figure 2.

2. Results and discussion

The synthesis starts with the alkylation of several arylacetic based (+)-(*S*,*S*)-pseudoephedrine amides with 2-aryl-1-iodoethane derivatives yielding products in good yields and excellent stereoselectivities, as ^{1}H NMR analysis of the crude products indicated. The amides **2** were hydrolyzed and subjected to intramolecular Friedel–Crafts acylation reaction yielding the desired 2-aryl tetralones in more than 99% enantiomeric excess by chiral HPLC analysis under conditions optimized for racemic standards (Scheme 1 and Table 1).[12] The selected Lewis acid employed to activate the acyl chloride in the acylation reaction was critical such that use of the standard $AlCl_3$, when methylenedioxy bridges were present in the starting acid, led to complex mixtures being obtained from which products arising from the breaking of the methylenedioxy could be detected. This difficulty could be circumvented with the use of the milder $SnCl_4$ Lewis acid.

The stereochemistry of the newly created stereogenic center was assigned as (*S*) according to a previously reported mechanism[10] 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 opened staggered conformation, which remains rigid by the help of bridging solvent or ^{i}PrNH (from LDA) molecules.



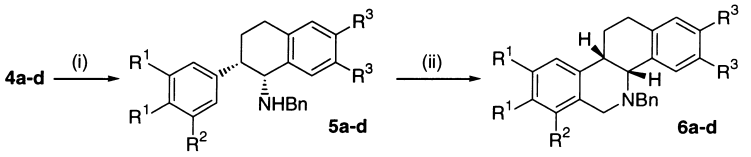
Scheme 1. *Reagents and conditions*: (i) (1) LDA, LiCl, THF, −78°C; (2) $ArCH_2CH_2I$, THF, 0°C. (ii) 4 M H_2SO_4, dioxane, reflux. (iii) (1) $SOCl_2$, toluene, reflux; (2) Lewis acid, CH_2Cl_2, −20°C

Table 1
Yields and enantioselectivities in the synthesis of the ketones **4**

Prod	R^1	R^2	R^3	Yield	d.e [a]	Prod	Yield	Prod	Yield	e.e.[b]
2a	OCH_3	H	OCH_3	85	>95	**3a**	93	**4a**	78	>99
2b	OCH_3	OCH_3	OCH_3	81	>95	**3b**	94	**4b**	74	>99
2c	OCH_2O	H	OCH_3	83	>95	**3c**	95	**4c**	71	>99
2d	OCH_3	H	OCH_2O	78	>95	**3d**	90	**4d**	76	>99

[a] Determined by integration of the resonances due to the NCH_3 protons in the ^{1}NMR spectrum.
[b] Determined by Chiral HPLC (Chiralcel OD, UV detector, hexanes *iso*-propanol 93:7, flow rate 1.00mL/min.)

Proceeding with the synthesis, the tetralones **4a–d** were subjected to a stereocontrolled reductive amination procedure by forming a non-isolated imine intermediate with benzylamine in the presence of Et_3N and $TiCl_4$ as the carbonyl activator and water scavenger, followed by $NaBH_4$ reduction of the C=N double bond (Scheme 2). In this way the required amines **5** were obtained as only the *syn* diastereoisomers. Careful temperature control was necessary during this procedure since on reaching temperatures over −20°C the amines **5** were obtained with a significant loss of enantiomeric purity (e.e. 70% at 0°C), although always as only the *syn* isomers. This indicates that the stereogenic center at C2 is able to exert a very effective 1,2 asymmetric induction on the new stereogenic center created during the reduction of the C=N bond and that at temperatures higher than −20°C epimerization takes place at this original stereogenic center, therefore leading to a loss of the enantiomeric purity in the final products. This racemization process is



Scheme 2. *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

most probably due to a fast imine–enamine tautomerism process in the non-isolated intermediate imine. The thus obtained 2-aryl-1,2,3,4-tetrahydro-1-naphthylamines were subjected to a standard Pictet–Spengler cyclization procedure yielding the target heterocycles in high yields.

The relative stereochemistry of the newly created stereogenic center during the reductive amination step was determined as *cis* by NOE difference spectroscopic experiments which also established the stereochemistry of the B/C ring junction in the final benzo[*c*]phenanthridines to be *cis* and therefore the absolute stereochemistry of the stereogenic centers in the final heterocycles **6a–d** could be assigned as (4b*R*,10b*S*) (Table 2). The observed stereochemistry of the naphthylamines **5a–d** arising from the hydride reduction of the C=N bond of the imine derived from the tetralones **4a–d** is consistent with a transition state in which the hydride reagent attacks from the less hindered face of the C=N plane, which is opposite to the 2-aryl substituent and therefore affording the products with a relative *cis* stereochemistry as the only detectable isomer. The determination of enantiomeric purities by chiral HPLC analysis under conditions optimized for a racemic standard[13] showed that all the products **5a–d** and **6a–d** were >99% which also indicates that all the synthetic steps proceeded without any isomerization, especially concerning the very sensitive benzylic position in the tetralones **4a–d.**

