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Tetrahedron: *Asymmetry* 15 (2004) 2921–2925
Tetrahedron: *Asymmetry*

Enzyme assisted enantioselective synthesis of the alkaloid (+)-aloperine

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Received 1 June 2004; accepted 29 June 2004
Available online 11 September 2004

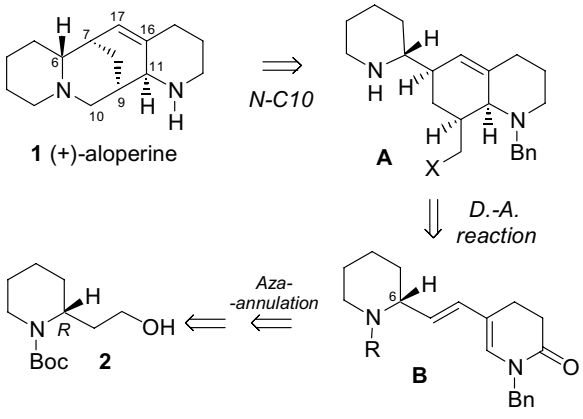
Abstract—The enantioselective synthesis of the lupinine alkaloid (+)-aloperine is described. The synthetic scheme presents three steps that are mediated by enzymes: kinetic resolution, oxidation of a primary alcohol to an aldehyde and oxidation of a secondary alcohol to a ketone.

1. Introduction

Aloperine **1**, a member of a small family of C_{15} lupinine alkaloids,[1] was first isolated in 1935 from the seeds and leaves of *Sophora alopecuroides*[2] a shrub that grows in China and Russia, and later from *Leptorhabdos parviflor* Benth. The use of the plant in traditional Chinese medicine[3] and the results of the recent investigation concerning the pharmacological activity (cardiovascular, anti-inflammatory, antiallergic) of the isolated alkaloid moved the Overman's group towards an intense synthetic interest in this molecule, culminating in its first enantioselective total synthesis.[4] We recently reported the synthesis of (±)-aloperine using as a crucial step an efficient intermolecular Diels–Alder reaction. The required diene was prepared following an aza-annulation reaction of an activated alkyne, easily accessible from racemic piperidine-2-ethanol *rac*-**2**.[5] We then turned our attention towards the enantioselective synthesis of the natural (+)-aloperine and to this end we recently described a convenient preparation of the enantiopure amino alcohol **2** by enzymatic resolution of piperidine-2-ethanol.[6] In continuing our efforts towards the development of general strategy for the enantioselective synthesis of piperidine-containing alkaloids we describe here the elaboration of **2** to **1**, which takes advantage of extensive use of enzymatic systems for the preparation of advanced intermediates.

2. Results and discussion

According to the retrosynthetic approach shown in Scheme 1, the enantiopure *N*-Boc derivative (*R*)-**2** was chosen as a starting material. This compound was made available on a gram-scale by sequential transesterifications mediated by two enzymes, Lipase PS and porcine pancreatic lipase (Scheme 2) showing opposite enantioselectivity.[6] The preparation of aldehyde **3** was carried out by Swern oxidation, but this process proved to be



Scheme 1. Retrosynthetic scheme of aloperine synthesis.

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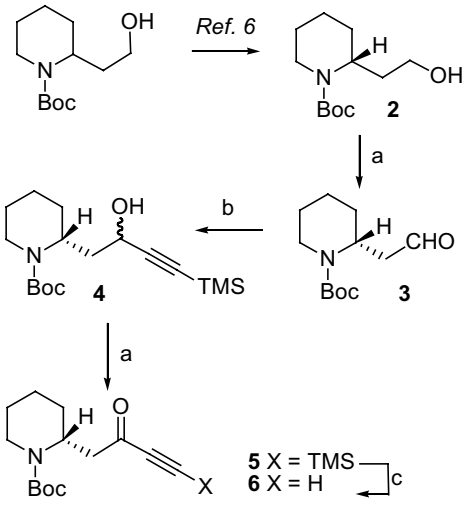
doi:10.1016/j.tetasy.2004.06.056

