Chinese Chemical Letters Vol. 15, No. 10, pp 1164-1166, 2004
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# A Concise Total Synthesis of *S*-(+)-Tylophorine

Zhong JIN, Shi Pu LI, Qing Min WANG, Run Qiu HUANG*

State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071

**Abstract:** A highly efficient total synthesis of S-(+)-tylophorine has been accomplished in fully asymmetric fashion.

**Keywords:** Phenanthroindolizidine alkaloid, tylophorine, biological activity.

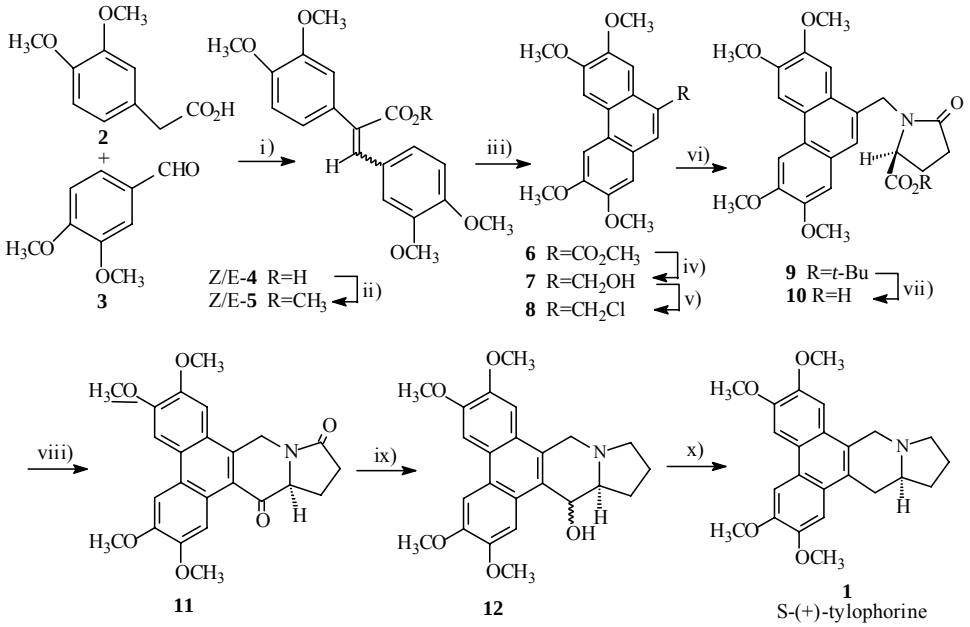
Phenanthroindolizidine alkaloids, which exhibit extensively biological properties, are widely present at various plants of the Asclepiadaceae family[1]. The significantly biological importance of these natural products has attracted considerable synthetic efforts[2]. We herein report an efficiently asymmetric synthesis of *S*-(+)-tylophorine **1**, as a typically representative alkaloids.

As depicted in **Scheme 1**, condensation of veratraldehyde **2** and homoveratric acid **3** in the presence of $Ac_2O$ and $Et_3N$ afforded 3, 4-dimethoxy- α- (3′, 4′-dimethoxyphenyl)-cinnamic acid **4** in 80% yield as a mixture of *Z/E*-isomer (*Z/E*=88:12). On the treatment with ethereal diazomethane, the resulting acid gave corresponding methyl ester **5** in virtually quantitative yield. Subjection of methyl ester to oxidation with vanadium oxytrichloride ($VOCl_3$) in dichloromethane at -78ºC afforded methyl 2, 3, 6, 7-tetramethoxyphenanthrene 9-carboxylate **6** in 99% yield. After subsequent reduction by $LiAlH_4$ in THF, the desired 2, 3, 6, 7-tetramethoxy-9-hydroxymethylphenanthrene **7** was obtained in 99% yield. Treatment of alcohol **7** with carbon tetrachloride and triphenylphosphine in dried chloroform gave 2, 3, 6, 7-tetramethoxy-9-chloromethyl-phenanthrene **8** in 95% yield.