Table 2
Yields and enantioselectivities in the synthesis of the benzo[*c*]phenanthridines **6a–d**

Prod	R^1	R^2	R^3	Yield	e.e.[a]	Prod	Yield	e.e.[a]
5a	OCH_3	H	OCH_3	80	>99	**6a**	93	>99
5b	OCH_3	OCH_3	OCH_3	72	>99	**6b**	88	>99
5c	OCH_2O	H	OCH_3	70	>99	**6c**	94	>99
5d	OCH_3	H	OCH_2O	82	>99	**6d**	86	>99

[a] Determined by Chiral HPLC (Chiralcel OD, UV detector, hexanes *iso*-propanol 90:10, flow rate 0.80mL/min for **5a-d** and 1.00mL/min for **6a-d**.).

In conclusion, a high yield synthetic procedure has been established for the asymmetric synthesis of hexahydrobenzo[*c*]phenanthridines with a *cis* B/C ring junction. This method also allows the introduction of different substitution patterns on the A and D aromatic rings by careful selection of the starting arylacetic acid and 2-aryl-1-iodoethane electrophiles, opening a general way for the preparation of a wide range of these types of alkaloids.

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. ^1H–$\{^1H\}$ NOE experiments were carried

out in the difference mode by irradiation of all the lines of a multiplet.[14] 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.[15] Flash chromatography[16] 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.[17] *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. Amides **1a–c** are known compounds[8c] and the 2-aryl-1-iodoethanes employed for their alkylation were prepared by iodination of the corresponding 2-arylethanols by standard procedure.[18]

3.2. General procedure for the asymmetric alkylation of the pseudoephedrine amides *1*

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

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 **1a** (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 the 2-(3,4-dimethoxyphenyl)-1-iodoethane (3.39 g, 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: 85%. $[\alpha]_D^{20}+89.4$ (c = 0.3, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) (2:1 rotamer ratio; only resonances from the major rotamer are reported): 1.11 (d, 3H, J = 6.6 Hz); 2.48 (m, 4H); 2.67 (s, 3H); 3.51 (t, 1H, J = 6.9 Hz); 3.86 (s, 12H); 3.92 (m, 1H); 4.13 (bs, 1H); 4.56 (d, 1H, J = 6.7 Hz); 6.62–6.82 (m, 6H); 7.26–7.37 (m, 5H). ^{13}C NMR ($CDCl_3$) (2:1 rotamer ratio; only resonances from the major rotamer are reported): 13.5; 27.0; 32.9; 36.4; 47.8; 55.4; 55.5; 57.4; 75.6; 110.0; 110.7; 111.4; 119.9; 125.9; 126.3; 127.6; 128.1; 129.1; 131.6; 133.9; 141.9; 146.7; 147.5; 148.2; 148.7; 174.5. IR ($CHCl_3$): 3389; 1625. MS (EI) m/z (rel. int): 507 (M^+,1), 489 (2), 342 (9), 325 (18), 178 (57), 164 (7), 151 (100), 147 (26), 107 (8), 105 (3), 91 (11), 79 (3), 77 (6), 56 (16). Anal. calcd for $C_{30}H_{37}NO_6$: C, 70.98; H, 7.35; N, 2.76. Found: C, 74.06; H, 7.39; N, 2.70.

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

Yield: 83%. $[\alpha]_D^{20}=+58.2$ (c = 0.2, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) (2:1 rotamer ratio; only resonances from the major rotamer are reported): 1.08 (d, 3H, J = 6.7 Hz); 2.45 (m, 4H); 2.66 (s, 3H); 3.45 (t, 1H, J = 7.2 Hz); 3.76 (s, 6H); 3.78 (s, 3H); 3.80 (s, 3H); 3.84 (s, 3H); 4.11 (m, 1H); 4.51 (m, 2H); 6.42 (s, 2H); 6.60–6.77 (m, 3H); 7.24–7.32 (m, 5H). ^{13}C NMR ($CDCl_3$) (2:1 rotamer ratio; only resonances from the major rotamer are reported): 13.8; 27.0; 33.1; 36.5; 48.7; 55.2; 55.8; 57.6; 60.5; 76.3; 104.2; 110.7; 111.2; 120.0; 126.0; 127.3; 127.5, 128.0; 133.9; 134.9; 136.3; 142.3; 146.8; 148.4; 153.1; 174.5. IR ($CHCl_3$): 3405; 1640. MS (EI) m/z (rel. int): 537 (M^+,1), 355 (3), 266 (4), 212 (100), 208 (5), 151 (13), 134 (9), 129 (7), 91 (12), 79 (2), 77 (7), 56 (4). Anal. calcd for $C_{31}H_{39}NO_7$: C, 69.25; H, 7.31; N, 2.61. Found: C, 69.21; H, 7.36; N, 2.58.

