

**A NEW INDOLE ALKALOID FROM *SARCOCEPHALUS LATIFOLIUS***Pedro Abreu<sup>a\*</sup> and António Pereira<sup>b</sup>

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**Abstract** — A new indole alkaloid, 19-*O*-ethylangustoline, as well as the known alkaloids angustoline, angustine, angustidine and nauclefine were isolated from the stem bark of *Sarcocephalus latifolius* (Smith) Bruce and characterised by spectral methods. The absolute stereochemistry at C-19 of angustoline and 19-*O*-ethylangustoline was determined by Horeau's method and optical rotatory dispersion.

As part of our phytochemical research on medicinal plants from Guinea-Bissau, we have investigated the Rubiaceae *Sarcocephalus latifolius* (Smith) Bruce (*Nauclea latifolia* Sm.). The leaves find some local use in the treatment of fever, while roots and bark are used in the treatment of venereal disease, wounds and as odontalgic remedy.<sup>1</sup> Previous work on *N. latifolia* collected in Senegal, Burkina-Faso, Nigeria and Zaïre, has yielded a total of fourteen indole alkaloids: angustoline,<sup>2</sup> nauclefine,<sup>2</sup> nauclefine,<sup>2</sup> decarbomethoxy-nauclechine,<sup>3</sup> naucleidinal,<sup>4</sup> 19-*epi*-naucleidinal,<sup>4</sup> angustine,<sup>2,5</sup> naufoline,<sup>3,5</sup> nauclefoline,<sup>6</sup> nauclechine,<sup>6</sup> naulafine,<sup>5</sup> cadambine,<sup>5</sup> 3 $\alpha$ -cadambine<sup>5</sup> and strictosamide.<sup>7,8</sup>

Fractionation of the ethanol-ammonia extract of stem bark of *S. latifolius* by silica gel chromatography, afforded five main alkaloid fractions, that were further submitted to successive normal phase LPLC and preparative TLC, yielding compounds (1-5). Their <sup>1</sup>H- and <sup>13</sup>C-NMR spectra display the characteristic resonances of the nauclefine nucleus, and are in good agreement with the reported data for angustine (2), angustoline (3), angustidine (4) and nauclefine (5).<sup>†</sup>

The less polar compound (1) has the molecular formula C<sub>22</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub> as established by HRMS. Its MS spectrum showed the base peak at *m/z* 315 (C<sub>20</sub>H<sub>17</sub>N<sub>3</sub>O) corresponding to the loss of C<sub>2</sub>H<sub>4</sub>O, and a fragment at *m/z* 286 [M - C<sub>4</sub>H<sub>9</sub>O]<sup>+</sup>, which suggests the presence of an oxygenated side chain at the nauclefine nucleus. <sup>1</sup>H-NMR spectrum of 1 is closely related to that of angustoline, showing a A<sub>3</sub>X<sub>1</sub>

<sup>†</sup> <sup>13</sup>C-NMR data of nauclefine and angustidine are here reported for the first time in literature.

system  $\text{CH}_3\text{CH}(\text{R})\text{O}-$  at  $\delta$  1.54 and  $\delta$  5.02, and an additional methyl triplet ( $\delta$  1.16,  $J = 6.8$  Hz) coupled to a methylene quartet at  $\delta$  3.46, whose carbon chemical shift ( $\delta$  64.0) indicates an oxygen attachment. The downfield chemical shift of C-19 ( $\delta$  79.6) in comparison to the corresponding resonance in **3** ( $\delta$  63.9), and the absence of an IR hydroxyl absorption, support the new structure as the *O*-ethyl derivative of angustoline. The attachment of the side chain at C-20 was confirmed by NOESY correlations (Figure 1),

