Chinese Journal of Chemistry, **2004**, *22*, 932—934

Article

Total Synthesis of Tetrahydroquinoline Alkaloid (+)-Angustureine†

LIN, Xian-Feng[a,b](林宪峰) LI, Yu[a](李瑜) MA, Da-Wei*[,b](马大为)

[a] *Department of Chemistry, Lanzhou University, Lanzhou 730000, China*
[b] *State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China*

(+)-(*S*)-Angustureine was synthesized using a CuI-catalyzed coupling reaction of iodobenzene with an enantiopure *β*-amino ester as the key step. The overall yield is 36% in 7 linear steps.

Keywords alkaloid, total synthesis, coupling

Introduction

Angustureine (**1**), galipeine (**2**), galipinine (**3**) and cuspareine (**4**) are four 2-substituted 1-methyltetrahydroquinoline alkaloids isolated from the bark of *Galipea officinalis* Hancock by professor Ingrid Jacquemond-Collet *et al.* in 1999.[1] *Galipea officinalis* Hancock is a shrub indigenous to the mountains of venezuela that has marked influence on the spinal motor nerves, thus, serves a cure for paralytic affections.[1] Further biological testing indicated that these four compounds possessed promising in vitro antimalarial activity with IC_{50} values from 0.09 to 38 mg/mL for the chloroquine-resistant strains.[2] Therefore, these alkaloids can serve as new leads for development of new antimalarial drugs. Very recently, Zhou and his co-workers have reported the first synthesis and stereochemical assignments of (−)-angustureine (**1**), (−)-galipinine (**3**) and (−)-cuspareine (**4**) (Figure 1) by using their newly developed enantioselective hydrogenation of substituted quinolines.[3] Herein we wish to disclose a facile route to these compounds exemplified by total synthesis of unnatural (+)-angustureine (**1**).

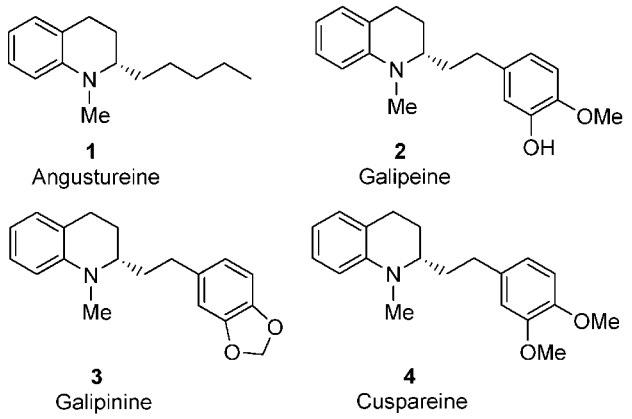


Figure 1 Structures of angustureine, galipeine, galipinine and cuspareine.

Results and discussion

As demonstrated in Figure 2, we planned to synthesize the target molecule through (*S*)-1-methyl-2-pentyl-2,3-dihydro-1*H*-quinolin-4-one (**5**) by Pd/C-catalyzed reduction of the ketone moiety. Based on our previous studies,[4] **5** could be assembled from a sequential CuI-catalyzed coupling product of iodobenzene with an enantiopure *β*-amino ester **6** and intramolecular acylation process.

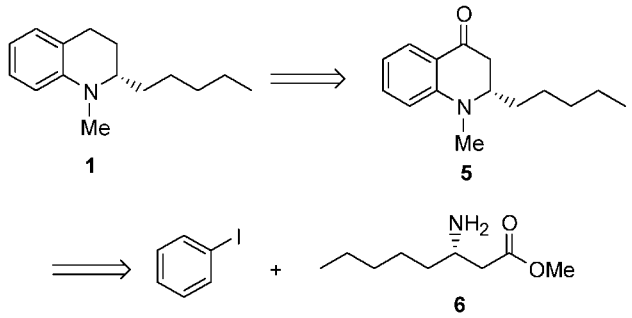


Figure 2 Retrosynthetic analysis of (+)-angustureine (**1**).

