Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 2327–2329
Tetrahedron Letters

Total synthesis of (−)-incarvilline

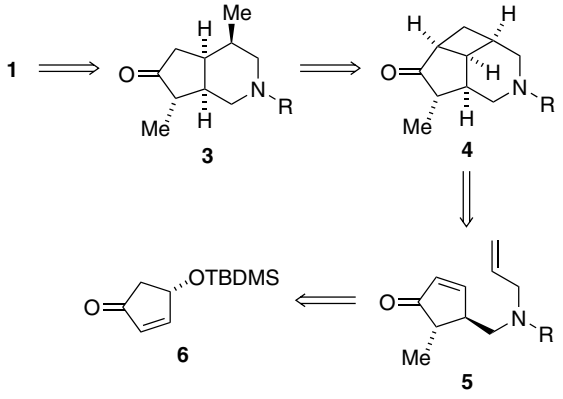
Masaya Ichikawa, Sakae Aoyagi and Chihiro Kibayashi*

School of Pharmacy, Tokyo University of Pharmacy and Life Science, Horinouchi, Hachioji, Tokyo 192-0392, Japan

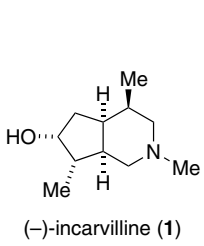
Received 14 January 2005; revised 26 January 2005; accepted 28 January 2005

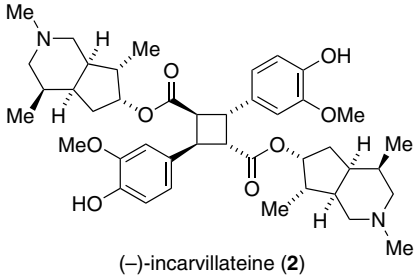
Abstract—An enantioselective synthesis of (−)-incarvilline is presented, employing a three-component coupling reaction and an intramolecular enone–olefin [2+2] photocycloaddition followed by a SmI_2-induced cyclobutane ring-opening reaction.

(−)-Incarvilline (**1**), isolated from the aerial parts of *Incarvillea sinensis* Lam.,[1] which has been traditionally used in treating rheumatism and relieving pain as the Chinese folk medicine 'jiaohao', is a monoterpene core unit of incarvillateine (**2**), which has been shown to exhibit significant antinociceptive activity in a formalin-induced pain model in mice.[2,3] After the structure and relative stereochemistry of **1** was established,[1] the absolute configuration for **1** has been determined as shown based on Mosher's method and X-ray crystallographic analysis of incarvilline methiodide.[4] We have recently published[5] the first total synthesis of **1** employing three-component coupling reaction and ring formation by reductive Heck-type reaction as key steps. In this letter, we describe an alternative method for the synthesis of **1** with full stereocontrol. Our synthetic strategy for **1** was based on the approach outlined in Scheme 1 involving an intramolecular enone–olefin [2+2] photocycloaddition[6] of the *N*-allyl enone **5**, which allows stereoselective construction of the decahydro-5-azacyclobuta[*cd*]indene skeleton **4** with three of the asymmetric centers established.



Scheme 1. Retrosynthetic analysis of (−)-incarvilline (**1**).

