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Article

Enantioselective Synthesis of both (−)-(*R*)- and (+)-(*S*)-Angustureine Controlled by Enzymatic Resolution

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Uma nova síntese dos enantiômeros (−)-(*R*)- e (+)-(*S*)-angustureina, assim como do racemato (±)-angustureina, a partir de um β-amino éster racêmico controlado por resolução cinética enzimática, é descrita. Esta estratégia permitiu, incorporar tanto o esqueleto básico como controlar o único estereocentro no carbono 2 de ambos enantiômeros. A sequência em cinco etapas a partir dos β-amino éster e o carboxilato de sódio quirais para a síntese de ambos os alcalóides foi feita com um rendimento global de 80 e 44%, respectivamente, e excelentes excessos enantiomericos (95 e 96%, respectivamente) e sem nenhuma proteção de grupos funcionais em todas as etapas.

The present study describes a new synthesis of (−)-(*R*)- and (+)-(*S*)-angustureine enantiomers, as well as of racemate (±)-angustureine, from a racemic β-amino ester controlled by kinetic enzymatic resolution. This strategy allowed to incorporate the basic skeleton, as well as to control the single stereocenter at carbon 2 in both enantiomers. The sequence of five steps starting from the chiral β-amino ester and sodium carboxylate for the synthesis of both alkaloids achieved overall yields of 80 and 44%, respectively, and produced excellent enantiomeric excesses (95 and 96%, respectively) with no protection of functional groups in any of the steps.

Keywords: angustureine, β-amino ester, enzymatic resolution, quinoline alkaloid

Introduction

Galipea officinalis Hancock, a tree found mainly in the Northern region of South America, popularly known as "angostura", is one of twenty species in the genus *Galipea* Aublet. This plant is widely used in Venezuelan folk medicine, mainly for paralysis treatment of the motor system. It also provides a tonic used for the treatment of ailments such as dyspepsia, dysentery, chronic diarrhoea and fever.[1] A novel 2-substituted quinoline alkaloid was isolated from the bark of this plant by Jacquemond-Collet *et al*.[2] The same plant was later investigated by Rakotoson *et al*.,[3] who reported on the isolation of five quinoline alkaloids. On the other hand, reports have shown that angustureine, galipeine, cuspareine and galipinine exhibit anti-malarial and cytotoxic activities.[4] It is believed that the medicinal properties of these species are related to the presence of various quinoline and tetrahydroquinoline alkaloids found in this plant.[3] Due to their structural simplicities associated with the promising pharmacological activities, these alkaloids, especially angustureine, have attracted the attention of the synthetic organic community. For this alkaloid alone, nearly 21 different syntheses have already been described.[5]

In our quest to synthesize natural products that possess remarkable pharmacological activities, we report here an alternative strategy for the enantioselective synthesis of both (*R*)- and (*S*)-angustureine **1** and **2**, respectively, as a supplement to this team previously published work,[5] by applying enzymatic resolution to control the single stereocenter at C-2 of (*R*)- and (*S*)-angustureine **1** and **2**. To the best of our knowledge, this approach is the first work that leverages both the hydrolysis product and the corresponding ester for both stereoisomers in the synthesis of natural products.

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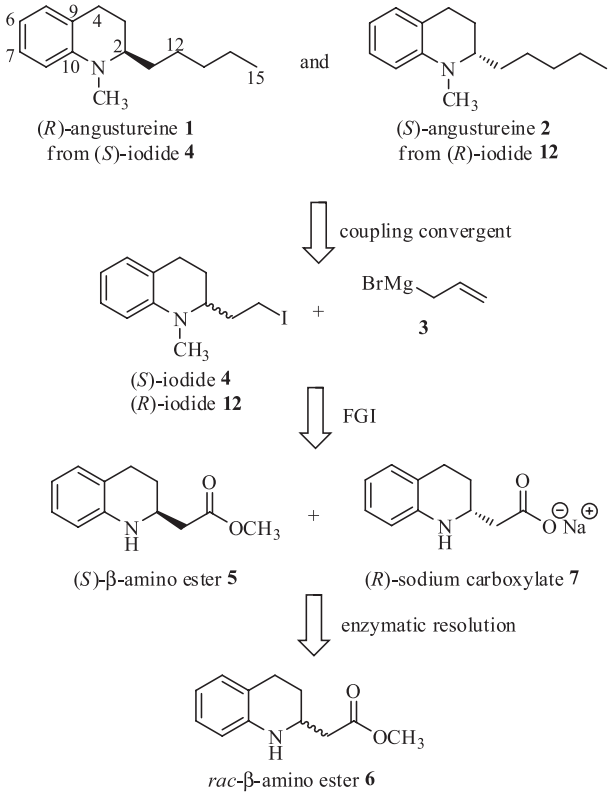
Results and Discussion