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

Yield: 81%. $[\alpha]_D^{20} = +74.3$ (c = 0.2, CH_2Cl_2). ^1H NMR ($CDCl_3$) (2:1 rotamer ratio; only resonances from the major rotamer are reported): 1.01 (d, 3H, $J = 6.4$ Hz); 2.32 (m, 4H); 2.55 (s, 3H); 3.37 (t, 1H, $J = 7.0$ Hz); 3.73 (s, 6H); 3.97 (m, 1H); 4.35 (d, 1H, $J = 7.9$ Hz); 4.47 (bs, 1H); 5.79 (s, 2H); 6.50–6.69 (m, 6H); 7.15–7.26 (m, 5H). ^{13}C NMR ($CDCl_3$) (2:1 rotamer ratio; only resonances from the major rotamer are reported): 13.6; 27.2; 32.8; 36.5; 47.7; 55.4; 55.5; 57.5, 75.6; 100.7; 107.8; 110.8; 111.3; 120.0; 120.8; 126.0; 127.1; 127.9; 128.3; 132.9; 133.9; 141.9; 146.1; 146.8; 147.7; 148.4; 174.3. IR ($CHCl_3$): 3420; 1636. MS (EI) *m/z* (rel. int.): 491 (M^+,1), 473 (2), 309 (25), 207 (4), 162 (46), 151 (100), 147 (37), 135 (8), 107 (11), 105 (6), 91 (20), 79 (6), 77 (11), 56 (34). Anal. calcd for $C_{29}H_{33}NO_6$: C, 70.86; H, 6.77; N, 2.85. Found: C, 70.89; H, 6.82; N, 2.79.

3.2.4. (+)-[2S,1′S,2′S]-N-(2′-Hydroxy-1′-methyl-2′-phenylethyl)-N-methyl-2-(3,4-dimethoxyphenyl)-4-(3,4-methylenedioxyphenyl)butanamide ***2d***

Yield: 78%. $[\alpha]_D^{20} = +65.9$ (c = 0.2, CH_2Cl_2). ^1H NMR ($CDCl_3$) (3:1 rotamer ratio; only resonances from the major rotamer are reported): 1.04 (d, 3H, $J = 6.6$ Hz); 2.34 (m, 4H); 2.58 (s, 3H); 3.39 (t, 1H, $J = 7.1$ Hz); 3.76 (s, 3H); 3.78 (s, 3H); 4.06 (m, 1H); 4.36 (bs, 1H); 4.49 (d, 1H, $J = 7.7$ Hz); 5.83 (s, 2H); 6.48–6.73 (m, 6H); 7.19–7.30 (m, 5H). ^{13}C NMR ($CDCl_3$) (3:1 rotamer ratio; only resonances from the major rotamer are reported): 13.7; 27.0; 33.0; 36.6; 47.8; 55.5; 55.6; 57.4; 75.9; 100.4; 107.8; 108.5; 109.9; 111.0; 119.9; 121.0; 125.9; 127.2; 128.0; 132.5; 133.7; 139.0; 143.3; 145.2; 147.6; 148.9; 174.7. IR ($CHCl_3$): 3396; 1629. MS (EI) *m/z* (rel. int.): 491 (M^+,1), 325 (13), 187 (5), 178 (41), 163 (9), 151 (6), 147 (24), 135 (100), 105 (7), 91 (10), 79 (9), 77 (21), 56 (21). Anal. calcd for $C_{29}H_{33}NO_6$: C, 70.86; H, 6.77; N, 2.85. Found: C, 70.90; H, 6.74; N, 2.81.

3.3. General procedure for the hydrolysis of the pseudoephedrine amides ***3***

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

A solution of the amide **2a** (775 mg, 2.15 mmol) in dioxane (17 mL) was slowly added to 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 acid **3a** as a yellowish oil. Yield: 93%. $[\alpha]_D^{20} = +52.5$ (c = 0.2, CH_2Cl_2). ^1H NMR ($CDCl_3$): 1.96 (m, 1H); 2.29 (m, 1H); 2.46 (t, 2H, $J = 7.4$ Hz); 3.42 (t, 1H, $J = 7.3$ Hz); 3.74 (s, 6H); 3.76 (s, 6H); 6.58–6.80 (m, 6H); 7.5–8.1 (bs, 1H). ^{13}C NMR ($CDCl_3$): 32.6; 34.3; 49.7; 55.3; 55.4; 110.6; 110.8; 111.3; 119.9 130.5; 133.3; 146.7; 147.8; 148.2; 148.5; 177.9. IR ($CHCl_3$): 3318; 1731. MS (EI) *m/z* (rel. int.): 361 ($M^+ + 1$, 11), 360 (M^+, 33), 207 (17), 196 (61), 178 (21), 165 (37), 164 (26), 163 (22), 152 (58), 151 (100), 137 (17), 121 (20), 107 (19), 91 (22), 77 (19). Anal. calcd for $C_{20}H_{24}O_6$: C, 66.65; H, 6.71. Found: C, 66.72; H, 6.59.