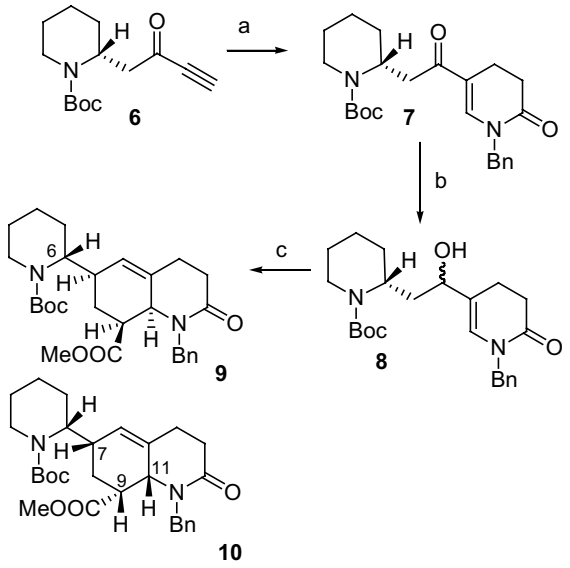


Scheme 2. Reagents and conditions: (a) Laccase–TEMPO, O_2; (b) EtMgBr, HC≡C–$SiMe_3$, −78 °C; (c) TBAF.

hard to reproduce on a large scale and the recovery of the reaction product was not free from troubles. Our desire to simplify the purification process and to improve the ecocompatibility of the process moved us to investigate the use of polymer supported reagents, such as TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl)-polystyrene in the presence of *N*-chlorosuccinimmide, but unfortunately this resulted in poor yields and long reaction times.[7] Recently it has been described that the oxidation of alcohols (especially primary) to carbonyl compounds can be performed using molecular oxygen and the oxidative enzymes laccase in the presence of TEMPO as a mediator. The mediator is capable of utilizing oxidation mechanisms not directly available through laccases, thereby expanding the synthetic usefulness of these enzymes.[8] Although the literature examples are confined to simple substrates,[9] we found this methodology very attractive and, exploiting the availability of the laccases from *Trametes pubescens* or from *Myceliophtora termophyla* in the laboratory of one of us,[10] we decided to study the enzymatic oxidation of **2**. The use of either one of the two laccases in biphasic systems made of water buffered solution and EtOAc was successful and after 4 h the reactions were complete.

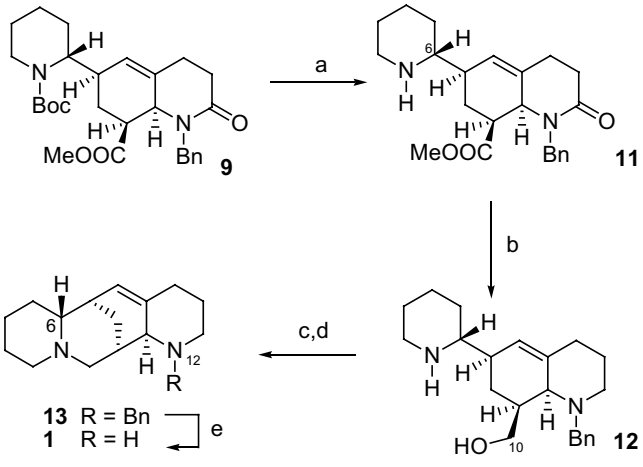
With a good method to get the aldehyde **3** in hand, ethynylation with a Grignard reagent, prepared from trimethylsilylacetylene gave, in a clean reaction, the diastereomeric alcohols **4** (1:1) in 86% yield. The oxidation of the sensitive activated secondary alcohols **4** to **5** was successful in Swern oxidation or using the system laccase (from *Trametes pubescens* or from *Myceliophtora termophyla*)—TEMPO, while the use of TEMPO–polystyrene was not productive.