Retrosynthetic analysis of (*R*)- and (*S*)-angustureine **1** and **2**

The retrosynthetic analysis of (*R*)- and (*S*)-angustureine **1** and **2**, outlined in Scheme 1, shows the key steps in the proposal. The source of the basic skeleton for both the (*R*)- and (*S*)-angustureine enantiomers comes from the racemic β-amino ester **6**. The single stereocenter at carbon 2 of the chiral (*S*)-β-amino ester **5** and of the (*R*)-sodium carboxylate **7** can effectively be controlled from its racemate **6** by kinetic resolution using the protocol of Katayama *et al.*[6] The preparation of the iodides **4** and **12** from both (*S*)-β-amino ester **5** and (*R*)-sodium carboxylate **7**, and their convergent coupling with allylmagnesium bromide **3**, allowed the incorporation of the *n*-pentyl side chain at the 2-position to complete the enantioselective synthesis of both (*R*)- and (*S*)-angustureine enantiomers **1** and **2**.



Scheme 1. Retrosynthetic analysis of (*R*)- and (*S*)-angustureine **1** and **2**.

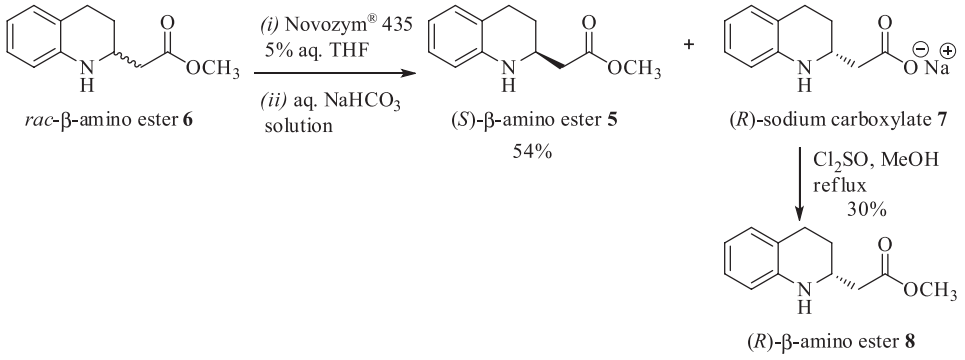
Preparation of the (*S*)- and (*R*)-β-amino esters **5** and **8** by enzymatic resolution

The synthesis of (*R*)- and (*S*)-angustureine stereoisomers **1** and **2** begins with the preparation of racemic methyl 2-(1,2,3,4-tetrahydroquinolin-2-yl)acetate **6**. This intermediate was prepared using the methodology described by Nagata *et al.*[7] The kinetic resolution of racemic ester **6** by treatment with Novozym® 435 was performed in a 5% aqueous solution of tetrahydrofuran (THF) under stirring at 30 °C for 3 days. After filtration, the (*S*)-β-amino ester **5** (54% yield and 91% ee) was obtained by adding an aqueous $NaHCO_3$ solution to remove the (*R*)-sodium carboxylate **7**, in addition to washing with water, extracting and purifying of the crude product by column chromatography (Scheme 2).

To compare retention times and check the enantiomeric ratio of both the (*S*)-and (*R*)-β-amino esters **5** and **8** from their respective chromatograms, the (*R*)-β-amino ester **8** was prepared. The aqueous layer containing the (*R*)-sodium carboxylate **7** (Scheme 2) from the enzymatic resolution reaction was dried under heating in vacuum. The ester **8** was prepared by treating the carboxylate **7**, it was dissolved in methanol, with thionyl chloride, and refluxed. After the addition of saturated sodium bicarbonate, extraction and concentration, the residue was purified to give the (*R*)-β-amino ester **8** (30% yield and 96% ee).