As outlined in Scheme 1, our synthesis started from a Micheal addition reaction of lithium (*S*)-*N*-benzyl-*α*-methylbenzylamide to 2-octenoic acid methyl ester **7** to afford *β*-amino ester **8** following Davies's procedure.[5] After Pd/C-catalyzed hydrogenolysis of **8** in acetic acid, the resulting free amine **6** was subjected to a CuI-catalyzed coupling reaction with iodobenzene to provide *N*-phenyl *β*-amino acid **9** in 86% yield. This intermediate was also prepared via a *L*-prolinepromoted CuI-

* E-mail: madw@mail.sioc.ac.cn
Received April 4, 2004; revised and accepted July 15, 2004.
Project supported by the National Natural Science Foundation of China (Nos. 20321202, 20132030).
† Dedicated to Professor Chengye Yuan on the occasion of his 80th birthday.

catalyzed coupling[6] of **6** and iodobenzene at 60 ℃ followed by hydrolysis of the ester moiety with aqueous K_2CO_3. The second method was obviously more suitable for some substrates with less stable functional groups in later SAR studies.

Introduction of a methyl group to N-1 was successfully accomplished with a S_N2 reaction of iodomethane with **9** in the presence of Ag_2O. At this time the carboxylate moiety was also esterified to give **10**. Hydrolysis of **10** with aqueous NaOH in methanol produced acid **11**. Next, treatment of **11** with thionyl chloride to provide the corresponding acyl chloride, which was exposed to $AlCl_3$ in methylene chloride to furnish the ketone **5** in 77% yield. Finally, hydrogenation of **5** worked well under the catalysis of Pd/C to afford (*S*)-angustureine (**1**) (Scheme 2) ($[\alpha]_D^{20}$ +8.0 (*c* 1.0, $CHCl_3$); lit.[1]: $[\alpha]_D^{20}$ −7.16 for natural angustureine; lit.[3]: $[\alpha]_D^{20}$ −6.7 (*c* 1.0, $CHCl_3$) for (−)-angus-tureine in 94%). The overall yield was 36% over 7 steps.

As a summary, we have developed a facile route to enantiopure 2-substituted 1-methyltetrahydroquinoline alkaloids using the CuI-catalyzed coupling reaction of aryl iodides with *β*-amino esters as the key steps. Since a variety of these two intermediates are conveniently available, the present protocol would allow to assemble a wide range of 2-substituted 1-methyltetrahydroquinoline alkaloids for biological evaluation. Further studies toward this direction are underway.