Compound **6**, obtained by the cleavage of the C–Si bond with TBAF, was reacted with benzylamine in THF at 25 °C, and the intermediate enamine was directly cyclized with acryloyl chloride in THF at 65 °C to give the dihydropyridinone **7** in 56% yield. The ees of compounds **5** and **7** were evaluated by chiral HPLC (Chiralcel OD) as 90% in agreement with the one of the starting compound **2**. Reduction of **7** with $NaBH_4$ gave a mixture of diastereoisomeric alcohols **8** that were dissolved in toluene and refluxed in the presence of pTSA and methyl acrylate to give, after 10 days, compounds **9** (56%) and **10** (28%) that differ for the configuration at C(9), C(11) and C(7) (Scheme 3).



Scheme 3. Reagents and conditions: (a) $BnNH_2$, $CH_2CHCOCl$; (b) $NaBH_4$; (c) pTSA, $CH_2CHCOOMe$, 110 °C.

Compound **9** was then elaborated to give the target (+)-aloperine by *N*-Boc hydrolysis, $LiAlH_4$ reduction, reaction with CBr_4–PPh_3 to form the N–C(10) bond and, finally, removal of the protecting benzyl group by ethylendiamine and lithium. The final compound presented an $[\alpha]_D^{25} = +68$ (*c* 1, EtOH), consistent with the expected 90% ee (Scheme 4).



Scheme 4. Reagents and conditions: (a) TFA; (b) $LiAlH_4$; (c) CBr_4–PPh_3; (d) Et_3N; (e) Li, NH_2–$(CH_2)_2$–NH_2.

3. Conclusion

The reported enantioselective synthesis of (+)-aloperine is a further demonstration of the importance of integrating biocatalysis into organic synthesis. Specifically, in the course of the synthetic scheme the target molecule has been obtained by combining a usual enzymatic kinetic resolution mediated by lipases with two oxidation steps accomplished by laccases. Needless to say, this work further exemplifies the synthetic usefulness of the chiral synthon *N*-Boc-piperidine-2-ethanol.

4. Experimental

4.1. Materials

The laccase from *Myceliophtora thermophyla* was from Novozymes while the laccase from *Trametes pubescens* was provided by Prof. Haltrich (Universitat fur Bodenkultur, Wien, Austria). Ee values were determined by chiral HPLC.

4.1.1. Enzymatic kinetic resolution of *N*-Boc-piperidine-2-ethanol[6]. Vinyl acetate (30 mL, 325 mmol) and lipase PS (1 g) were added to a solution of *N*-Boc-piperidine-2-ethanol (10 g, 43.7 mmol) in hexane (250 mL). The mixture was stirred at room temperature (19 °C) for 190 min, following the course of the reaction by HPLC (Chiracel OD column). The enzyme was removed by filtration and the solvent and the residual vinyl acetate were evaporated. The resulting oil was then dissolved in methyl *tert*-butyl ether (120 mL), and vinyl butyrate (15 mL) and the porcine pancreatic lipase (4 g) were added to this solution. The new reaction mixture was stirred for 12 h at rt (19 °C), following the course of the reaction by HPLC (two consecutive Chiracel OD columns). The enzyme was removed by filtration and the solvent was evaporated to give a yellow oil, which was purified by flash chromatography (AcOEt–hexane, 1:9) to afford **2** (OAc) (5.4 g, 45%, 63% ee), *ent*-**2** (OCOPr-*S*) (3.846 g, 30%, 85% ee) (HPLC) and *rac*-**2** (2.4 g, 24%, 4% ee). To a solution of **2** (OAc) (2.17 g, 8 mmol) dissolved in MeOH (85 mL), Na_2CO_3 (4.39 g) was added. The solution was stirred at room temperature for 4 h, then Na_2CO_3 was filtered and the solvent was evaporated. The resulting oil was dissolved in CH_2Cl_2 (50 mL) and washed with water and brine. The organic layer was evaporated to give **2** (1.78 g, 98%, 63% ee) as a pale yellow oil, which required no further purification. Lipase PS (130 mg) and vinyl acetate (11.7 mL) were added to a solution of **2** (63% ee) (4 g, 17.46 mmol) dissolved in hexane (75 mL). The reaction mixture was stirred at room temperature for 3 h 30 min, following the course of the reaction by HPLC (Chiracel OD column). The enzyme was removed by filtration and the solvent was evaporated. The resulting oil was purified by flash chromatography (AcOEt–hexane, 1:4) to give **2** (OAc) (2.263 g, 48%, ee 90%) and *rac*-**2** (1.887 g, 47%). The hydrolysis of **2** (OAc) in MeOH and Na_2CO_3 gave **2** (90% ee). Compound **2**: $[\alpha]_D^{25} = +19.3$ (*c* 1, $CHCl_3$).[6]