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

Yield: 95%. $[\alpha]_D^{20} = +29.8$ (c = 0.2, CH_2Cl_2). ^1H NMR ($CDCl_3$): 2.02 (m, 1H); 2.34 (m, 1H); 2.51 (t, 2H, $J = 7.5$ Hz); 3.43 (t, 1H, $J = 7.6$ Hz); 3.77 (s, 3H); 3.79 (s, 3H); 3.80 (s, 6H); 3.83 (s, 3H); 6.47 (s, 2H); 6.62–6.74 (m, 3H); 9.4–9.8 (bs, 1H). ^{13}C NMR ($CDCl_3$): 32.8; 34.4; 50.6; 55.5;

55.6; 55.8; 60.5; 104.7; 110.8; 111.4; 120.0; 133.2; 136.9; 147.0; 148.4; 148.5; 152.9; 178.9. IR ($CHCl_3$): 3405; 1718. MS (EI) *m/z* (rel. int.): 390 (M^+, 21), 181 (100), 148 (9), 136 (5), 91 (4), 77 (4), 65 (3). Anal. calcd for $C_{21}H_{26}O_7$: C, 64.60; H, 6.71. Found: C, 64.69; H, 6.66.

3.3.3. (+)-(S)-4-(3,4-Dimethoxyphenyl)-2-(3,4-methylenedioxyphenyl)butanoic acid ***3c***

Yield: 94%. $[\alpha]_D^{20} = +32.5$ (c = 0.5, CH_2Cl_2). ^1H NMR ($CDCl_3$): 2.04 (m, 1H); 2.30 (m, 1H); 2.49 (t, 2H, $J = 7.3$ Hz); 3.43 (t, 1H, $J = 7.5$ Hz); 3.81 (s, 6H); 5.89 (s, 2H); 6.52–6.80 (m, 6H); 7.4–7.9 (bs, 1H). ^{13}C NMR ($CDCl_3$): 32.6; 34.3; 49.9; 55.5; 55.6; 100.8; 108.0; 109.5; 110.8; 111.3; 120.0; 121.4; 131.4; 133.3; 146.7; 146.9; 147.6; 148.4; 179.7. IR ($CHCl_3$): 3461; 1720. MS (EI) *m/z* (rel. int.): 344 (M^+, 10), 300 (23), 298 (69), 283 (26), 267 (42), 164 (26), 163 (22), 152 (100), 151 (67), 136 (80), 121 (48), 107 (28), 91 (56), 79 (30), 77 (87), 65 (48), 51 (53). Anal. calcd for $C_{19}H_{20}O_6$: C, 66.27; H, 5.85. Found: C, 66.32; H, 5.78.

3.3.4. (+)-(S)-2-(3,4-Dimethoxyphenyl)-4-(3,4-methylenedioxyphenyl)butanoic acid ***3d***

Yield: 90%. $[\alpha]_D^{20} = +31.0$ (c = 0.1, CH_2Cl_2). ^1H NMR ($CDCl_3$): 1.99 (m, 1H); 2.31 (m, 1H); 2.45 (t, 2H, $J = 7.3$ Hz); 3.43 (t, 1H, $J = 7.7$ Hz); 3.80 (s, 6H); 5.85 (s, 2H); 6.51–6.88 (m, 6H); 9.5–10.0 (bs, 1H). ^{13}C NMR ($CDCl_3$): 32.8; 34.4; 49.8; 55.5; 100.5; 107.8; 108.6; 110.7; 110.8; 120.0; 120.9; 130.2; 134.6; 145.4; 147.3; 148.0; 148.5; 179.4. IR ($CHCl_3$): 3450; 1711. MS (EI) *m/z* (rel. int.): 344 (M^+, 10), 298 (100), 267 (60), 237 (24), 209 (16), 165 (20), 159 (21), 152 (13), 145 (28), 135 (13), 121 (48), 91 (10), 77 (25). Anal. calcd for $C_{19}H_{20}O_6$: C, 66.27; H, 5.85. Found: C, 66.35; H, 5.89.

