

Asymmetric Synthesis of (–)(2*R*,3*R*,6*S*)-Irnigaine

MA, Nan^a (马楠) MA, Da-Wei^{* b} (马大为)

^a Department of Chemistry, Fudan University, Shanghai 200433, China

^b State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

Asymmetric synthesis of irnigaine was achieved starting from an enantiopure β -amino ester **5** using the condensation of amino alcohol **2** with acetylacetone and the subsequent intramolecular cyclization as the key steps.

Keywords asymmetric synthesis, β -amino ester, piperidine, condensation

Introduction

As a relatively new member of natural alkaloids with 2,6-disubstituted-3-piperidinol skeleton, irnigaine **1** was isolated from the tubers of *Arisarum Vulgare* (Araceae) in 1995 by Melhaoui and Bode.¹ Its structure and relative configurations were elucidated by ¹H NMR studies and the absolute configuration was proposed on the basis of its optical rotation.¹ Soon after then, Meyer and his co-workers reported the first synthesis of (–)(2*R*,3*R*,6*S*)-irnigaine and the configuration confirmation. Although their synthesis route was short and efficient, the starting material used there needed to be prepared in many steps.²

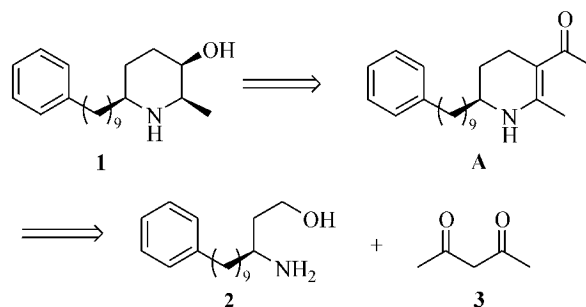
As part of our effort on the synthesis of natural alkaloids from enantiopure β -amino esters,³ a new protocol to synthesize (–)(2*R*,3*R*,6*S*)-irnigaine was developed.

Result and discussion

As outlined in Scheme 1, (–)-irnigaine was envisioned to be obtained through intermediate **A** via a diastereoselective hydrogenation and subsequent conversions. The cyclic enamine **A** may be prepared by the condensation reaction of acryl acetone **3** and an enantiopure γ -amino alcohol **2** and the subsequent intramolecular cyclization. The γ -amino alcohol **2** may be obtained from the corresponding enantiopure β -amino ester.⁴

The detailed synthesis was illustrated in Scheme 2. The β -amino ester **5** was obtained in greater than 97% diastereoselectivity by a Micheal addition reaction of lithium (S)-*N*-benzyl- α -methylbenzylamide to α,β -unsaturated

Scheme 1



ester **4** using Davies' procedure⁴ in 89% yield. Reduction of **5** with LAH converted the ester to the corresponding alcohol, which was subjected to Pd(OH)₂-catalyzed hydrogenolysis to remove the two benzyl protecting groups to provide the desired γ -amino alcohol **2**. The condensation reaction of **2** and acryl acetone **3** was carried out in refluxing toluene to afford the enamine **6** in 74% yield.