Subsequently, *tert*-butyl L-pyroglutamate was alkylated with 2, 3, 6, 7-tetramethoxy-9-chloromethyl-phenanthrene **8** utilizing a modification of Smith's method[3]. *N*-Substituted *tert*-butyl pyroglutamate **9** was obtained in 96% yield. After treatment with catalytic trifluoroacetic acid in the dichloromethane at room temperature, amido acid **10** was obtained in 98% yield with complete preservation of optical activity. Intramolecular Friedel-Craft cyclization of acid chloride of 10 catalyzed by $SnCl_4$ was smoothly performed in refluxing dichloromethane to give amido ketone **11** in 94% overall yield. Straightforward reduction of **11** to corresponding amino alcohol **12** by $LiAlH_4$ was achieved in refluxing THF[4]. Two diastereoisomer 14α-**12** and 14β-**12** were obtained in

* E-mail: rqhuang@163.com

**Scheme 1**




Reagents and conditions: i) $Ac_2O$, $Et_3N$, reflux; ii) $CH_2N_2$, r.t.; iii) $VOCl_3$, -78º→r.t.; iv) $LiAlH_4$, THF; v) $PPh_3$, $CCl_4$, $CHCl_3$; vi) NaH, DMSO, r.t.; vii) $CF_3COOH$, $CH_2Cl_2$; viii) (a) $(COCl)_2$, DMF, $CH_2Cl_2$; (b)$SnCl_4$, reflux; ix) $LiAlH_4$, THF, 94%; x) $Et_3SiH$, $CF_3CO_2H$.

an approximate ratio of 55:45 on the basis of HPLC analysis. Followed by hydrogenation with triethyl silane in the trifluoroacetic acid, the target optically active alkaloid *S*-(+)-**1** was obtained with 92% overall yield[5]. All spectral data of the alkaloid thus synthesized are identical to those of the natural products[6].

In summary, we have developed a highly efficient pathway for synthesis of *S*-(+)-tylophorine in ten linear steps. On this basis, access to other structurally related phenanthroindolizidine alkaloids is under investigation.

## Acknowledgment

We thank the National Natural Science Foundation of China (NNSFC) (No. 20002003) for financial support.

## References and Notes

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4. Amino alcohol **12** is extremely sensitive to light. All operations should carry out rapidly and avoid exposing to light.
5. Analytic data for *S*-(+)-tylophorine **1**: m.p. 288-290ºC (dec.), IR (KBr) 1620, 1540, 1515 $cm^{-1}$; $^{1}$HNMR ($CDCl_3$, 200 MHz) δ ppm 7.78 (s,1H), 7.77 (s,1H), 7.24 (s,1H), 7.05 (s,1H), 3.98 (AB q,2H, *J*=15 Hz, Δυ= 220 Hz, $\delta_A$ 4.60, $\delta_B$ 3.65), 4.09 (s,3H), 4.07 (s,3H), 4.02 (s,3H), 4.00 (s,3H), 3.43 (t, 1H, *J*=7.4), 3.36 (d, 1H, *J*=5.7 Hz), 2.89 (t, 1H, *J*=12 Hz), 2.56-2.45 (m, 2H), 2.17-2.10 (m, 1H), 2.05-1.80 (m, 3H). $^{13}$CNMR ($CDCl_3$, 75.5MHz) δ ppm 147.6, 147.5, 125.1, 124.6, 123.2, 123.0, 122.6, 122.4, 103.6, 102.8, 102.5, 102.2, 59.2, 55.0, 54.8, 54.0, 52.8, 32.5, 29.1, 28.7, 20.5; $[\alpha]_D^{25}$ +74.9 (*c* 1.0, $CHCl_3$); MS (EI, 70eV) *m/z* 393.20 ($M^+$), calcd. *m/z*=393.19, 324 (100%); Anal. calcd. for $C_{24}H_{27}NO_4$ C, 73.26; H, 6.92; N 3.56; Found. C, 73.38; H, 6.60; N, 3.55.
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Received 8 September, 2003