3.4. General procedure for the intramolecular Friedel–Crafts acylation of the acids ***3***

3.4.1. Synthesis of (+)-(2S)-6,7-dimethoxy-2-(3,4-dimethoxyphenyl)-3,4-dihydronaphthalen-1(2H)-one ***4a***

To a cooled (0°C) solution of the starting acid **3a** (380 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 added dropwise within 40 min to a stirred suspension of $AlCl_3$ (358 mg, 2.46 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 **4a** after flash column chromatography purification (hexanes:ethyl acetate 1:1). An analytically pure sample was obtained by crystallization in EtOH. Yield: 78%, mp 144–146 (EtOH). $[\alpha]_D^{20} = +55.3$ (c = 0.2, CH_2Cl_2). ^1H NMR ($CDCl_3$): 2.35 (m, 2H); 2.95 (m, 2H); 3.67 (t, 1H, $J = 9.1$ Hz); 3.82 (s, 3H); 3.83 (s, 3H); 3.89 (s, 3H); 3.92 (s, 3H); 6.67–6.82 (m, 4H); 7.55 (s, 1H). ^{13}C NMR ($CDCl_3$): 28.0; 31.4; 52.8; 55.4; 55.5; 55.7; 108.4; 109.8; 110.7; 111.4; 119.9; 125.5; 132.3; 138.6; 147.4; 147.5; 148.4; 153.1; 196.9. IR (KBr): 1666. MS (EI) *m/z* (rel. int.): 342 (M^+, 62), 204 (27), 191 (86), 178 (67), 152 (18), 151 (61), 150 (100), 135 (11), 107 (12), 91 (14), 79 (10), 77 (20), 51 (7). Anal. calcd for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 70.22; H, 6.41.

3.4.2. (+)-(2S)-6,7-Dimethoxy-2-(3,4,5-trimethoxyphenyl)-3,4-dihydronaphthalen-1(2H)one ***4b***

Yield: 71%, mp 164–167 (EtOH). $[\alpha]_D^{20} = +23.9$ (c = 0.1, CH_2Cl_2). ^1H NMR ($CDCl_3$): 2.25 (m, 2H); 2.86 (m, 2H); 3.54 (t, 1H, $J = 8.9$ Hz); 3.68 (s, 6H); 3.71 (s, 3H); 3.78 (s, 3H); 3.81 (s, 3H);

6.28 (s, 2H); 6.57 (s, 1H); 7.43 (s, 1H). ^{13}C NMR ($CDCl_3$): 28.4; 31.7; 54.0; 55.8; 55.9; 60.5; 105.3; 108.6; 110.0; 125.6; 135.8; 138.4; 147.8; 152.9; 153.4; 154.2; 196.8. IR (KBr): 1668. MS (EI) *m/z* (rel. int.): 372 (M^+, 100), 357 (11), 204 (39), 191 (58), 181 (39), 178 (39), 150 (61), 135 (9), 107 (9), 91 (9), 79 (8), 77 (14), 63 (4), 51 (4). Anal. calcd for $C_{21}H_{24}O_6$: C, 67.73; H, 6.50. Found: C, 67.80; H, 6.46.

3.4.3. (+)-(2S)-6,7-Dimethoxy-2-(3,4-methylenedioxyphenyl)-3,4-dihydronaphthalen-1(2H)one ***4c***

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: 74%, mp 120–123 (EtOH). $[\alpha]_D^{20} = +28.6$ (c = 0.2, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): 2.34 (m, 2H); 2.93 (m, 2H); 3.66 (dd, 1H, J = 5.9, 9.4 Hz); 3.91 (s, 3H); 3.94 (s, 3H); 5.92 (s, 2H); 6.60–6.89 (m, 4H); 7.55 (s, 1H). ^{13}C NMR ($CDCl_3$): 28.0; 31.5; 53.0; 55.7; 55.8; 100.6; 108.0; 108.5; 108.6; 109.8; 121.2; 125.6; 133.5; 138.6; 146.1; 147.4; 147.7; 153.2; 196.8. IR (KBr): 1654. MS (EI) *m/z* (rel. int.): 326 (M^+, 69), 204 (13), 191 (90), 178 (62), 150 (100), 135 (28), 107 (12), 91 (10), 89 (12), 79 (9), 77 (22), 63 (10), 51 (8). Anal. calcd for $C_{19}H_{18}O_5$: C, 69.93; H, 5.56. Found: C, 70.01; H, 5.62.

3.4.4. (+)-(2S)-6,7-Methylenedioxy-2-(3,4-dimethoxyphenyl)-3,4-dihydronaphthalen-1(2H)one ***4d***

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: 76%, mp 136–139 (EtOH). $[\alpha]_D^{20} = +20.6$ (c = 0.3, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): 2.33 (m, 2H); 2.93 (m, 2H); 3.63 (t, 1H, J = 8.6 Hz); 3.81 (s, 3H); 3.82 (s, 3H); 5.97 (s, 2H); 6.63–6.80 (m, 4H); 7.47 (s, 1H). ^{13}C NMR ($CDCl_3$): 28.7; 31.2; 53.1; 55.5; 101.4; 106.3; 107.7; 110.8; 111.4; 120.0; 127.2; 132.1; 140.7; 146.7; 147.6; 148.5; 151.8; 196.4. IR (KBr): 1670. MS (EI) *m/z* (rel. int.): 326 (M^+, 100), 188 (22), 175 (46), 165 (10), 163 (55), 151 (49), 134 (69), 104 (14), 76 (21), 63 (4), 53 (3), 51 (6). Anal. calcd for $C_{19}H_{18}O_5$: C, 69.93; H, 5.56. Found: C, 69.88; H, 5.59.