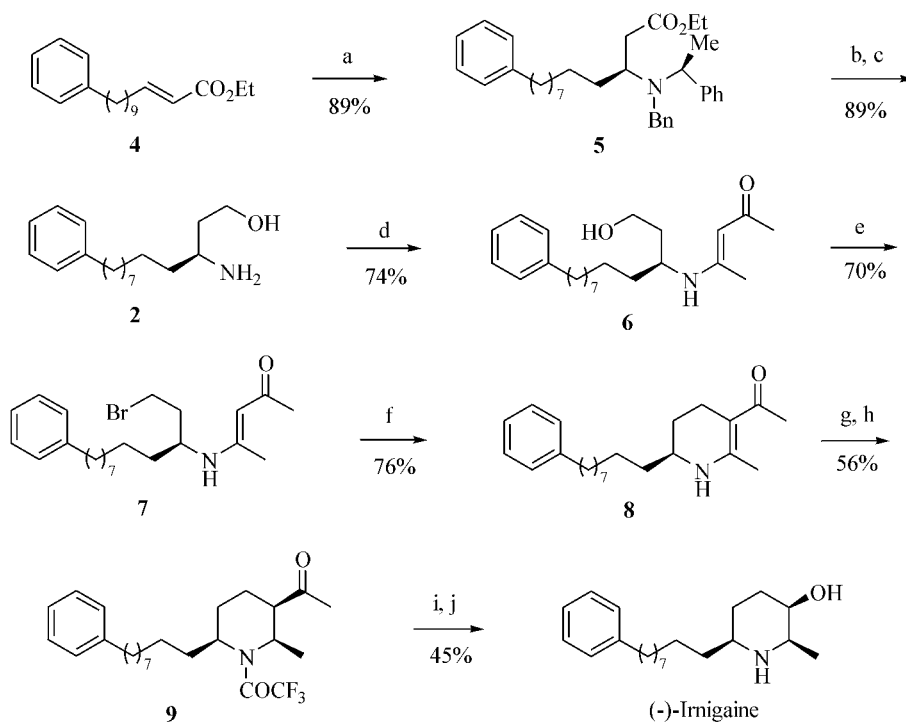
Treatment of **6** with triphenylphosphine and carbon tetrabromide assisted by triethylamine produced the bromide **7** in 70% yield. Next, intramolecular cyclization of **7** was carried out in refluxed MeCN with Et₃N as a base, giving the cyclic enamine **8** in 76% yield. In order to reduce the carbon-carbon double bond of **8**, PtO₂-catalyzed hydrogenation was employed. It was found that in acetic acid and at the ordinary pressure and temperature the hydrogenation worked well to afford the corresponding saturated piperidine, which was protected with trifluoroacetic anhydride to provide the amide **9** in 56% yield for two steps. No other isomer was determined by ¹H NMR spectra in **9** which implied that the diastereoselectivity was over 97% in the hydrogenation step. Finally, subjecting **9** to Bayer-Villager oxidation⁵ with newly generated peroxytrifluoroacetic acid from 95% H₂O₂/(CF₃CO)₂O afforded the oxidation product, which was hydrolyzed with 6 N HCl in methanol to remove all protecting groups to give (–)-irnigaine **1** in 45% yield for two steps.

* E-mail: madw@mail.sioc.ac.cn

Received April 1, 2003; revised May 4, 2003; accepted June 20, 2003.

Project supported by Chinese Academy of Sciences and the National Natural Science Foundation of China (No. grant 29725205).

Scheme 2



Reagents and conditions : a) $(S)(-)-N$ -benzyl- α -methylbenzylamine, n -BuLi, THF, -78 °C and then adding **4**; b) LAH, THF, 0 °C—r. t. ; c) 10% Pd(OH)₂-C, H₂, MeOH, 50 °C, 50×10^5 Pa ; d) **3**, toluene, reflux ; e) Ph₃P, CBr₄, Et₃N, CH₂Cl₂, 0 °C—r. t. ; f) Et₃N, MeCN, 80 — 85 °C ; g) PtO₂, H₂, r. t. ; h) Et₃N, (CF₃CO)₂O, DMAP, CH₂Cl₂, r. t. ; i) 95% H₂O₂, Na₂HPO₄, (CF₃CO)₂O, CH₂Cl₂, reflux ; j) HCl-MeOH, 65 °C.

Experimental

General procedure

¹H NMR spectra were recorded with CDCl₃ as solvent and tetramethylsilane as internal standard at a Bruker AM-300 spectrometer. All chemical shifts (δ) were reported in δ and J values in Hz. Optical rotations were obtained on a Perkin-Elmer 241 Autopol polarimeter. Low resolution mass (EIMS) spectra were taken with a HP-5989A spectrometer, and high resolution mass (HREIMS) spectra were obtained on a Finnigan MAT spectrometer.