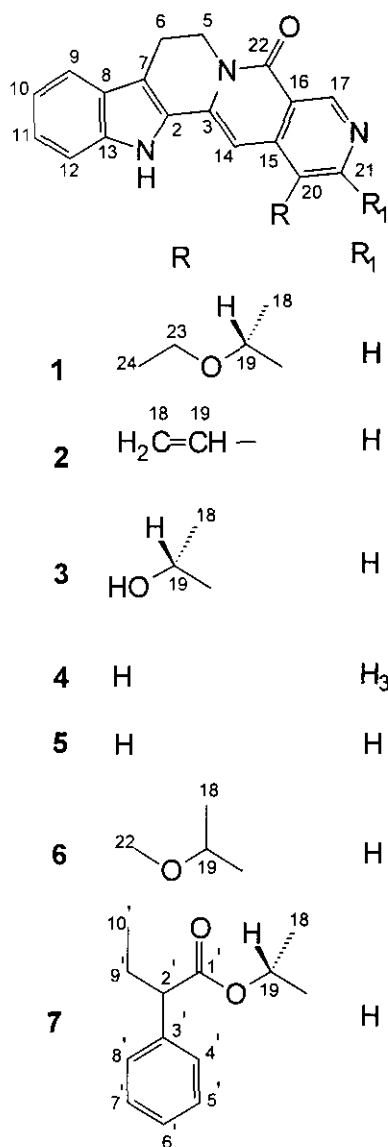


Table 1

$^1\text{H}$ - and $^{13}\text{C}$ -NMR spectral data of <b>1</b>		
	$\delta_{\text{C}}$	$\delta_{\text{H}}$
2	127.5	
3	137.0	
5 <sub>a</sub>	40.4	4.34 (1H, dd, $J = 13.6, 6.8$ )
5 <sub>b</sub>		4.44 (1H, dd, $J = 13.6, 6.8$ )
6 <sub>a,b</sub>	19.5	3.13 (2H, t, $J = 6.0$ )
7	116.6	
8	126.5	
9	120.1	7.63 (1H, d, $J = 8.0$ )
10	120.1	7.10 (1H, t, $J = 8.0$ )
11	124.8	7.29 (1H, t, $J = 8.0$ )
12	112.3	7.49 (1H, d, $J = 8.0$ )
13	139.0	
14	98.9	7.27 (1H, s)
15	139.5	
16	119.5	
17	150.1	9.26 (1H, s)
18	23.5	1.54 (3H, d, $J = 8.0$ )
19	72.9	5.02 (1H, q, $J = 8.0$ )
20	132	
21	148.5	8.66 (1H, s)
22	161	
23	64.1	3.46 (2H, q, $J = 8.0$ )
24	15.8	1.16 (3H, t, $J = 8.0$ )
NH		11.82 (1H, s)

Spectra in  $\text{DMSO}-d_6$ ,  $\delta$  in ppm and coupling constants ( $J$ ) in Hz.

whereas carbon and hydrogen resonances have been assigned by  $^1\text{H}$ - $^1\text{H}$  COSY and HMQC experiments (Table 1). This is the first reported occurrence of an *O*-alkyl derivative of angustoline in *Sarcocephalus*

*sp.*, although the related *O*-methyl compound (**6**) has been previously isolated from the seeds of *Camptotheca acuminata*.<sup>9</sup>

The absolute configuration of 19-*O*-ethylangustoline was determined on the basis of the comparison of its ORD curve with that of angustoline (Figure 2). It is well known that the ORD curves of compounds having an aromatic center attached to asymmetric carbon placed at an open chain system and bearing an hetero atom, exhibit conformation dependent Cotton effects.<sup>10,11</sup> According to the observed NOESY correlations for angustoline and 19-*O*-ethylangustoline, their side chains adopt a similar preferred conformation, in which the methine proton H-19 nearly eclipses the pyridine ring along the C-15–C-20 bond. This conclusion follows from the unique observed interaction of H-19 with H-14, and the absence of interaction of H-18 with H-14 and H-21. Once ORD curves of **1** and **3** are virtually superimposable, the absolute configuration of the chiral center of these two alkaloids must be identical.