Preparation of electrophiles **4**, **9** and **10** and synthesis of (*R*)-angustureine **1**

The synthesis of (*R*)-angustureine **1**, first involved the preparation of the electrophilic substrates: iodide **4**, mesylate **9** and bromide **10** from (*S*)-β-amino ester **5** in



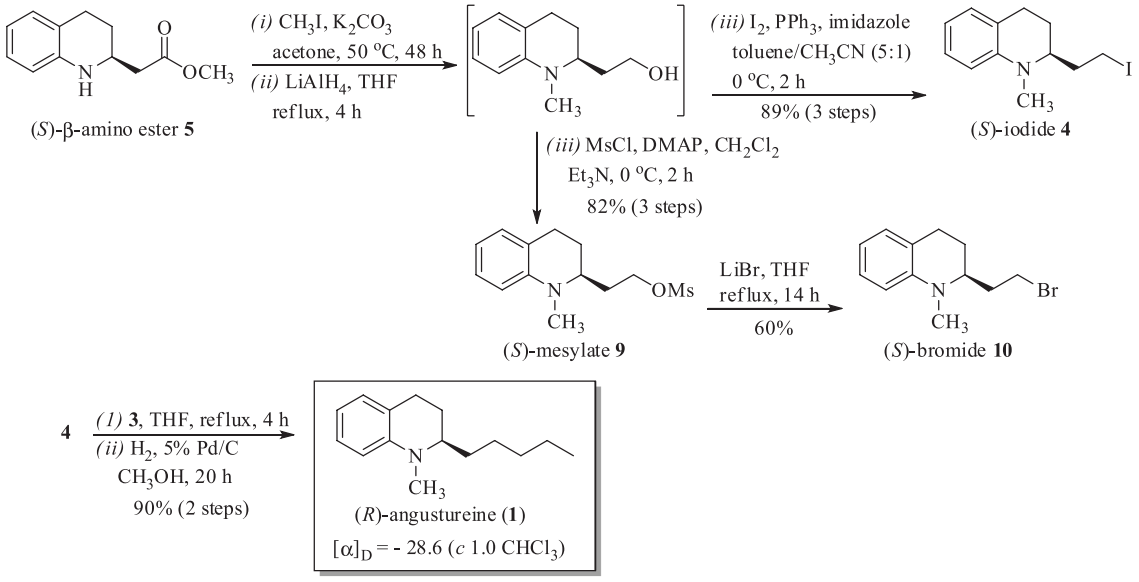
Scheme 2. Preparation of the (*S*)- and (*R*)-β-amino esters **5** and **8** by enzymatic resolution.

an attempt to optimize the convergent coupling with the allylmagnesium bromide **3**. The iodide **4** was prepared in a one pot sequence in three steps. *N*-methylation of **5** was performed by treatment with iodomethane and K_2CO_3, followed by the reduction of the ester function with $LiAlH_4$. Iodination of the resulting alcohol by treatment with I_2 and PPh_3, produced the iodide **4** (89%, three steps), as shown in Scheme 3. The mesylate **9** was prepared following the same procedure above for the two first steps from **5**, followed by treatment of the resulting alcohol with MsCl, in turn yielding the corresponding mesylate **9** (82% yield, three steps). Bromide **10** was prepared from mesylate **9** by refluxing with LiBr in THF for 24 h.