4.1.2. 2-(2-Oxo-ethyl)-piperidine-1-carboxylic acid *tert*-butyl ester 3. A solution of DMSO (0.16 mL, 2.25 mmol) in CH_2Cl_2 (1 mL) was added dropwise at −78 °C and under nitrogen atmosphere to a 2 M solution of $(COCl)_2$ (0.47 mL, 0.94 mmol) in CH_2Cl_2 (4 mL). After 10 min of stirring at −78 °C, a solution of **2** (180 mg, 0.785 mmol) in CH_2Cl_2 (2 mL) was added to the mixture at −78 °C. After 20 min, freshly distilled Et_3N (0.52 mL, 3.73 mmol) was added to the reaction mixture at −78 °C. The mixture was allowed to warm up to room temperature and was left stirring for 4 h. Water (10 mL) and HCl 1 N (10 mL) were added and the solution was extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford a pale yellow oil (140 mg). Column chromatography on silica gel (hexane–AcOEt, 4:1) afforded 130 mg of **3** (0.62 mmol, 80% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (9H, s), 1.50–1.71 (6H, m), 2.45–2.61 (1H, m), 2.72–2,81 (2H, m), 3.94 (1H, br d, J = 13 Hz), 4.75–4.90 (1H, m), 9.72 (1H, t, J = 4 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 17.0, 23.4, 27.1 (3C), 27.8, 37.4. 42.8, 44.1, 78.1, 152.9, 199.0. $[\alpha]_D^{25} = +48.0$ (*c* 1, $CHCl_3$).

4.1.3. Enzyme laccase oxidation mediated by TEMPO. Preparation of 3 and 5. To a solution of **2** or **4** (0.2 mmol) in EtOAc (10 mL) and water (10 mL) buffered at pH 4–5 (sodium acetate), TEMPO (9 mg, 0.06 mmol) and laccase (80 units) were added. The reaction time was 2–4 h. For compound **2**, the resulting mixture was extracted with EtOAc, dried over Na_2SO_4, filtrated and evaporated under reduce pressure, providing the crude product (41 mg, yield 90%), that was directly used for the next step. The same procedure was applied to product **4**, which gave the crude product with 95% yield (61 mg).

4.1.4. 2-(2-Oxo-but-3-ynyl)-piperidine-1-carboxylic acid *tert*-butyl ester 6. Trimethylsilylacetylene (373 mg, 3.80 mmol) was added to a cold (0 °C) solution of ethylmagnesiumbromide (506 mg, 3.80 mmol) dissolved in THF (10 mL). This solution was stirred for 1 h at 5–15 °C and for 15 min at room temperature. A solution of the aldehyde **3** (724 mg, 3.18 mmol) in THF (6 mL) was then added dropwise over a 30 min period. The reaction solution was allowed to stir for an additional 30 min before being quenched with $NH_4Cl_{(satd)}$ and concentrated. The resulting mixture was extracted with AcOEt, the organic phase was washed with $NH_4Cl_{(satd)}$ and brine. The evaporation of the solvent gave a mixture of diastereoisomers **4** (890 mg, 86%) that were directly used for the next step. A DMSO solution (280 μL, 3.91 mmol) in CH_2Cl_2 (2 mL) was added to a solution of oxalyl chloride (170 μL, 1.96 mmol) in CH_2Cl_2 (13 mL) at −78 °C over a period of 5 min. After the mixture was stirred for 30 min, a solution of **4** (198 mg, 0.61 mmol) was added to the CH_2Cl_2 solution and the reaction mixture was stirred at the same temperature for 90 min. Et_3N (115 μL, 8.15 mmol) was then added to the reaction mixture, which was gradually warmed to room temperature and diluted with CH_2Cl_2. The CH_2Cl_2 solution was washed with water and brine, dried and concentrated to dryness to give **5** as a brown oil (172 mg, 87%, ee 90%).