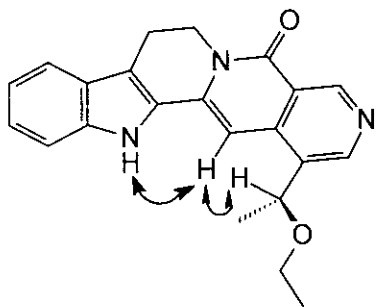


Figure 1. NOE selected interactions of **1**

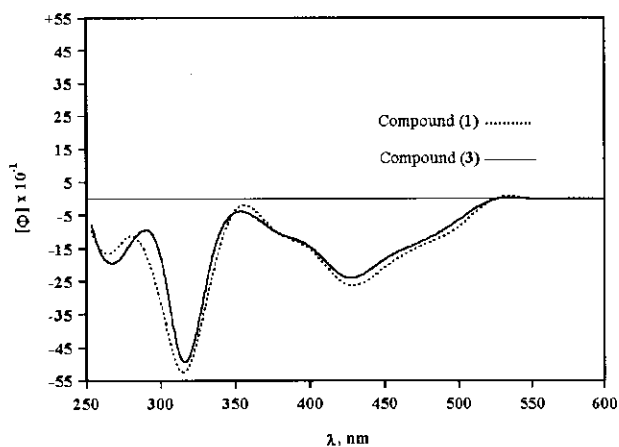


Figure 2. ORD curves of compounds (**1**) and (**3**)

Determination of the absolute configuration of C-19 of angustoline was achieved by a modified Horeau's method using HPLC.<sup>12</sup> The reaction of **3** with racemic 2-phenylbutanoic anhydride, followed by the addition of (*R*)-(+)-1-(1-naphthyl)ethylamine afforded a mixture of (1*R*,2'*S*)- and (1*R*,2'*R*)-*N*-[1-(1-naphthyl)ethyl]-2-phenylbutanamides, in the proportion of 68:32 as calculated by HPLC, which is indicative of a (*R*) configuration of the secondary hydroxy group of angustoline. In order to check the accuracy of this result, we have isolated and characterised the phenylbutyrate (**7**), formed *via* standard Horeau's method.<sup>13</sup> Its <sup>1</sup>H-NMR spectrum in CDCl<sub>3</sub> displays one discernible singlet for each NH, H-14 and H-17 protons of the corresponding 2'*R* and 2'*S* stereoisomers, in a ratio of 56:44. The negative optical rotation of the resulting phenylbutyric acid confirms the 19(*R*) configuration of angustoline, although this last result must be taken with same precaution, due to the low optical yield of the esterification (2.2 %).

To our knowledge, so far, the absolute configuration of natural angustoline has remained unknown,<sup>2,14,15</sup> whereas its total synthesis led to a racemic mixture.<sup>16</sup> Sticher *et al.* reported the isolation of the C-19 epimers of 3,14-dihydroangustoline, but the attempts to determine their absolute configuration were unsuccessful.<sup>15</sup>

## EXPERIMENTAL

*General.* Mps were determined on a Reichert microscope. Optical rotations and ORD were run on a Perkin-Elmer 241-MC polarimeter. UV spectra were recorded in EtOH on a Milton Roy Spectronic 1201 spectrophotometer, and FTIR spectra were measured on a Perkin-Elmer 157G infrared spectrophotometer. EIMS spectra (70 eV) were carried out on a Shimadzu QP-1000EX and HREIMS were calculated on a Finnigan MAT 711. <sup>1</sup>H (400 MHz) and <sup>13</sup>C (100.61 MHz) one- and two-dimensional NMR spectra were recorded on a Bruker ARX-400 spectrometer. HPLC determination of absolute configuration of angustoline was carried out on a Spectra Physics 100 chromatograph, equipped with a UV detector. Flash chromatography was performed on Merck silica gel of 230-400 mesh. Michel-Miller columns filled with Merck Lichroprep Si-60 were used in LPLC. The mobile phase was delivered by a Fluid Metering QSY pump at a maximum flow rate of 15 mL/min. The LPLC system was equipped with a Isco UA-6 detector set at 254 nm and a 5 mm preparative flow cell. Merck silica gel plates 0.25 mm and 0.50 mm thick were used for analytical and preparative TLC respectively.