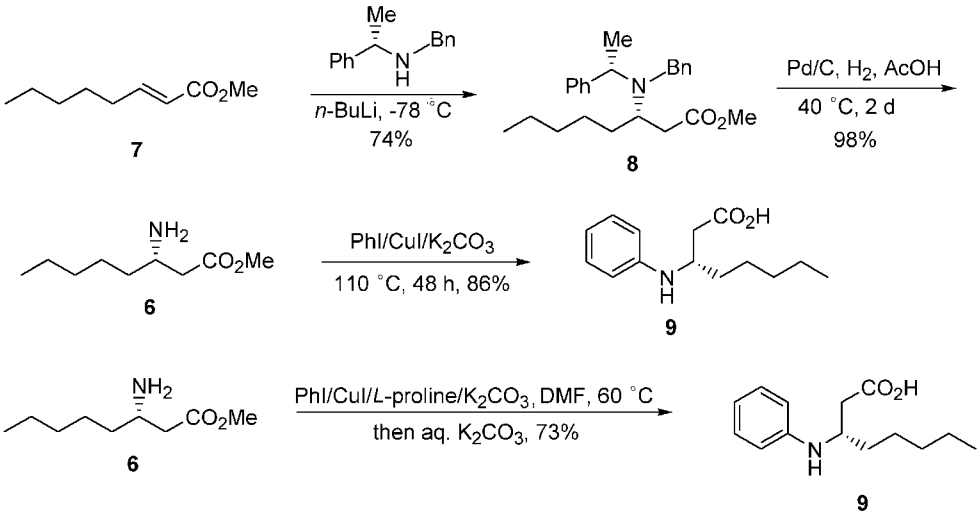
Experimental

IR spectra were measured on a Schimadzu 440 spectrometer. ^{1}H NMR spectra were recorded with TMS as an internal standard on a Brucker AM-300 or Varian EM-360. MS spectra were determined on an HP-5989A spectrometer. HRMS (MALDI) spectra were obtained on a IonSpec FTMS. Optical rotations were obtained on a Perkin-Elmer 241 Autopol polarimeter. All reactions were run in flame-dried glassware under an argon atmosphere unless stated otherwise.

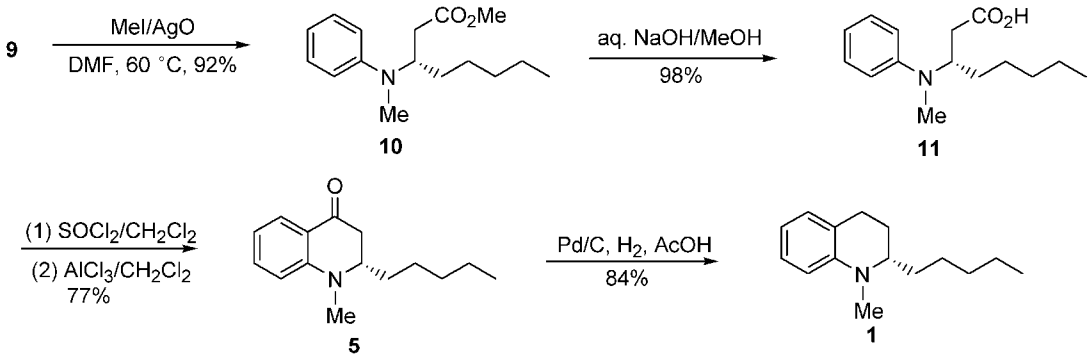
(*S*)-3-[Benzyl-(1-phenylethyl)amino]octanoic acid methyl ester (8)[7]: $[\alpha]_D^{20}$ −9.9 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 7.44—7.21 (m, 10H), 3.85 (d, *J*= 13.5 Hz, 1H), 3.83 (q, *J*=6.3 Hz, 1H), 3.72 (d, *J*=13.5 Hz, 1H), 3.53 (s, 3H), 3.27—3.28 (m, 1H), 2.03 (d, *J*=6.0 Hz, 2H), 1.55—1.57 (m, 2H), 1.35—1.11 (m, 9H), 0.88 (t, *J*=6.6 Hz, 3H); IR (KBr) *v*: 1737, 1150 cm^{-1}; ESI-MS *m*/*z* 368 $(M+H)^+$.

(*S*)-3-Aminooctanoic acid methyl ester (6)[7]: $[\alpha]_D^{20}$ +11.5 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*:

Scheme 1



Scheme 2



3.70 (s, 3H), 3.21—3.16 (m, 1H), 2.48 (dd, J=15.6, 3.9 Hz, 1H), 2.26 (dd, J=15.6, 5.9 Hz, 1H), 1.40—1.28 (m, 8H), 0.88 (t, J=6.6 Hz, 3H); IR (KBr) v: 3302, 1737, 1639 cm^{-1}; ESI-MS m/z 174 $(M+H)^+$.