3.5. General procedure for the reductive amination of the ketones ***4***

*3.5.1. Synthesis of (+)-(1R,2S)-*N*-benzyl-6,7-dimethoxy-2-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydro-1-naphthylamine* ***5a***

To a stirred solution of the ketone **4a** (2.17 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 added dropwise 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 **5a** after flash column chromatography purification (hexanes:ethyl acetate 1:1). Yield: 80%. $[\alpha]_D^{20} = +53.5$ (c = 0.2, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): 1.64 (bs, 1H); 1.96 (m, 1H); 2.48 (m, 1H); 2.73 (m, 1H); 2.81 (m, 1H); 3.11 (dt, J = 2.9, 14.1 Hz); 3.38 (d, 1H, J = 13.8 Hz); 3.47 (d, 1H, J = 13.7 Hz); 3.77 (s, 3H); 3.81 (d, 1H, J = 2.9 Hz); 3.85 (s, 6H); 3.90 (s, 3H); 6.51 (s, 1H); 6.62 (s, 1H); 6.82 (d, 1H, J = 5.6 Hz); 6.88 (s, 1H); 7.05 (dd, 1H, J = 1.6, 5.6 Hz); 7.21–7.27 (m, 5H). ^{13}C NMR ($CDCl_3$): 22.9; 28.7; 44.1; 52.1; 55.7; 55.8; 58.2; 110.8; 111.3; 111.4; 119.8; 126.6; 128.0; 128.1; 128.5; 131.2; 136.1; 140.7; 140.9; 146.7; 147.4; 147.8; 148.7. IR ($CHCl_3$): 3330. MS (EI) *m/z* (rel. int.): 433 (M^+, 1), 326 (100), 311 (40), 163 (14), 151 (24), 145 (15), 107 (8), 91 (2), 76 (3), 63 (2). Anal. calcd for $C_{27}H_{31}NO_4$: C, 74.80; H, 7.21; N, 3.23. Found: C, 78.89; H, 7.15; N, 3.19.

3.5.2. (+)-(1R,2S)-N-Benzyl-6,7-dimethoxy-2-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydro-1-naphthylamine ***5b***

Yield: 70%. $[\alpha]_D^{20} = +60.5$ (c = 0.1, CH_2Cl_2). ^1H NMR ($CDCl_3$): 1.51 (bs, 1H); 1.97 (m, 1H); 2.49 (m, 1H); 2.69 (m, 1H); 2.78 (m, 1H); 3.01 (dt, $J = 2.6$, 14.1 Hz); 3.40 (d, 1H, $J = 13.7$ Hz); 3.47 (d, 1H, $J = 13.7$ Hz); 3.76 (s, 3H); 3.81 (s, 6H); 3.83 (s, 3H); 3.85 (s, 3H); 3.95 (d, 1H, $J = 2.6$ Hz); 6.49 (s, 1H); 6.53 (s, 2H); 6.53 (s, 1H); 7.19–7.31 (m, 5H). ^{13}C NMR ($CDCl_3$): 22.4; 28.4; 44.5; 51.9; 55.3; 55.4; 55.6; 58.0; 60.5; 104.7; 110.9; 111.5; 126.3; 127.6; 127.8; 130.9; 136.0; 139.2; 140.4; 146.4; 147.6; 152.6; 152.8. IR ($CHCl_3$): 3340. MS (EI) *m/z* (rel. int.): 463 (M^+, 1), 356 (100), 341 (64), 252 (4), 237 (3), 225 (4), 207 (2), 189 (3), 178 (9), 165 (6), 145 (7), 135 (3), 127 (3), 115 (3), 89 (2), 76 (4). Anal. calcd for $C_{28}H_{33}NO_5$: C, 72.55; H, 7.18; N, 3.02. Found: C, 72.50; H, 7.21; N, 3.06.

3.5.3. (+)-(1R,2S)-N-Benzyl-6,7-dimethoxy-2-(3,4-methylenedioxyphenyl)-1,2,3,4-tetrahydro-1-naphthylamine ***5c***

Yield: 72%. $[\alpha]_D^{20} = +59.3$ (c = 0.3, CH_2Cl_2). ^1H NMR ($CDCl_3$): 1.51 (bs, 1H); 1.87 (m, 1H); 2.38 (m, 1H); 2.76 (m, 1H); 2.85 (m, 1H); 3.02 (dt, $J = 2.7$, 14.3 Hz); 3.31 (d, 1H, $J = 13.7$ Hz); 3.47 (d, 1H, $J = 13.7$ Hz); 3.73 (s, 3H); 3.82 (s, 3H); 3.93 (d, 1H, $J = 2.7$ Hz); 5.92 (s, 2H); 6.45 (s, 1H); 6.57 (s, 1H); 6.76 (s, 1H); 6.83 (d, 1H, $J = 5.6$ Hz); 7.06 (dd, 1H, $J = 1.6$, 5.6 Hz); 7.12–7.27 (m, 5H). ^{13}C NMR ($CDCl_3$): 22.9; 28.5; 44.1; 52.2; 55.5; 55.6; 58.2; 100.5; 107.8; 108.6; 111.0; 111.6; 120.8; 126.5; 128.0; 128.2; 131.0; 137.3; 140.5; 140.7; 145.7; 146.6; 147.4; 147.7. IR ($CHCl_3$): 3321. MS (EI) *m/z* (rel. int.): 417 (M^+, 1), 310 (100), 295 (33), 267 (3), 252 (2), 249 (3), 237 (4), 209 (5), 207 (3), 189 (3), 165 (14), 151 (2), 145 (14), 135 (37), 126 (6), 105 (4), 89 (5), 76 (4), 63 (4). Anal. calcd for $C_{26}H_{27}NO_4$: C, 74.80; H, 6.52; N, 3.35. Found: C, 78.70; H, 6.58; N, 3.29.