*Plant material.* *S. latifolius* was collected in January 1994 at Contuboeil, Guinea-Bissau, and identified at the Herbarium of Botany Centre (LISC), where a voucher specimen is deposited.

*Extraction and isolation.* Stem bark of *S. latifolius* (680 g) was previously extracted (Soxhlet) with ethanol (95 %, 4 L), for 48 h under gentle reflux, yielding 110 g of brown residue, followed by maceration with 5 L of ethanol/ammonia (10 %) at rt. The resulting extract was neutralized with AcOH and shaken out with CHCl<sub>3</sub>. The residue (3 g) obtained after solvent removal, was subjected to flash chromatography on 10 % deactivated silica gel 60, using a gradient elution of CHCl<sub>3</sub>/MeOH. Five fractions were ultimately obtained on combining the eluates on the basis of TLC composition. Normal phase LPLC (CHCl<sub>3</sub>/MeOH, 95:5) of the less polar fraction (121 mg) afforded compounds (1) and (2), that were further purified by preparative TLC (CHCl<sub>3</sub>/MeOH, 95:5). Compounds (3, 4 and 5) were isolated by LPLC (AcOEt) of the second fraction, and purified by preparative TLC (CHCl<sub>3</sub>/MeOH, 95:5).

*19-O-ethylangustoline (1):* 4 mg, mp 230-240°C; [ $\alpha$ ]<sub>D</sub> - 0.006° (*c* 0.09, CHCl<sub>3</sub>); ORD data: [ $\phi$ ]<sub>254</sub> - 1.0°, [ $\phi$ ]<sub>265</sub> - 1.7°, [ $\phi$ ]<sub>280</sub> - 1.1°, [ $\phi$ ]<sub>302</sub> - 3.5°, [ $\phi$ ]<sub>313</sub> - 5.2°, [ $\phi$ ]<sub>334</sub> - 2.4°, [ $\phi$ ]<sub>350</sub> - 0.4°, [ $\phi$ ]<sub>400</sub> - 1.5°, [ $\phi$ ]<sub>450</sub> - 1.8°, [ $\phi$ ]<sub>500</sub> - 0.7°; HREIMS: [M<sup>+</sup>] *m/z* (rel int) 359.16340 (calcd 359.16338 for C<sub>22</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub>) (16), 344.13971 (calcd 344.13990 for C<sub>21</sub>H<sub>18</sub>N<sub>3</sub>O<sub>2</sub>) (9), 315.13720 (calcd 315.13710 for C<sub>20</sub>H<sub>17</sub>N<sub>3</sub>O) (100), 300.11364

(calcd 300.11369 for  $C_{19}H_{14}N_3O$ ) (17), 286.09802 (calcd 286.09804 for  $C_{18}H_{12}N_3O$ ) (8); UV  $\lambda_{\max}$  nm: 393, 374, 298, 247; IR  $\nu_{\max}^{KBr}$   $cm^{-1}$ : 3225, 2924, 2853, 1659, 1606, 1462, 1324, 1105, 743;  $^1H$ - and  $^{13}C$ -NMR see Table 1.