(*S*)-3-(*N*-Phenyl)aminooctanoic acid (9): To a mixture of **6** (1.37 g, 8.6 mmol), potassium carbonate (3.57 g, 25.8 mmol), CuI (164 mg, 0.86 mmol), 1 mL of H_2O and 20 mL of DMF was added iodobenzene (1.93 mL, 17.26 mmol) dropwise. The resulting suspension was heated at 110 ℃ for 48 h. The cooled reaction mixture was acidified with 1 mol/L HCl to pH=2, and then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residual oil was chromatographed eluting with 1∶3 (ethyl acetate/petroleum ether) to afford **9** (1.56 g, 86%). $[\alpha]_D^{20}$ +1.8 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.20 (t, J=7.5 Hz, 2H), 6.76 (t, J=7.5 Hz, 1H), 6.67 (d, J=7.5 Hz, 2H), 3.78 (m, 1H), 2.58 (dd, J=6.0, 1.8 Hz, 2H), 1.59 (q, J=6.6 Hz, 2H), 1.45—1.35 (m, 2H), 1.35—1.24 (m, 4H), 0.87 (t, J=6.6 Hz, 3H); IR (KBr) v: 3377, 3054, 1709, 1603 cm^{-1}; EI-MS m/z 235 (M^+). HRMS (MALDI) calcd for $C_{14}H_{22}NO_2$ $(M+H)^+$ 236.1645, found 236.1656.

(*S*)-3-(*N*-Methyl-*N*'-phenyl)aminooctanoic acid methyl ester (10): A mixture of **9** (2.3 g, 7.3 mmol), Ag_2O (774 mg, 29.2 mmol) and iodomethane (3.6 mL, 58.4 mmol) in 15 mL of DMF was stirred at room temperature for 3 h, and then allowed to warm to 60 ℃ overnight. After the starting material disappeared as monitored by TLC, the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with 1∶50 (ethyl acetate/petroleum ether) to afford **10** (2.3 g, 92%). $[\alpha]_D^{20}$ −18.6 (c 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.22 (t, J=7.5 Hz, 2H), 6.84 (d, J=7.6 Hz, 2H), 6.70 (t, J=7.5 Hz, 1H), 4.31—4.33 (m, 1H), 3.55 (s, 3H), 2.71 (s, 3H), 2.60 (dd, J=14.1, 8.1 Hz, 1H), 2.44 (dd, J=14.1, 8.1 Hz, 1H), 1.71—1.55 (m, 1H), 1.55—1.41 (m, 1H), 1.35—1.15 (m, 1H), 0.85 (t, J=6.9 Hz, 3H); IR (KBr) v: 1740, 1600 cm^{-1}; EI-MS m/z 263 (M^+), 192, 160, 132. HRMS (MALDI) calcd for $C_{16}H_{26}NO_2$ $(M+H)^+$ 264.1958, found 264.1964.

(*S*)-3-(*N*-Methyl-*N*'-phenyl)aminooctanoic acid (11): A mixture of **10** (472 mg, 1.8 mmol) and NaOH (360 mg, 9 mmol) in the mixed solvent of methanol (5 mL) and water (5 mL) was heated at 60 ℃ for 2 h. The cooled solution was acidified with 1 mol/L HCl to pH=2 and extracted thoroughly with ethyl acetate. The extract was washed with brine, dried over Na_2SO_4 and concentrated. The residual oil was chromatographed eluting with 1∶4 (ethyl acetate/petroleum ether) to afford **11** (417 mg, 98%). $[\alpha]_D^{20}$ −8.2 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.26 (t, J=7.5 Hz, 2H), 6.98 (d, J=7.5 Hz, 2H), 6.87 (t, J=7.5 Hz, 1H), 4.11—4.13 (m, 1H), 2.75 (s, 3H), 2.70—2.45 (m, 2H), 2.16—1.54 (m, 1H), 1.50—1.40 (m, 1H), 1.31—1.22 (m, 6H), 0.87 (t, J=6.4 Hz, 3H); IR (KBr) v: 1708, 1599 cm^{-1}; EI-MS m/z 249 (M^+). HRMS (MALDI) calcd for $C_{15}H_{24}NO_2$ $(M+H)^+$ 250.1802, found 250.1806.