Synthesis of β -amino ester **5**

Treatment of $(S)(-)-N$ -benzyl- α -methylbenzylamine (14 g, 66 mmol) in 200 mL of THF at -78 °C with n -BuLi (33 mL, 1.6 mol/L) generated a red solution. After the reaction mixture was warmed to -20 °C, it was cooled to -78 °C again. To this solution was added a solution of **4** (16.4 g, 54 mmol) in THF. The mixture was stirred for 30 min before adding saturated solution of ammonium chloride to quench the reaction. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over Na₂SO₄, and concentrated. The residue was purified with column chromatography to afford a pale yellow oil 24.8 g (89%) of **5**. [α]_D²⁰ = -3.4 (c 0.75, CHCl₃); ¹H NMR

(CDCl₃, 300 MHz) δ : 1.17 (t, J = 7.1 Hz, 3H), 1.20—1.45 (m, 16H), 1.42—1.72 (m, 5H), 2.62 (t, J = 7.2 Hz, 2H), 3.21—3.36 (m, 1H), 3.54 (d, J = 14.8 Hz, 1H), 3.80 (d, J = 14.8 Hz, 1H), 3.84 (q, J = 6.7 Hz, 1H), 3.99—4.02 (m, 2H), 7.18—7.43 (m, 15H); EIMS m/z : 514.3 (M⁺ + 1); HRMS calcd for C₃₅H₄₈NO₂ 514.3686 (M⁺ + 1), found 514.3667.

(S) -12-Phenyl-3-aminododecan-1-ol (**2**)

A solution of the β -amino ester **5** (20 g, 39 mmol) in THF was added dropwise into the suspended solution of LAH in THF under 0 °C. The reaction mixture was warmed until the starting material disappeared monitored by TLC. The reaction was quenched by adding water, and then 15% sodium hydroxide solution was added. The resultant mixture was stirred until the white solid precipitated. The solution was filtered on silica gel and the filtrate was concentrated to dryness. The residual oil was dissolved in 100 mL of methanol before 10% wt Pd(OH)₂/C was added. The mixture was stirred under hydrogen (50×10^5 Pa) at 50 °C for 20 h. After the Pd/C was filtered off, the filtrate was concentrated to afford γ -amino alcohol 9.6 g (89%) of **2** as pale yellow solid. [α]_D²⁰ = -3.7 (c 0.6, CHCl₃); ¹H NMR (CDCl₃, 300 MHz) δ : 1.18—1.37 (m, 14H), 1.50—1.70 (m, 3H), 2.59 (t, J = 7.7 Hz, 2H), 3.05—3.07 (m, 1H), 3.10—3.54 (m,

3H), 3.63 (t, $J = 6.6$ Hz, 1H), 3.79 (t, $J = 8.5$ Hz, 1H), 3.87 (m, 1H), 7.17 (d, $J = 7.1$ Hz, 3H), 7.23—7.34 (m, 2H); EI-MS m/z : 278.2 ($M^+ + 1$); HRMS calcd for $C_{18}H_{32}NO$ 278.2480 ($M^+ + 1$), found 278.2476.

Condensation of the amino alcohol **2** and acetylacetone

To a stirred solution of **2** (2.8 g, 10 mmol) in 100 mL of toluene was added acetyl acetone **3** (2.0 g, 20 mmol) at r.t. The solution was heated at reflux with azeotropic removal of water. After the reaction completed monitored by TLC the solution was concentrated in vacuum. The residue was purified by column chromatography to afford a yellow oil 2.6 g (74%) of **6**. [α] $_D^{20}$ -30.9 (c 0.4, $CHCl_3$); 1H NMR ($CDCl_3$, 300 MHz) δ : 1.26—1.29 (m, 18H), 1.66 (m, 1H), 1.81 (s, 3H), 1.95 (s, 3H), 2.58 (t, $J = 7.6$ Hz, 2H), 3.64—3.72 (m, 3H), 4.91 (s, 1H), 7.17 (m, 3H), 7.27 (m, 2H), 10.81 (d, $J = 10$ Hz, 1H); EIMS m/z : 360.3 ($M^+ + 1$); HRMS calcd. for $C_{23}H_{38}NO_2$ 360.2863 ($M^+ + 1$), found 360.2824.