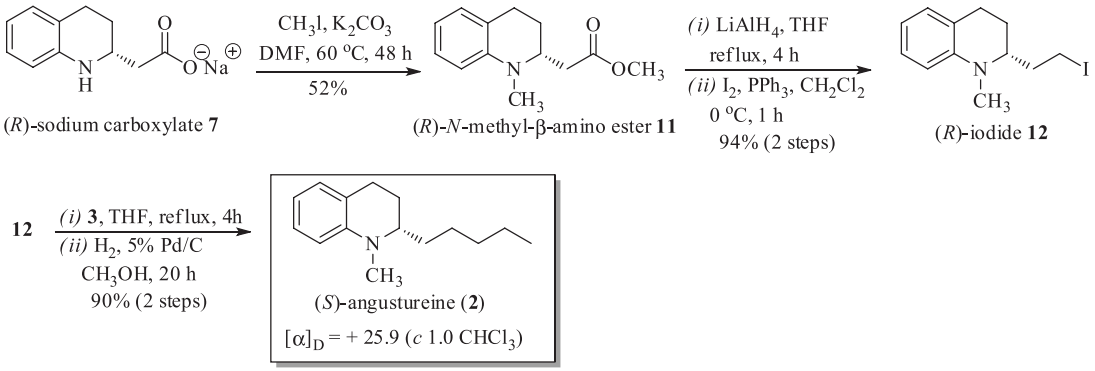
With the electrophiles **4**, **9** and **10** in hand, attempts at convergent coupling with allylmagnesium bromide **3** for the synthesis of (*R*)-angustureine **1** were begun. These first attempts were carried out at −78 °C and at room temperature. Unfortunately, all of these attempts were unsuccessful since only traces of the products could be obtained when all these reactions were carried out at these temperatures. Due to these disappointing results, the parameter of temperature had to be changed. Further attempts to couple iodide **4** with Grignard **3** under reflux were performed, which surprisingly, generated a high yield of the desired crude product (Scheme 3). After having completed the hydrogenation of the double bond of the side chain of the resulting alkene, the residue was then purified by flash chromatography to give **1** (90% yield and 95% ee, two steps) as a pale yellow oil; $[\alpha]_D$ −28.6 (*c* 1.0, $CHCl_3$) ($[\alpha]_D$ −7.16 (*c* 1.0, $CHCl_3$)).[5]

Preparation of iodide **12** and synthesis of (*S*)-angustureine **2**

Moreover, for the synthesis of (*S*)-angustureine **2**, a change was needed to be made in the esterification step of the carboxylate **7**. Thus, the yield of this step was very low when the (*R*)-β-amino ester **8** was prepared (see Scheme 2). A further analysis showed that, in addition to the esterification of carboxylate **7**, the *N*-methylation may also be possible if carried out in a single step. Therefore, treatment of **7** with iodomethane and K_2CO_3 in dimethylformamide (DMF) generated the ***N***-methyl-β-amino ester **11** (52% yield), as can be seen in Scheme 4. The subsequent steps were carried out following the same procedure as described for the synthesis of (*R*)-angustureine **1** in Scheme 3. Reduction of the ester function and iodination of the resulting alcohol yielded iodide **12** (94% yield, two steps). Then, treatment of **12** with allylmagnesium bromide **3**, and after hydrogenation of the double bond of the resulting alkene produced **2** (90% yield and 96% ee, two steps) as a pale yellow oil; $[\alpha]_D$ +25.9 (*c* 1.0, $CHCl_3$), ($[\alpha]_D$ +7.9 (*c* 1.0, $CHCl_3$)).[5] The spectra data of both (*R*)- and (*S*)-angustureine enantiomers **1** and **2** are fully consistent with those reported in the literature.[5] However, a deviation could be observed as regards their specific rotations, $[\alpha]_D$ +7.9 (*c* 1.0, $CHCl_3$) and $[\alpha]_D$ −7.16 (*c* 1.0, $CHCl_3$)[5] for (*S*)- and (*R*)-enantiomers, which may well be related to the high enantiomeric purity of our samples, given that, in the present work, a high levo- and dextrorotatory correlation could be identified between both synthesized enantiomers, $[\alpha]_D$ +25.9 (*c* 1.0, $CHCl_3$) and $[\alpha]_D$ −28.6 (*c* 1.0, $CHCl_3$) for (*S*)- and (*R*)-angustureine, respectively.



Scheme 3. Synthesis of (*R*)-angustureine **1**.



Scheme 4. Synthesis of (*S*)-angustureine **2**.

Preparation of rac-angustureine **13**

Finally, to compare retention times and determine the enantiomeric excesses of the (*R*)- and (*S*)-angustureine stereoisomers **1** and **2**, from their respective chromatograms, *rac*-angustureine **13** was prepared (see Supplementary Information). Angustureine **13** was synthesized from *rac*-β-amino ester **6**, in a similar manner as performed with chiral angustureine **1**, shown in Scheme 3, but inverting the sequence of the three first steps (i.e., reduction, iodination and *N*-methylation to give *rac*-iodide **14**) in an attempt to improve the yield. However, this change generated only an 80% yield of **13** (five steps), which was equal to the yield for **1**.