*Angustine (2)*: 15 mg, mp > 320°C, lit.,<sup>2</sup> mp > 320°C; EIMS: [M<sup>+</sup>]  $m/z$  (rel int) 313 (100), 298 (29), 255 (13), 186 (26), 157 (21), 129 (56); UV  $\lambda_{\max}$  nm: 397, 379, 300, 290, 254, 217; IR  $\nu_{\max}^{KBr}$   $cm^{-1}$ : 3224, 2922, 2851, 1644, 1601, 1529, 1468, 1399, 1321, 1148, 829, 817, 738;  $^1H$ -NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 3.15 (2H, t,  $J = 6$  Hz, H-6<sub>a</sub>, H-6<sub>b</sub>), 4.40 (t,  $J = 6$  Hz, H-5<sub>a</sub>, H-5<sub>b</sub>), 5.63 (1H, d,  $J = 10.8$  Hz, H-18<sub>a</sub>), 6.06 (1H, d,  $J = 17.6$  Hz, H-18<sub>b</sub>), 7.12 (1H, t,  $J = 7.2$  Hz, H-10), 7.29 (3H, m, H-11, H-14, H-19), 7.47 (1H, d,  $J = 8$  Hz, H-12), 7.63 (1H, d,  $J = 8$  Hz, H-9), 8.87 (1H, s, H-21), 9.23 (1H, s, H-17), 11.81 (1H, s, NH);  $^{13}C$ -NMR (100.61 MHz, DMSO- $d_6$ )  $\delta$ : 19.2 (C-6), 40.4 (C-5), 93.8 (C-14), 112.0 (C-12), 114.8 (C-7), 119.8 (C-16, C-18), 119.9 (C-9, C-10), 124.6 (C-11), 125.5 (C-8), 126.8 (C-2), 127.8 (C-20), 130.2 (C-19), 136.9 (C-3), 138.5 (C-13), 139.0 (C-15), 147.7 (C-21), 149.7 (C-17), 161.1 (C-22).

*Angustoline (3)*: 45 mg, mp 290-300°C, lit.,<sup>2</sup> mp 285°C; EIMS: [M<sup>+</sup>]  $m/z$  (rel int) 331 (2), 313 (42), 298 (1), 157 (3), 129 (12), 55 (100); UV  $\lambda_{\max}$  nm: 392, 373, 298, 288, 248, 227; IR  $\nu_{\max}^{KBr}$   $cm^{-1}$ : 3368, 2921, 2851, 1670, 1604, 1527, 1495, 1326, 1232, 1117, 816, 744;  $[\alpha]_D - 0.04^\circ$  ( $c$  0.1,  $CHCl_3$ ), lit.,<sup>2</sup>  $[\alpha]_{578} - 31.5^\circ$  ( $c$  1.1, pyridine), lit.,<sup>14</sup>  $[\alpha]_D - 34^\circ$  ( $CHCl_3$ ), lit.,<sup>15</sup>  $[\alpha]_D 0^\circ$ ; ORD data:  $[\phi]_{254} - 0.8^\circ$ ,  $[\phi]_{265} - 1.9^\circ$ ,  $[\phi]_{280} - 1.3^\circ$ ,  $[\phi]_{302} - 2.1^\circ$ ,  $[\phi]_{313} - 4.7^\circ$ ,  $[\phi]_{334} - 1.8^\circ$ ,  $[\phi]_{350} - 0.4^\circ$ ,  $[\phi]_{400} - 1.5^\circ$ ,  $[\phi]_{450} - 1.8^\circ$ ,  $[\phi]_{500} - 0.7^\circ$ ;  $^1H$ -NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 1.51 (3H, d,  $J = 6.2$  Hz, 18-H), 3.12 (2H, t,  $J = 6.4$  Hz, H-6<sub>a</sub>, H-6<sub>b</sub>), 4.40 (2H, t,  $J = 6.2$  Hz, H-5<sub>a</sub>, H-5<sub>b</sub>), 5.32 (1H, d,  $J = 5.6$  Hz, 19-H), 5.55 (1H, s, OH), 7.09 (1H, t,  $J = 7.6$  Hz, 10-H), 7.24 (1H, s, 14-H), 7.27 (1H, t,  $J = 7.6$  Hz, 11-H), 7.48 (1H, d,  $J = 8.0$  Hz, 12-H), 7.62 (1H, d,  $J = 8.4$  Hz, 9-H), 8.77 (1H, s, H-21), 9.24 (1H, s, H-17), 11.87 (1H, s, NH);  $^{13}C$ -NMR (100.61 MHz, DMSO- $d_6$ )  $\delta$ : 19.2 (C-6), 25.3 (C-18), 40.3 (C-5), 63.9 (C-19), 93.9 (C-14), 111.9 (C-12), 114.6 (C-7), 119.0 (C-16), 119.8 (C-10), 119.9 (C-9), 124.5 (C-11), 125.5 (C-8), 127.8 (C-2), 134.9 (C-20), 136.5 (C-3), 138.5 (C-13, C-15), 147.6 (C-21), 149.2 (C-17), 161.2 (C-22).