3.5.4. (+)-(1R,2S)-N-Benzyl-6,7-methylenedioxy-2-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydro-1-naphthylamine ***5d***

Yield: 82%. $[\alpha]_D^{20} = +44.3$ (c = 0.3, CH_2Cl_2). ^1H NMR ($CDCl_3$): 1.48 (bs, 1H); 1.92 (m, 1H); 2.42 (m, 1H, H_{4ax}); 2.77 (m, 1H); 2.83 (m, 1H); 3.15 (dt, $J = 2.6$, 14.1 Hz); 3.39 (d, 1H, $J = 13.7$ Hz); 3.48 (d, 1H, $J = 13.7$ Hz); 3.75 (d, 1H, $J = 2.6$ Hz); 3.88 (s, 3H); 3.90 (s, 3H); 5.90 (s, 2H); 6.43 (s, 1H); 6.55 (s, 1H); 6.78 (s, 1H); 6.83 (d, 1H, $J = 5.6$ Hz); 7.10 (dd, 1H, $J = 1.6$, 5.6 Hz); 7.29–7.29 (m, 5H). ^{13}C NMR ($CDCl_3$): 22.8; 28.9; 43.8; 51.8; 55.6; 55.7; 58.9; 100.6; 107.8; 108.6; 111.8; 111.0; 121.1; 126.4; 128.2; 128.4; 131.3; 137.1; 140.5; 140.6; 145.7; 146.2; 147.1; 147.7. IR ($CHCl_3$): 3320. MS (EI) *m/z* (rel. int.): 417 (M^+, 1), 310 (100), 308 (4), 295 (24), 165 (12), 151 (18), 135 (9), 126 (4), 107 (15), 89 (7), 76 (6), 63 (4). Anal. calcd for $C_{26}H_{27}NO_4$: C, 74.80; H, 6.52; N, 3.35. Found: C, 78.73; H, 6.61; N, 3.40.

3.6. General procedure for the Pictet–Spengler cyclization of the amines ***5***

3.6.1. Synthesis of (−)-(4bR,10bS)-N-benzyl-4b,5,6,10b,11,12-hexahydro-2,3,8,9-tetramethoxybenzo[c]phenanthridine ***6a***

A solution of the amine **5a** (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). Yield: 93%. $[\alpha]_D^{20} = -88.3$ (c = 0.1, CH_2Cl_2). ^1H NMR ($CDCl_3$): 2.05 (m, 1H); 2.45 (m, 1H); 2.66 (m, 2H); 3.19 (m, 1H); 3.51 (d, 1H, $J = 16.2$ Hz); 3.65 (d, 1H, $J = 16.2$ Hz); 3.74 (d, 1H, $J = 15.1$ Hz); 3.79 (s, 3H); 3.83 (s, 3H);

3.88 (d, 1H, $J=15.1$ Hz); 3.91 (s, 3H); 3.94 (s, 3H); 4.05 (d, 1H, $J=5.1$ Hz); 6.41 (s, 1H); 6.53 (s, 1H); 6.86 (s, 1H); 7.24–7.40 (m, 6H). ^{13}C NMR ($CDCl_3$): 26.7; 27.3; 32.5; 50.2; 52.8; 55.6; 55.9; 59.0; 109.3; 110.0; 110.7; 112.3; 126.5; 126.7; 126.8; 128.1; 128.3; 128.4; 129.0; 130.2; 140.4; 147.2; 147.5; 147.8. MS (EI) *m/z* (rel. int.): 445 (M^+, 1), 281 (31), 207 (100), 191 (14), 177 (7), 167 (19), 151 (10), 146 (59), 147 (21), 133 (19), 128 (11), 117 (23), 105 (26), 96 (25), 91 (39), 79 (19), 77 (25), 65 (10), 57 (64). Anal. calcd for $C_{28}H_{31}NO_4$: C, 75.48; H, 7.01; N, 3.14. Found: C, 75.54; H, 7.06; N, 3.18.