(*S*)-4-[1-(2-Bromoethyl)-(10-phenyldecyl)amino]pent-3-en-2-one (**7**)

To a stirred solution of the enamine **6** (4.0 g, 11 mmol) in dichloromethane was added CBR_4 (5.1 g, 16 mmol) at 0 °C. After all CBR_4 was dissolved, Ph_3P (4.4 g, 17 mmol) was added. The resultant mixture was warmed to room temperature and the stirring was continued until **6** disappeared monitored by TLC. To this solution 1.3 mL of triethylamine was added and the resultant solution was stirred for another hour. After the solvent was removed in vacuum, the residue was chromatographed by eluting with 1/5 ethyl acetate/*n*-hexane to afford 3.3 g (70%) of **7** as a yellow oil. [α] $_D^{20}$ -30 (c 0.4, $CHCl_3$); 1H NMR ($CDCl_3$, 300 MHz) δ : 1.26 (m, 12H), 1.52 (m, 6H), 2.02 (s, 6H), 2.59 (t, $J = 7.6$ Hz, 2H), 3.40 (m, 1H), 3.48 (m, 1H), 3.71 (m, 1H), 4.94 (m, 1H), 7.17 (d, $J = 6.8$ Hz, 3H), 7.27 (m, 2H), 10.8 (m, 1H); EIMS m/z : 422.2 ($M^+ + 1$); HRMS calcd for $C_{23}H_{37}NOBr$ 422.2061 ($M^+ + 1$), found 422.2059.

(*S*)-1-[6-(9-Phenyl)nonyl-2-methyl-1,4,5,6-tetrahydropyrid-3-yl]ethanone (**8**)

To a solution of compound **7** (3.0 g, 7.1 mmol) in 600 mL of anhydrous acetonitrile was added triethylamine (780 mg, 7.8 mmol). The mixture was heated at 80—85 °C until **7** disappeared monitored by TLC. The solvent was evaporated by vacuum. The residue was separated by column chromatography to give the cyclic enamine **8** 1.9 g as a white solid in 76% yield. [α] $_D^{20}$ +43.6 (c 0.6, $CHCl_3$); 1H NMR ($CDCl_3$, 300 MHz) δ : 1.25—1.44 (m, 12H), 1.46—4.49 (m, 3H), 1.59—1.62 (m,

2H), 1.88—1.91 (m, 1H), 2.12 (s, 3H), 2.26 (s, 3H), 2.37—2.39 (m, 1H), 2.45—2.48 (m, 1H), 2.59 (t, $J = 7.6$ Hz, 2H), 3.15—3.16 (m, 1H), 4.12—4.16 (m, 1H), 7.17 (d, $J = 7.2$ Hz, 3H), 7.27 (d, $J = 7.6$ Hz, 2H); EIMS m/z : 342.2 ($M^+ + 1$); HRMS calcd. for $C_{23}H_{36}NO$: 342.2880 ($M^+ + 1$), found 342.2798.

1-[(2*R*,3*R*,6*S*)-3-Acetyl-6-(9-phenyl)nonyl-2-methylpiperidin-1-yl]-2,2,2-trifluoroethanone (**9**)

The cyclic enamine **8** (1.9 g, 5.5 mmol) was dissolved in acetic acid. To the solution 100 mg of PtO_2 was added before it was hydrogenated under 1×10^5 Pa. After the hydrogenation was over monitored by TLC, PtO_2 was filtered off and the filtrate was evaporated by vacuum. The residue oil was dissolved in dichloromethane before triethylamine (3.7 g, 37 mmol) and cat. DMAP were added. To this stirred solution was added trifluoroacetic anhydride (3.9 g, 18.5 mmol). After the resultant mixture was stirred for 1 h, the solvent was moved by vacuum. The residue was separated by column chromatography to afford compound **9** 1.4 g as a brown oil in 56% yield for two steps. [α] $_D^{20}$ -33.3 (c 0.4, $CHCl_3$); 1H NMR ($CDCl_3$, 300 MHz) δ : 1.09 (d, $J = 7.2$ Hz, 3H), 1.20—1.50 (m, 12H), 1.64—1.76 (m, 5H), 1.98—2.04 (m, 2H), 2.20 (s, 3H), 2.60 (t, $J = 8.2$ Hz, 2H), 2.67—2.70 (m, 1H), 3.91—3.92 (m, 1H), 4.57—4.61 (m, 1H), 5.20 (t, $J = 6.6$ Hz, 1H), 7.17 (d, $J = 7.1$ Hz, 3H), 7.26—7.28 (m, 2H); EIMS m/z : 439.3 (M^+); HRMS calcd for $C_{25}H_{36}NO_2F_3$ 439.2698 (M^+), found 439.2704.