*Angustidine (4)*: 8 mg, mp 300-308°C, lit.,<sup>14</sup> mp 309-311°C; EIMS: [M<sup>+</sup>]  $m/z$  (rel int) 301 (97), 300 (100), 286 (26), 270 (7), 257 (5), 243 (6), 230 (7), 217 (4), 204 (4), 194 (7), 177 (38), 150 (27), 115 (15); UV  $\lambda_{\max}$  nm: 387, 369, 298; IR  $\nu_{\max}^{KBr}$   $cm^{-1}$ : 3321, 3235, 2923, 2853, 1713, 1651, 1615, 1598, 1537, 1464, 1414, 1236, 1154, 743;  $^1H$ -NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 2.58 (3H, s, H-19), 3.11 (2H, t,  $J = 6.5$  Hz, H-6<sub>a</sub>, H-6<sub>b</sub>), 4.38 (2H, t,  $J = 6.8$  Hz, H-5<sub>a</sub>, H-5<sub>b</sub>), 6.94 (1H, s, 14-H), 7.09 (1H, t,  $J = 7.6$  Hz, 10-H), 7.23 (1H, t,  $J = 7.2$  Hz, 11-H), 7.35 (1H, s, H-20), 7.45 (1H, d,  $J = 8.4$  Hz, 12-H), 7.62 (1H, d,  $J = 8.0$  Hz, 9-H), 9.21 (1H, s, H-17), 11.82 (1H, s, NH);  $^{13}C$ -NMR (100.61 MHz, DMSO- $d_6$ )  $\delta$ : 19.3 (C-6), 24.3 (C-19), 40.3 (C-5), 97.0 (C-14), 112.0 (C-12), 114.6 (C-7), 117.2 (C-20), 119.7 (C-9), 119.9 (C-10, C-16), 124.4

(C-11), 125.5 (C-8), 127.7 (C-2), 137.0 (C-3), 138.5 (C-13), 141.9 (C-15), 145.0 (C-21), 150.2 (C-17), 160.2 (C-22).

*Nauclefine (5)*: 12 mg, mp 283-293°C, lit.,<sup>2</sup> mp 310°C; EIMS: [M<sup>+</sup>] *m/z* (rel int) 287 (94), 286 (92), 272 (23), 257 (15), 229 (11), 222 (9), 203 (6), 177 (9), 151 (15), 143 (27), 129 (25), 122 (19), 115 (36), 31 (100); UV  $\lambda_{\max}$  nm: 389, 371, 259, 287; IR  $\nu_{\max}^{\text{KBr}}$  cm<sup>-1</sup>: 3345, 2923, 2851, 1713, 1651, 1609, 1535, 1455, 1326, 1178, 1042, 840, 730; <sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$ : 3.13 (2H, t, *J* = 6.8 Hz, H-6<sub>a</sub>, H-6<sub>b</sub>), 4.40 (2H, t, *J* = 6.8 Hz, H-5<sub>a</sub>, H-5<sub>b</sub>), 7.02 (1H, s, H-14), 7.09 (1H, t, *J* = 7.6 Hz, H-10), 7.26 (1H, t, *J* = 7.2 Hz, H-11), 7.45 (1H, d, *J* = 8.4 Hz, H-12), 7.52 (1H, d, *J* = 5.6 Hz, H-20), 7.63 (1H, d, *J* = 8 Hz, H-9), 8.66 (1H, d, *J* = 4.8 Hz, H-21), 9.32 (1H, s, H-17), 11.80 (1H, s, NH); <sup>13</sup>C-NMR (100.61 MHz, DMSO-*d*<sub>6</sub>)  $\delta$ : 19.3 (C-6), 40.3 (C-5), 97.0 (C-14), 112.0 (C-12), 114.8 (C-7), 119.0 (C-16, C-20), 119.7 (C-9), 119.9 (C-10), 124.5 (C-11), 125.4 (C-8), 127.6 (C-2), 137.2 (C-3), 138.6 (C-13), 141.6 (C-15), 150.5 (C-17), 151.0 (C-21), 161.1 (C-22).