Conclusions

In summary, the total synthesis of both (*R*)- and (*S*)-angustureine stereoisomers **1** and **2** was achieved in five steps, starting from chiral (*S*)-amino ester **5** and (*R*)-sodium carboxylate **7**, with overall yields of 80 and 44%, respectively. The single stereocenter at C-2 of **5** and **7** was controlled by kinetic enzymatic resolution from *rac*-β-amino ester **6.** This is the first work that leverages both the hydrolysis product and the corresponding ester for the enantiomeric synthesis of both natural products applying an enzymatic resolution. Further studies on the synthesis of other congeners applying this same methodology are currently in progress.

Experimental

General procedures

^{1}H and ^{13}C NMR (nuclear magnetic resonance) spectra were recorded on a 400 and 600 MHz spectrometer using $CDCl_3$ as the deuterated solvent, respectively. The chemical shifts (δ) are reported in parts *per* million (ppm) relative to the residual $CHCl_3$ peak (7.26 ppm for ^{1}H NMR and 77.0 ppm for ^{13}C NMR). The coupling constants (*J*) are reported in Hertz (Hz). IR spectra were recorded on a FTIR spectrometer with a diamond ATR (attenuated total reflectance) accessory as a thin film. Mass spectra were recorded using electrospray ionization (ESI) or electron impact (EI). Yields refer to isolated material judged to be ≥ 95% pure by ^{1}H NMR spectroscopy following silica gel chromatography. All of the chemicals were used as received unless otherwise stated. The purifications were performed by flash chromatography using silica gel F-254 (mesh particle size 230-499); HPLC (Daicel ChiralceL OD-H: *n*-hexane/*i*-PrOH 90:10, detector: 254 nm, flow rate: 1.6 mL min^{-1}), (*S*)-**2** = 2.91 min and (*R*)-**1** = 3.03 min.

Synthesis

(*S*)-methyl 2-(1,2,3,4-tetrahydroquinolin-2-yl)acetate (**5**)

Novozym® 435 (350 mg) was added to a solution of a racemic mixture of methyl 2-(1,2,3,4-tetrahydroquinolin-2-yl)acetate (**6**) (1.96 g, 9.6 mmol) in THF (87.4 mL) containing 5% water (4.4 mL). The mixture was stirred at 30 °C for 96 h and then filtered to remove the catalyst beads. After evaporation of the filtrate, the residue was washed with aq. $NaHCO_3$ solution to remove the (*R*)-sodium carboxylate **7** and extracted with EtOAc. The organic layer was washed with water and brine, dried and evaporated. The residue was purified by flash chromatography over silica using (20% EtOAc/hexanes) as eluent to give 1.06 g (54% yield, 91% ee) of (*S*)-β-amino ester (**5**) as a yellow oil; $[\alpha]_D$ +81.2 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max}/ cm^{-1} 3393, 3016, 2949, 2845, 1727, 1607, 1586, 1484, 1435, 1291, 1178, 749, 717; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02-7.0 (m, 1H, H6), 6.98-6.96 (m, 1H, H8) 6.65 (td, 1H, *J* 7.4, 1.1 Hz, H7), 6.53 (dd, 1H, *J* 7.9, 1.0 Hz, H5), 4.49 (bs, 1H, NH), 3.80-3.71 (m, 1H, H2), 3.74 (s, 3H, OCH$_3$), 2.86 (dq, 1H, *J* 16.2, 5.6 Hz, H4), 2.75 (dt, 1H, *J* 16.4, 5.2 Hz, H4), 2.55 (s, 1H, H11), 2.53 (d, 1H, *J* 1.2 Hz, H11), 2.01-1.95 (m, 1H, H3), 1.78-1.69 (m, 1H, H3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6 (C_0), 143.9 (C_0), 129.1 (CH), 126.8 (CH), 120.7 (C_0), 117.3 (CH), 114.5 (CH), 51.6 (OCH$_3$), 47.7

(CH), 40.6 (CH_2), 27.9 (CH_2), 25.5 (CH_2); HRMS (CI^+) calcd. for $C_{12}H_{16}NO_2$ $(M + H)^+$ 206.1181, found 206.1178.