Synthesis of irniganie

Trifluoroacetic anhydride (869 mg, 4.1 mmol) was added dropwise to the solution of 95% H_2O_2 (165 mg, 4.6 mmol) in cold dichloromethane. The resultant solution was added dropwise to mixture of **9** (1.0 g, 2.3 mmol) and Na_2HPO_4 (326 mg, 2.3 mmol) in dichloromethane. The reaction mixture was heated at reflux for 30 min. The cooled solution was filtrated and the filtrate was washed with saturated $Na_2S_2O_3$. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with brine and water subsequently. After it was dried over Na_2SO_4 , the solution was concentrated. The residue was dissolved in 10 mL methanolic hydrochloride before it was heated at 65 °C for 24 h. The solvent was removed and the residue was dissolved in MeOH before 30% NaOH was added. The mixture was extracted with chloroform. The organic phase was dried over Na_2SO_4 , and concentrated. The residual oil was purified by column chromatography to afford 325 mg (45%) of **1** as a white solid. [α] $_D^{20}$ -13 (c 0.3, $CHCl_3$) {lit. [α] $_D^{20}$ -14 (c 0.3, $CHCl_3$)}; [α] $_D^{20}$ -9.2 (c 1.085, $CHCl_3$); 1H NMR ($CDCl_3$, 300 MHz) δ : 1.10 (d, $J = 6.4$ Hz, 3H), 1.26—1.33 (m, 14H), 1.43—

1.72 (m, 7H), 1.86 (m, 1H), 2.50 (m, 1H), 2.59 (t, $J = 7.6$ Hz, 2H), 2.75 (m, 1H), 3.56 (s, 1H), 7.17 (d, $J = 6.4$ Hz, 3H), 7.28 (m, 2H); EMIS m/z : 318.3 ($M^+ + 1$); HRMS calcd for $C_{23}H_{36}NO$ 318.2798 ($M^+ + 1$), found 318.2796.

References

- 1 Melhaoui, A.; Bodo, B. *Nat. Prod. Lett.* **1995**, *7*, 101.
- 2 Pahl, A.; Warchow, R.; Meyer, H. H. *Tetrahedron Lett.* **1998**, 2095.
- 3 (a) Ma, D.; Ma, N. *Tetrahedron Lett.* **2003**, *44*, 3963.
(b) Ma, D.; Pu, X.; Wang, J. *Tetrahedron: Asymmetry* **2002**, *13*, 2257.
- (c) Ma, D.; Zhu, W. *Org. Lett.* **2001**, *3*, 3927.
- (d) Ma, D.; Xia, C.; Jiang, J.; Zhang, J. *Org. Lett.* **2001**, *3*, 2189.
- (e) Wang, Y.; Ma, D. *Tetrahedron: Asymmetry* **2001**, *12*, 725.
- (f) Ma, D.; Sun, H. *J. Org. Chem.* **2000**, *65*, 6009.
- (g) Ma, D.; Sun, H. *Tetrahedron Lett.* **2000**, *41*, 1947.
- (h) Ma, D.; Sun, H. *Org. Lett.* **2000**, *2*, 2503.
- (i) Ma, D.; Sun, H. *Tetrahedron Lett.* **1999**, *40*, 3609.
- (j) Ma, D.; Zhang, J. *Tetrahedron Lett.* **1998**, *39*, 9067.
- 4 Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry*, **1991**, *2*, 183.
- 5 Krow, G. R. *Org. React.* **1993**, *43*, 251.

(E0304014 ZHAO, X. J.; LU, Z. S.)