*Determination of absolute configuration of angustoline.*

*a) modified Horeau's method using HPLC*: Angustoline (1.70 mg) in pyridine (51  $\mu$ L) was treated with ( $\pm$ )-2-phenylbutanoic anhydride (3.16 mg) in toluene (54  $\mu$ L), followed by addition of (R)-(+)-1-(1-naphthyl)ethylamine (5.23 mg) in toluene (153  $\mu$ L), according to the described procedure.<sup>12</sup> After work-up, the reaction mixture was analysed by HPLC using a Nucleosil-100 column (5  $\mu$ m, 25 cm x 4.6 mm id), Hexane/AcOEt 9:1 as eluent.

*b) standard Horeau's method*: Angustoline (20 mg) was dissolved in dry pyridine (35  $\mu$ L) containing ( $\pm$ )-2-phenylbutanoic anhydride (37.4 mg), and left under argon at room rt for 16 h. One drop of water was added and the reaction mixture was heated for 30 min in a water bath. C<sub>6</sub>H<sub>6</sub> (3 mL) and H<sub>2</sub>O (2 mL) were added, and the free phenylbutanoic acid was titrated with 0.1 N NaOH (1.95 mL) in the presence of phenolphthalein. The aqueous phase was extracted with CHCl<sub>3</sub> (2 x 10 mL), acidified with 1 N HCl (1 mL) and extracted again with C<sub>6</sub>H<sub>6</sub> (2 x 10 mL). The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent evaporated to yield the pure phenylbutanoic acid (32 mg), [ $\alpha$ ]<sub>D</sub> + 0.75° (*c* 3.2, C<sub>6</sub>H<sub>6</sub>). The esterification yield (72 %) and optical yield (2.2 %) were calculated as previously described.<sup>17</sup> Compound (7) (12.5 mg) was isolated from the CHCl<sub>3</sub> phase.

*Phenylbutyric ester of angustoline (7)*: oil, [ $\alpha$ ]<sub>D</sub> - 19° (*c* 1.1, CHCl<sub>3</sub>); UV  $\lambda_{\max}$  nm: 395, 376, 300, 250;  $\nu_{\max}^{\text{KBr}}$  cm<sup>-1</sup>: 3227, 2926, 2853, 1735, 1661, 1606, 1533, 1454, 1326, 1163, 1076, 818, 747, 699; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 0.92 (3H, t, *J* = 7.0 Hz, H-10'), 1.65 (3H, d, *J* = 6.4 Hz, H-18), 1.86 (1H, m, H-9'<sub>a</sub>), 2.15 (1H, m, H-9'<sub>b</sub>), 2.97 (1H, m, H-6<sub>a</sub>), 3.02 (1H, m, H-6<sub>b</sub>), 4.26 (1H, m, H-5<sub>a</sub>), 4.43 (1H, m, H-5<sub>b</sub>), 6.16 (1H, d, *J* = 6.2 Hz, H-19), 6.59 (14/25H, s, H-14, 2'*R* form), 6.80 (11/25H, s, H-14, 2'*S* form), 7.04-7.30 (9H, m, H-9, H-10, H-11, H-12, H-4', H-5', H-6', H-7', H-8'), 7.56 (1H, br s, H-21), 8.46

(11/25H, s, H-17, 2'S form), 8.53 (14/25H, s, H-17, 2'R form), 9.27 (14/25H, s, NH, 2'R form), 9.30 (11/25H, s, NH, 2'S form).

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