(*S*)-2-(2-Iodo-ethyl)-1-methyl-1,2,3,4-tetrahydro-quinoline (**4**)

K_2CO_3 (680 mg, 4.88 mmol) in THF (4 mL) and MeI (1.33 mL, 24.4 mmol) were added to the (*S*)-β-amino ester (**5**) (520 mg, 2.44 mmol) dissolved in THF (12 mL) under an argon atmosphere. After the reaction, the mixture was heated at 50 °C and stirred for 48 h, the reaction was quenched by water. Organic compounds were extracted with Et_2O and the combined organic layers washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give the crude residue. To a suspension of $LiAlH_4$ (278 mg, 7.3 mmol) in THF (6.0 mL), the crude residue dissolved in THF (10.6 mL) was added dropwise at room temperature. The mixture was refluxed for 4 h, and then excess reagent was decomposed by addition of aqueous THF. The mixture was treated with 1 mol L^{-1} aqueous NaOH (6 mL), water (6 mL) and Et_2O (60 mL), in succession. The organic layer was separated, washed with brine, dried over $MgSO_4$ and concentrated. The resulting crude alcohol was dissolved in a mixed solvent of 5:1 toluene/acetonitrile (8 mL) treated with imidazole (399 mg, 5.86 mmol) and triphenylphosphine (768 mg, 2.93 mmol) and cooled at 0 °C. Iodine (618 mg, 2.44 mmol) was added to the mixture and it was stirred for 2 h at 0 °C. An aqueous solution of sodium thiosulfate solution (16 mL) was then added and extracted with diethyl ether (80 mL). The organic layer was separated, washed with brine, dried over magnesium sulfate and concentrated. The residue was triturated with diethyl ether and the insoluble materials were removed by filtration. The filtrate was concentrated and the residue was purified by column chromatography on silica gel (20% CH_2Cl_2/hexanes) to give 654 mg (89%, 3 steps) of (*S*)-iodide (**4**) as a pale yellow oil; $[\alpha]_D$ +220.5 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max}/cm^{-1} 3018, 2929, 2795, 1601, 1574, 1497, 1214, 741, 718; ^1H NMR (400 MHz, $CDCl_3$) δ 7.13 (td, 1H, *J* 7.7, 1.5 Hz, H6), 7.01 (d, 1H, *J* 7.1 Hz, H8), 6.65 (td, 1H, *J* 7.3, 1.0 Hz, H7), 6.58 (d, 1H, *J* 8.2 Hz, H5), 3.49-3.44 (m, 1H, H2), 3.30 (dq, 1H, *J* 10.0, 7.5 Hz, H12), 3.17 (dt, 1H, *J* 10.0, 7.6 Hz, H12), 3.01 (s, 3H, $NC\underline{H}_3$), 2.85-2.71 (m, 2H, H4), 2.22-2.13 (m, 1H, H3), 2.00-1.85 (m, 3H, H3/H11); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9 (C_0), 128.8 (CH), 127.2 (CH), 121.3 (C_0), 115.8 (CH), 110.9 (CH), 58.9 (CH), 38.4 ($N\underline{C}H_3$), 35.2 (CH_2), 23.8 (CH_2), 23.4 (CH_2), 3.1 (CH_2); HRMS (ESI^+) calcd. for $C_{12}H_{17}IN$ $(M + H)^+$ 302.0406, found 302.0304.

(–)-(*R*)-angustureine (**1**)