*3.6.2. (−)-(4b*R*,10b*S*)-*N*-Benzyl-4b,5,6,10b,11,12-hexahydro-2,3,7,8,9-pentamethoxy-benzo[c]-phenanthridine* ***6b***

Yield: 94%. $[\alpha]_D^{20}=-67.6$ (c = 0.2, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): 2.02 (m, 1H); 2.42 (m, 1H); 2.66 (m, 2H); 3.15 (m, 1H); 3.53 (d, 1H, $J=16.2$ Hz); 3.62 (d, 1H, $J=16.2$ Hz); 3.71 (s, 3H); 3.76 (d, 1H, $J=15.3$ Hz); 3.86 (s, 6H); 3.83 (d, 1H, $J=15.3$ Hz); 3.89 (s, 3H); 3.94 (s, 3H); 4.06 (d, 1H, $J=5.3$ Hz); 6.52 (s, 1H); 6.68 (s, 1H); 7.19–7.71 (m, 6H). ^{13}C NMR ($CDCl_3$): 26.0; 29.0; 30.1; 43.9; 55.0; 55.5; 55.7; 56.0; 60.0; 106.3; 110.6; 111.9; 126.2; 126.7; 127.1; 128.8; 128.9; 129.2; 129.5; 130.6; 141.3; 145.6; 147.4; 148.0; 150.3. MS (EI) *m/z* (rel. int.): 475 (M^+, 1), 385 (3), 325 (4), 223 (6), 205 (3), 167 (4), 149 (100), 132 (2), 104 (11), 76 (11), 65 (7), 57 (55), 51 (7). Anal. calcd for $C_{29}H_{33}NO_5$: C, 73.24; H, 6.99; N, 2.95. Found: C, 73.31; H, 7.06; N, 2.83.

*3.6.3. (−)-(4b*R*,10b*S*)-*N*-Benzyl-4b,5,6,10b,11,12-hexahydro-2,3-dimethoxy-8,9-methylenedioxy-benzo[c]phenanthridine* ***6c***

Yield: 88%. $[\alpha]_D^{20}=-97.1$ (c = 0.6, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): 1.96 (m, 1H); 2.37 (m, 1H); 2.59 (m, 2H); 3.15 (m, 1H); 3.57 (d, 1H, $J=16.2$ Hz); 3.66 (d, 1H, $J=16.2$ Hz); 3.73 (d, 1H, $J=15.1$ Hz); 3.78 (s, 3H); 3.82 (d, 1H, $J=15.1$ Hz); 3.91 (s, 3H); 3.99 (d, 1H, $J=4.9$ Hz); 5.85 (s, 2H); 6.33 (s, 1H); 6.47 (s, 1H); 6.82 (s, 1H); 7.21–7.32 (m, 6H). ^{13}C NMR ($CDCl_3$): 26.1; 27.0; 32.2; 50.0; 52.6; 55.4; 55.7; 58.6; 100.2; 106.4; 106.8; 110.5; 111.8; 126.6; 126.7; 127.9; 128.2; 129.4; 129.9; 131.2; 138.9; 140.8; 145.4; 147.0; 147.5. MS (EI) *m/z* (rel. int.): 429 (M^+, 1), 355 (100), 320 (26), 292 (40), 277 (11), 248 (16), 190 (9), 167 (11), 131 (9), 95 (16). Anal. calcd for $C_{27}H_{27}NO_4$: C, 75.50; H, 6.34; N, 3.26. Found: C, 75.56; H, 6.28; N, 3.31.

*3.6.4. (−)-(4b*R*,10b*S*)-*N*-Benzyl-4b,5,6,10b,11,12-hexahydro-2,3-methylenedioxy-8,9-dimethoxy-benzo[c]phenanthridine* ***6d***

Yield: 86%. $[\alpha]_D^{20}=-91.6$ (c = 0.1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): 1.93 (m, 1H); 2.31 (m, 1H); 2.63 (m, 2H); 3.11 (m, 1H); 3.56 (d, 1H, $J=16.2$ Hz); 3.61 (d, 1H, $J=16.2$ Hz); 3.70 (d, 1H, $J=15.1$ Hz); 3.77 (s, 3H); 3.82 (d, 1H, $J=15.1$ Hz); 3.94 (s, 3H); 4.03 (d, 1H, $J=5.1$ Hz); 5.87 (s, 2H); 6.31 (s, 1H); 6.47 (s, 1H); 6.80 (s, 1H); 7.20–7.36 (m, 6H). ^{13}C NMR ($CDCl_3$): 26.0; 27.2; 32.5; 50.4; 53.1; 55.5; 55.7; 58.9; 100.0; 106.3; 106.8; 110.4; 111.8; 126.5; 126.7; 127.8; 128.1; 129.5; 130.1; 131.2; 138.5; 140.9; 145.3; 147.0; 147.4. MS (EI) *m/z* (rel. int.): 429 (M^+, 1), 367 (10), 355 (100), 320 (11), 292 (32), 277 (25), 190 (19), 167 (4), 131 (6), 95 (11), 91 (7), 77 (26), 56 (22). Anal. calcd for $C_{27}H_{27}NO_4$: C, 75.50; H, 6.34; N, 3.26. Found: C, 75.51; H, 6.41; N, 3.20.

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