$[\alpha]_D^{25} = -32.5$ (*c* 1, $CHCl_3$). To a solution of compound **5** (112 mg, 0.34 mmol) in THF–MeOH (5 mL–138 μL), TBAF (1 M in THF, 130 μL) was added at −20 °C. After 30 min, NH_4Cl solution was added and the solution was extracted with CH_2Cl_2. Evaporation of the organic solvent, gave compound **6** as an oil (71 mg, 84%). R_f (EtOAc–hexane, 1:4) 0.2; ^1H NMR (300 MHz, $CDCl_3$) δ 4.88–4.77 (1H, m), 4.08–3.93 (1H, br d, $J = 13$ Hz), 2.90–2.65 (3H, m), 1.80–1.30 (7H, m), 1.45 (9H, s). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 184.9, 154.5, 81.6, 79.8, 78.8, 47.3, 45.8, 39.2, 28.7, 28.3 (3C), 25.1, 18.8. Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.85. H, 8.48. N, 5.50. $[\alpha]_D^{25} = -30$ (*c* 1, $CHCl_3$). Chiral HPLC Analysis (Analytical) of **5**. Column: Chiracel OD; UV detector: λ 210 nm; solvent: petroleum ether–*i*-PrOH, 19:1; flow rate: 0.7 mL/min; retention time: **5**, 7.15 min; *ent*-**5**, 6.05 min.

4.1.5. 2-[2-Benzyl-6-oxo-1,4,5,6-tetrahydro-pyridin-3-yl)-2-oxo-ethyl]-piperidine-1-carboxylic acid *tert*-butyl ester 7. Benzylamine (354 μL, 3.25 mmol) was added to a solution of **6** (743 mg, 2.96 mmol) at 0 °C. After the solution was warmed to room temperature, stirring was maintained for 18 h. Acryloyl chloride (263 μL, 3.25 mmol) was added at room temperature. After being heated for 18 h at reflux, the solution was washed with a saturated aqueous $NaHCO_3$ and the organic layer extracted with EtOAc. Evaporation of the solvent and column chromatography (AcOEt–cyclohexane, 1:3) gave **7** as a yellow oil (683 mg, 56%). R_f (EtOAc) 0.55; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70–7.20 (6H, m), 4.92 (1H, A portion of AB system), 4.68 (1H, B portion of AB system), 4.60–4.52 (1H, m), 3.90 (1H, br d, $J = 13$ Hz), 2.82–2.65 (5H, m), 2.57 (2H, br s), 1.98–1.40 (6H, m), 1.45 (9H, s). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 195.8, 169.8, 155.1, 136.6, 128.8 (2C), 128.0, 127.8 (3C), 118.5, 79.6, 50.2, 49.1, 39.8, 38.4, 30.7, 28.4 (3C), 27.5, 25.1, 18.8, 18.6. Anal. Calcd for $C_{24}H_{32}N_2O_4$: C, 69.88; H, 7.82; N, 6.79. Found: C, 69.93. H, 7.80. N, 6.82. EIMS 412 (6%), 356 (10%), 339 (16%), 312 (100%), 214 (80%). $[\alpha]_D^{25} = -46$ (*c* 1, $CHCl_3$). Ee 90%. Chiral HPLC Analysis (Analytical). Column: Chiracel OD; UV detector: λ 254 nm; solvent: petroleum ether–*i*-PrOH, 9:1; flow rate: 0.7 mL/min; retention time: **7**, 14.02 min; *ent*-**7**, 15.80 min.