A solution of (*S*)-iodide (**4**) (100 mg, 0.33 mmol) in THF (4.0 mL) at 0 °C was treated with a 1 mol L^{-1} solution in Et_2O of allylmagnesium bromide (**3**) (1.66 mL, freshly prepared) under an atmosphere of nitrogen. The mixture was refluxed for 4 h, quenched with a saturated aqueous solution of NH_4Cl (20 mL) and extracted with Et_2O. The organic layer was separated, washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in dry methanol (1.8 mL), treated with 5% Pd/C (21 mg) and stirred for 20 h under a balloon atmosphere of hydrogen. After filtration through Celite with CH_2Cl_2, the solvent was concentrated. The residue was purified by flash chromatography on silica (20% CH_2Cl_2/hexanes) to give 65 mg (90%, 2 steps) of **1** as a pale yellow oil; $[\alpha]_D$ –28.6 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max}/cm^{-1} 2927, 2857, 1602, 1498, 1214, 741, 717; ^1H NMR (600 MHz, $CDCl_3$) δ 7.09 (t, 1H, *J* 7.6 Hz, H6), 6.98 (d, 1H, *J* 7.3 Hz, H8), 6.59 (td, 1H, *J* 7.3, 0.9 Hz, H7), 6.53 (d, 1H, *J* 8.2 Hz, H5), 3.24 (sext, 1H, *J* 4.4 Hz, H2), 2.94 (s, 3H, $NC\underline{H}_3$), 2.84-2.78 (m, 1H, H4), 2.66 (dt, 1H, *J* 16.1, 4.1 Hz, H4), 1.94-1.85 (m, 2H, H3), 1.63-1.58 (m, 1H, H11), 1.44-1.25 (m, 7H, H11/H12/H13/H14), 0.92 (t, 3H, *J* 7.0 Hz, H15); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.4 (C10), 128.6 (C8), 127.0 (C6), 121.8 (C9), 115.1 (C7), 110.4 (C5), 58.9 (C2), 37.9 ($N\underline{C}H_3$), 32.0 (C13), 31.2 (C11), 25.7 (C3), 24.4 (C12), 23.6 (C4), 22.7 (C14), 14.0 (C15); HRMS (ESI^+) calcd. for $C_{15}H_{24}N$ $(M + 1)^+$ 218.19087, found 218.19100.

(*R*)-(1-Methyl-1,2,3,4-tetrahydro-quinolin-2-yl)-acetic acid methyl ester (**11**)

The remaining crude sodium carboxylate (**7**) (800 mg, 3.75 mmol) obtained from the aqueous layer of the enzymatic resolution reaction of (**6**) was dissolved in DMF (20 mL) and treated with K_2CO_3 (1.0 g, 7.5 mmol) and CH_3I (2.34 mL, 37.5 mmol). The mixture was stirred for 48 h under heating at 60 °C. The reaction was quenched by slow addition of an aqueous solution of 2 mol L^{-1} HCl (90 mL) at 0 °C. Organic compounds were extracted with Et_2O and the combined organic layers washed with H_2O and brine and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (20% CH_2Cl_2/hexanes) to give 428 mg (52%) of ***N***-methyl-β-amino ester (**11**) as a pale yellow oil; $[\alpha]_D$ –14.1 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max}/cm^{-1} 2947, 1731, 1602, 1576, 1497, 1435, 1215, 1010, 744, 717; ^1H NMR (400 MHz, $CDCl_3$) δ 7.13 (dd, 1H, *J* 8.0, 7.5 Hz, H6), 7.02 (d, 1H, *J* 7.4 Hz, H8), 6.67 (td, 1H, *J* 7.3, 1.0 Hz, H7), 6.58 (d, 1H, *J* 8.2 Hz, H5), 3.88-3.83 (m, 1H, H2), 3.73 (s, 3H, $OC\underline{H}_3$), 2.95 (s, 3H, $NC\underline{H}_3$), 2.93-2.84 (m, 1H, H4), 2.74 (dq, 1H, *J* 16.6, 2.7 Hz, H4), 2.65 (dd, 1H, *J* 14.7, 5.0 Hz, H11), 2.44 (dd, 1H, *J* 14.7, 8.7 Hz, H11), 2.09-2.0 (m, 1H, H3), 1.92 (dquint, 1H, *J* 13.4, 2.8 Hz, H3); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 172.5 (C_0), 144.5 (C_0), 128.8 (CH), 127.1 (CH), 121.3 (C_0), 116.0 (CH), 110.8 (CH), 55.8 (CH), 51.6 ($O\underline{C}H_3$), 37.5 ($N\underline{C}H_3$), 36.1 (CH_2), 25.3 (CH_2), 23.1 (CH_2); HRMS (CI^+) calcd. for $C_{13}H_{18}NO_2$ $(M + H)^+$ 220.1337, found 220.1335.