1-Methyl-2-pentyl-2,3-dihydro-1H-quinolin-4-one (5): To a solution of **10** (379 mg, 1.6 mmol) in 10 mL of anhydrous CH_2Cl_2 at 0 ℃ was added thionyl chloride (0.7 mL, 8 mmol) and then allowed to stir for 2 h at room temperature. The solvent was removed *in vacuo* to afford a brown oil residue, which was dissolved in 10 mL of anhydrous CH_2Cl_2 followed by the addition of $AlCl_3$ (1.05 g, 8 mmol). The mixture was stirred at room temperature for 24 h before the reaction was quenched with 10 mL of water. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residual oil was chromatographed eluting with 1∶50 (ethyl acetate/petroleum ether) to afford **5** (280 mg, 77%). $[\alpha]_D^{20}$ −199.8 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.85 (d, J=7.5 Hz, 1H), 7.39 (t, J=7.5 Hz, 1H), 6.67 (t, J=7.5 Hz, 1H), 6.60 (d, J=7.5 Hz, 1H), 3.49—3.51 (m, 1H), 3.03 (s, 1H), 2.97 (dd, J=15.9, 6.2 Hz, 1H), 2.65 (dd, J=15.9, 2.4 Hz, 1H), 1.58—1.52 (m, 2H), 1.35—1.39 (m, 6H), 0.86 (t, J=6.8 Hz, 3H); IR (KBr) v: 1675, 1604 cm^{-1}; EI-MS m/z 231 (M^+). HRMS (MALDI) calcd for $C_{15}H_{22}NO$ $(M+H)^+$ 232.1696, found 232.1707.

(*S*)-Angustureine (1): A mixture of **5** (93 mg, 0.4 mmol) and 10% Pd/C (30 mg) in 5 mL of methanol and 1 mL of acetic acid was stirred at room temperature overnight under 101 kPa H_2. After removing Pd/C by filtration, the filtrate was concentrated and then purified by flash chromatography eluting with petroleum ether to give **1** (74 mg, 84%). $[\alpha]_D^{20}$ +8.0 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.08 (t, J=7.5 Hz, 1H), 6.97 (d, J=7.5 Hz, 1H), 6.57 (t, J=7.5 Hz, 1H), 6.51 (t, J=7.5 Hz, 1H), 3.22—3.24 (m, 1H), 2.92 (s, 3H), 2.80—2.62 (m, 2H), 1.91—1.84 (m, 2H), 1.42—1.22 (m, 6H), 0.89 (t, J=6.9 Hz, 3H); IR (KBr) v: 2955, 1604 cm^{-1}; EI-MS m/z 217 (M^+). HRMS (MALDI) calcd for $C_{15}H_{24}N$ $(M+H)^+$ 218.1903, found 218.1917.

References

1 Jacquemond-Collet, I.; Hannedouche, S.; Fabre, N.; Fourasté, I.; Moulis, C. *Phytochemistry* **1999,** *51*, 1167.

2 Jacquemond-Collet, I.; Benoit-Vical, F.; Valentin, M. A.; Stanislas, E.; Mallie, M.; Fouraste, I. *Planta Med.* **2002**, *68*, 68.

3 Wang, W.-B.; Lu, S.-M.; Yang, P.-Y.; Han, X.-W.; Zhou, Y.-G. *J. Am. Chem. Soc.* **2003**, *125*, 10536.

4 (a) Ma, D.; Xia, C. *Org. Lett.* **2001**, *3*, 2583.
(b) Ma, D.; Jiang, J.; *Tetrahedron*: *Asymmetry* **1998**, *9*, 1137.

5 Davies, S. G.; Ichihara, O. *Tetrahedron*: *Asymmetry* **1991**, *2*, 183.

6 Ma, D.; Cai, Q.; Zhang, H. *Org. Lett.* **2003**, *5*, 2453.

7 Ma, D.; Pu, X.; Wang, J. *Tetrahedron*: *Asymmetry* **2002**, *13*, 2257.

(E0404071 LU, Y. J.)