4.1.6. 1-Benzyl-2-oxo-6-piperidin-2-yl-1,2,3,4,6,7,8,8a-octahydro-quinoline-8-carboxylic acid methyl ester 11. To a solution of **7** (424 mg, 1.03 mmol) in THF–MeOH (1:2, 30 mL), $NaBH_4$ (56 mg, 1.48 mmol) was added at 0 °C. After 2 h, the reaction mixture was poured into a $NH_4Cl_{(satd)}$ and extracted with AcOEt. The crude **8** was directly dissolved in toluene (10 mL) and refluxed in presence of pTSA (8 mg, 0.043 mmol) and methyl acrylate (6 mL, 66.7 mmol). After 10 days, the solution was concentrated in vacuum and the mixture of **9** and **10** was directly submitted to the next reaction. **9**: R_f (EtOAc) 0.46; **10**: R_f (EtOAc) 0.42. To a solution of **10** and **9** (417 mg, 0.86 mmol) in CH_2Cl_2 (28 mL), CF_3COOH (6.5 mL, 83 mmol) was added. After 2 h at room temperature, water was added and the solution was basificated with NH_4OH. Evaporation of the organic layer and column chromatography (AcOEt–*i*-PrOH–Et_3N, 27:1:2) gave a yellow oil of **11** (214 mg). Compound **11**: R_f (CH_2Cl_2–EtOH–NH_4OH concd 5% 4:1) 0.5; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.05 (5H, m), 5.50 (1H, br s), 5.20 (1H, A portion of AB system), 4.31 (1H, B portion of AB system), 3.92–3.83 (1H, m), 3.56 (3H, s), 3.12–2.95 (2H, m), 2.70–0.85 (16H, m). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 172.7, 172.2, 137.2, 133.6, 128.6 (2C), 127.8 (2C), 127.3, 123.1, 59.8, 56.7, 51.5, 47.2, 46.6, 39.3, 38.1, 32.7, 30.4, 29.3, 26.3, 26.1, 25.4. Anal. Calcd for $C_{23}H_{30}N_2O_3$: C, 72.22; H, 7.91; N, 7.32. Found: C, 72.27. H, 7.95. N, 7.32. EIMS 382 (23%), 322 (48%), 299 (100%). $[\alpha]_D^{25} = +162$ (*c* 1, $CHCl_3$).

4.1.7. 1-Benzyl-8-hydroxymethyl-6-piperidin-2-yl-1,2,3,4,6,7,8,8a-octahydro-1*H*-quinoline 12. To a suspension of $LiAlH_4$ (115 mg, 3.03 mmol) in THF (15 mL), a solution of **11** (430 mg, 1.12 mmol) was added dropwise at 0 °C. The reaction mixture was maintained at 0 °C for 6 h. $LiAlH_4$ (402 mg, 10.58 mmol) was added in several portions and after 4 days at room temperature the reaction was concluded. AcOEt was added and after 2 h the reaction mixture was poured into water. The organic layer was concentrated to give a yellow oil (361 mg, 94%) that was directly used in the next step. A small amount was purified by chromatography (AcOEt–MeOH–Et_3N 15:1:1). Compound **12**: R_f (AcOEt–MeOH–Et_3N, 15:1:1) 0.13; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55–7.10 (5H, m), 5.51 (1H, br s), 4.00 (1H, A portion of AB system), 3.91 (1H, dd, $J = 12.5$, 10 Hz), 3.65 (1H, dd, $J = 12.5$, 10 Hz), 3.31 (1H, B portion of AB system), 3.22 (1H, br d, $J = 7.5$ Hz), 3.13 (1H, br d, $J = 12.5$ Hz), 2.88–2.75 (1H, m), 2.70–1.22 (19H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 139.2,135.9, 128.8 (2C), 128.7 (2C), 127.3, 124.4, 63.3, 61.6, 60.9, 51.6, 47.2, 39.9, 36.4, 34.4 (2C), 31.0, 30.1, 26.3, 24.9, 23.4. Anal. Calcd for $C_{22}H_{32}N_2O$: C, 77.60; H, 9.47; N, 8.23. Found: C, 77.62; H, 9.49; N, 8.20. $[\alpha]_D^{25} = +14$ (*c* 1, $CHCl_3$).