(*R*)-2-(2-Iodo-ethyl)-1-methyl-1,2,3,4-tetrahydro-quinoline (**12**)

To a suspension of $LiAlH_4$ (172 mg, 4.53 mmol) in THF (2.7 mL), *N*-methyl-β-amino ester (**11**) (310 mg, 1.51 mmol) in THF (6.4 mL) was added dropwise at room temperature. The mixture was refluxed for 4 h, and then excess reagent was decomposed by addition of water (2.7 mL) at 0 °C. To the mixture, an aqueous solution 1 mol L^{-1} NaOH (3.7 mL), H_2O (2.7 mL) and diethyl ether was added, in succession. The organic layer was separated, washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The crude alcohol was dissolved in a mixed solvent of 5:1 toluene/acetonitrile (3.8 mL), treated with imidazole (180 mg, 2.64 mmol), and triphenylphosphine (346 mg, 1.3 mmol) and cooled at 0 °C. The mixture was next treated with iodine (307 mg, 1.21 mmol) and stirred for 2 h at 0 °C. An aqueous sodium thiosulfate solution (10 mL) was added and extracted with diethyl ether. The organic layer was separated, washed with brine and dried over magnesium sulfate. After removal of the solvent, the residue was purified by column chromatography on silica gel (20% CH_2Cl_2/hexanes) to give 311 mg (94%, 2 steps) of (*R*)-iodide (**12**) as a pale yellow oil; $[\alpha]_D$ –222.4 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max}/cm^{-1} 3018, 2934, 2841, 2795, 1601, 1497, 1214, 741, 718; ^1H NMR (400 MHz, $CDCl_3$) δ 7.15 (t, 1H, *J* 7.8 Hz, H6), 7.03 (d, 1H, *J* 7.3 Hz, H8), 6.67 (t, 1H, *J* 7.3, H7), 6.61 (d, 1H, *J* 8.2 Hz, H5), 3.48 (sext, 1H, *J* 4.3 Hz, H2), 3.34-3.29 (m, 1H, H12), 3.19 (q, 1H, *J* 7.7 Hz, H12), 3.03 (s, 3H, $NC\underline{H}_3$), 2.87-2.73 (m, 2H, H4), 2.19 (sext, 1H, *J* 7.6 Hz, H3), 2.02-1.87 (m, 3H, H3/H11); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9 (C_0), 128.8 (CH), 127.1 (CH), 121.3 (C_0), 115.8 (CH), 110.9 (CH), 58.9 (CH), 38.4 ($N\underline{C}H_3$), 35.2 (CH_2), 23.8 (CH_2), 23.4 (CH_2), 3.1 (CH_2); HRMS (ESI^+) calcd. for $C_{12}H_{17}IN$ $(M + H)^+$ 302.04057, found 302.04034.

(+)-(*S*)-angustureine (**2**)

The synthesis of **2** was performed as described in the synthesis of **1** from (*R*)-iodide (**12**) (100 mg, 0.33 mmol) to give 65 mg (90%, 2 steps) of **1** as a pale yellow oil; $[\alpha]_D$ +25.9 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max}/cm^{-1} 2928, 2857, 1602, 1575, 1499, 1215, 742, 718, 521; ^1H NMR (600 MHz, $CDCl_3$) δ 7.12 (t, 1H, *J* 7.5 Hz, H6), 7.01 (d, 1H, *J* 7.3 Hz, H8), 6.62 (td, 1H, *J* 7.3, 0.9 Hz, H7), 6.56 (d, 1H, *J* 8.2 Hz, H5), 3.27 (sext, 1H, *J* 4.4 Hz, H2), 2.96 (s, 3H, $NC\underline{H}_3$), 2.87-2.81 (m, 1H, H4), 2.69 (dt, 1H, *J* 16.2, 4.1 Hz, H4), 1.96-1.88 (m, 2H, H3), 1.66-1.61 (m, 1H, H11), 1.47-1.28 (m, 7H, H11/H12/H13/H14), 0.95 (t, 3H, *J* 7.0 Hz, H15); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.4 (C10), 128.6 (C8), 127.0 (C6), 121.8 (C9), 115.1 (C7), 110.4 (C5), 58.9 (C2), 37.9 ($N\underline{C}H_3$), 32.0 (C13), 31.2 (C11), 25.7 (C3), 24.4 (C12), 23.5 (C4), 22.7 (C14), 14.0 (C15); HRMS (EI^+) calcd. for $C_{15}H_{23}N$ (M^+) 217.1830, found 217.1837.

Supplementary Information

Supplementary data (experimental procedures, IV, NMR and mass spectra, and chiral HPLC analyses) associated with this article are available free of charge at http://jbcs.sbq.org.br as PDF file.

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