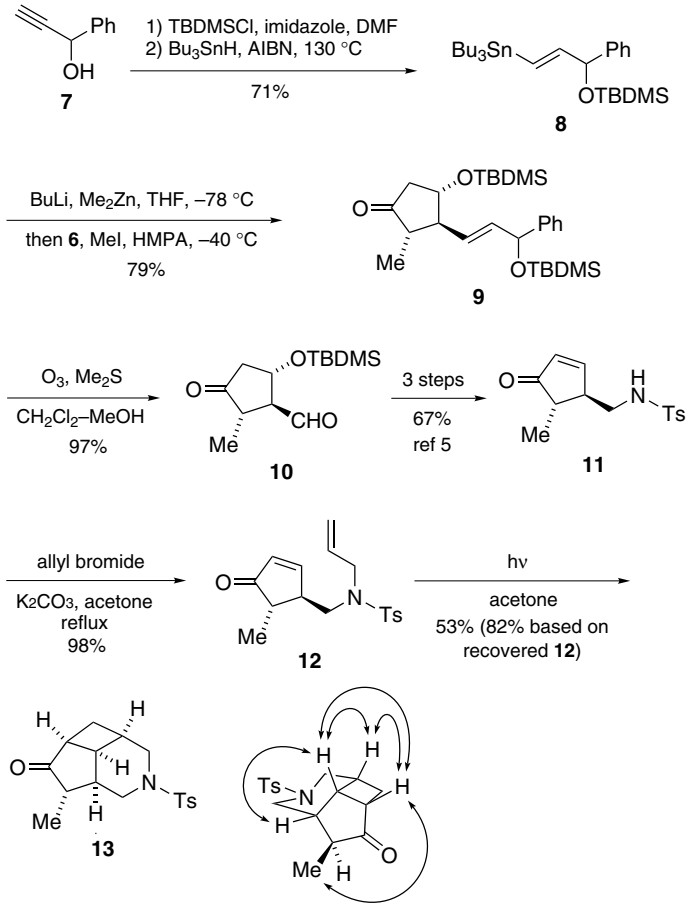

(−)-incarvilline (**1**)


(−)-incarvillateine (**2**)

Our synthesis started with the three-component coupling reaction[7] using the (*S*)-cyclopentenone **6** in a similar manner previously reported by us.[5] Thus, the (*E*)-alkenylstannane **8**, prepared from 1-phenyl-2-propyn-1-ol (**7**) via TBDMS protection of the secondary alcohol group followed by hydrostannylation of the alkyne, was subjected to transmetalation to generate a corresponding zincate, which was allowed to react with the (*S*)-enone **6**, followed by quenching with iodomethane in the presence of HMPA to give the 2,3,4-trisubstituted cyclopentanone **9** in 79% yield based on **6** (Scheme 2). Although **9** was an inseparable 1:1 mixture of diastereomers epimeric at the stereogenic center bearing the

Keywords: (−)-Incarvilline; Three-component coupling; Intramolecular [2+2] photocycloaddition; Cyclobutane ring opening.
* Corresponding author. Tel.: +81 426 76 3275; fax: +81 426 76 4475; e-mail: kibayasi@ps.toyaku.ac.jp

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.01.173



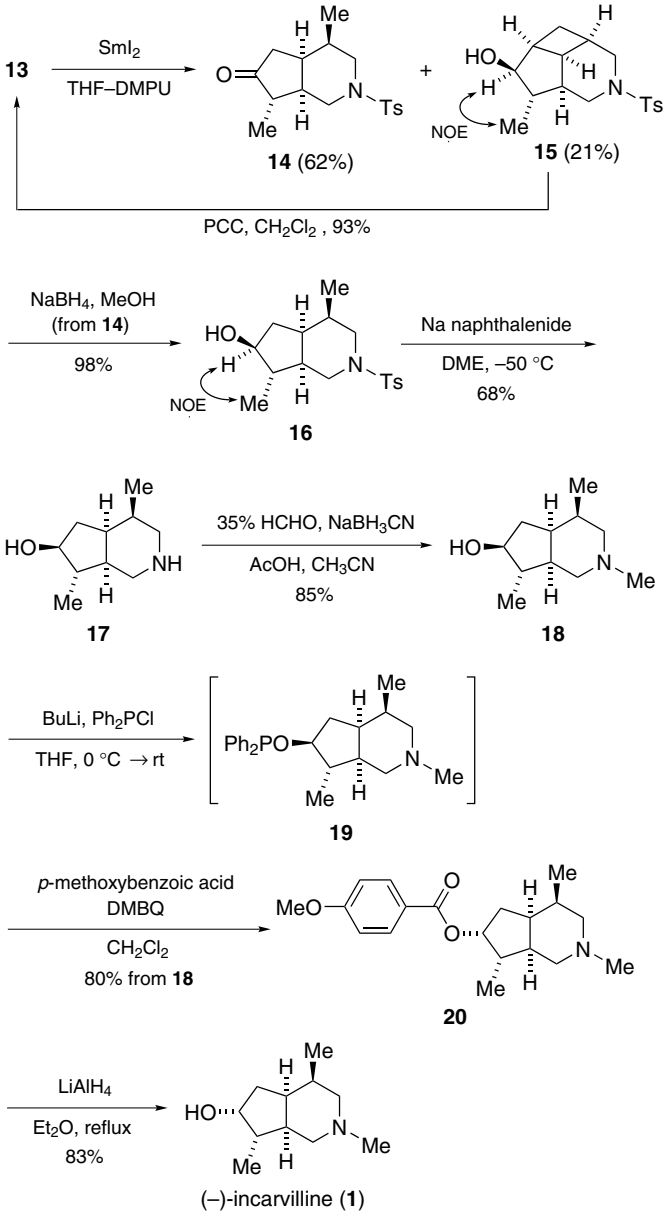
Selected NOESY correlations for **13**

Scheme 2.