4.1.8. *N*-Benzyl-aloperine 13. To a solution of **12** (361 mg, 1.06 mmol) in CH_2Cl_2 (40 mL), PPh_3 (695 mg, 2.65 mmol) and CBr_4 (421 mg, 1.27 mmol) were added and the reaction mixture was stirred at room temperature for 3 h. Dry Et_3N (361 μL, 2.60 mmol) was added and, after 15 h, the solution was poured into HCl 1 N. The aqueous solution was basified with NH_4OH concd and extracted with CH_2Cl_2. Evaporation of the solvent and chromatographic purification (hexane–Et_3N, 30:1) gave **13** (153 mg, 45%). R_f (AcOEt–hexane–Et_3N, 15:10:1) 0.48; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.11 (5H, m), 5.58 (1H, d, $J = 4.5$ Hz), 4.12 (1H, A portion of AB system), 3.01 (1H, B portion of AB system), 2.98–1.25 (22H, m). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 139.6, 133.8, 128.6 (2C), 128.1 (2C), 127.9, 126.6, 65.6, 65.1, 57.8, 55.8, 52.5, 51.7, 35.7, 33.7, 32.6, 29.6, 25.6 (2C), 25.2, 23.5. Anal. Calcd for $C_{22}H_{30}N_2$: C, 81.93; H, 9.38; N, 8.69. Found: C, 81.90. H, 9.41. N, 8.73. EIMS 322 (25%), 231 (100%). $[\alpha]_D^{25} = +56$ (*c* 0.7, EtOH).

4.1.9. (+)-Aloperine 1. To a solution of **13** (50 mg, 0.15 mmol) in THF (600 μL) maintained at room temperature, Et_3N (1.20 mL), lithium (53 mg, 7.57 mmol)

and ethylendiamine (redistilled from Na, 123 μL, 1.82 mmol) were added. After 2 h, THF (600 μL), Et_3N (1.20 mL) and ethylendiamine (123 μL) were added. After 3 h, NH_4Cl 5% (5 mL) and water (5 mL) were added and the reaction mixture was stirred for 10 min. The aqueous layer was basified with Na_2CO_3 and extracted with $CHCl_3$. After evaporation of organic layer, a yellow oil was obtained. Chromatography purification (AcOEt–MeOH–Et_3N 15:5:2) gave **1** (28 mg, 80%). R_f (AcOEt–MeOH–Et_3N 15:5:2) 0.15; ^1H NMR (300 MHz, CD_3COCD_3) δ 5.50 (1H, d, $J = 6.5$ Hz), 3.22 (1H, d, $J = 5.8$ Hz), 3.15–3.05 (1H, m), 2.90 (1H, dd, $J = 11.4$, 6 Hz), 2.87–2.75 (1H, m), 2.68 (1H, td, $J = 12.1$, 2.8 Hz), 2.65–2.45 (2H, m), 2.40–1.15 (16H, m). ^{13}C NMR (300 MHz, $CDCl_3$) δ 136.1, 126.9, 60.1, 58.1, 55.1, 47.6, 46.0, 34.9, 32.5, 31.6, 29.6, 27.1, 25.4 (2C), 20.2. Anal. Calcd for $C_{15}H_{24}N_2$: C, 77.53; H, 10.42; N, 12.05. Found: C, 77.58. H, 10.42. N, 12.02. $[\alpha]_D^{25} = +68$ (*c* 1, EtOH).

Acknowledgements

The authors express their gratitude to Ministero dell'Istruzione dell'Universitá e della Ricerca for the financial support. The work was partially supported by DGICYT, Spain (BQU2000-0651).

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