siloxy group on the olefinic side chain, the reaction proceeded with complete all-*trans* stereoselection with respect to the stereocenters of the cyclopentane ring. Ozonolysis of **9** with a reductive workup (Me_2S) gave the aldehyde **10** (97% yield), which was then converted to the enone **11** according to our previously developed approach[5] using a three-step sequence involving $NaBH_4$ reduction, Mitsunobu reaction with *N*-Boc-*p*-toluenesulfonamide, and treatment with trifluoroacetic acid. The *N*-allyl enone **12**, obtained by allylation of **11** in 98% yield, underwent UV irradiation through Pyrex resulted in the intramolecular enone–olefin [2+2] cycloaddition and provided the cyclobutyl ketone **13** as a single stereoisomer in 53% yield with recovery of the unreacted **12** in 36%, thus based on recovered **12**, the photocycloadduct **13** was formed in 82% yield. Construction of the decahydro-5-azacyclobuta[*cd*]indene ring system was thus achieved, generating three contiguous asymmetric centers in the proper stereochemical relationship in a one-pot procedure. The stereochemistry shown in **13** was proven to be correct on the basis of NOESY spectral data (Scheme 2).

Treatment of **13** with SmI_2 in THF containing DMPU as a cosolvent effected radical ring-opening reaction[8] of the cyclobutyl ketone[9] to give the *cis*-perhydro-2-pyrindine **14** in 62% yield along with the alcohol **15** (21%), the latter of which could be recycled to the cyclobutyl ketone **13** by oxidation with PCC (Scheme 3). Reduction of the ketone **14** with $NaBH_4$ exclusively yielded the (6*S*)-alcohol **16** (98%). The stereochemistry of the hydroxy group of **16** was confirmed by NOE analysis. After reductive removal of the tosyl group from **16** (sodium naphthalenide, DME, −50 °C), *N*-methylation of **17** with aqueous formaldehyde and $NaBH_3CN$ provided (+)-6-*epi*-incarvilline (**18**), which was identical in all respects to an authentic sample previously prepared by us.[5] Inversion of configuration of the C6 hydroxy stereocenter was accomplished by employing Mukaiyama's method.[10] Accordingly, **18** was treated with BuLi and chlorodiphenylphosphine to give the alkoxydiphenylphosphine intermediate **19**, which, upon treatment with *p*-methoxybenzoic acid and 2,6-dimethyl-1,4-benzoquinone (DMBQ), was converted into the *p*-methoxybenzoate **20** as a single diastereomer with complete inversion of the configuration at C6. Reduction of **20** with $LiAlH_4$ afforded (−)-incarvilline (**1**) as a white crystals (from cyclohexane): mp 94.6–95.3 °C (lit.[1] mp 93.4–93.8 °C, lit.[5] mp 94.4–95.5 °C); $[\alpha]_D^{20}$ −8.2 (*c* 0.577, $CHCl_3$) [lit.[1] $[\alpha]_D^{24}$ −8.0 (*c* 1.24, $CHCl_3$), lit.[5] $[\alpha]_D^{20}$ −8.1 (*c* 0.18, $CHCl_3$)].

In summary, we have thus achieved the enantioselective synthesis of (−)-incarvilline (**1**) starting with (*S*)-cyclopentenone **6**, which converted to the 2,3,4-trisubstituted cyclopentanone **9** by a three-component coupling reaction using an alkenylstannane. The synthetic route to **1**



Scheme 3.

utilizing **9** as a key intermediate employs an intramolecular enone–olefin [2+2] photocycloaddition followed by a SmI_2-induced cyclobutane ring-opening reaction.

References and notes

1. Chi, Y.-M.; Yan, W.-M.; Chen, D.-C.; Noguchi, H.; Iitaka, Y.; Sankawa, U. *Phytochemistry* **1992**, *31*, 2930–2932.
2. Chi, Y.-M.; Yan, W.-M.; Li, J.-S. *Phytochemistry* **1990**, *29*, 2376–2378.
3. Nakamura, M.; Chi, Y.-M.; Yan, W.-M.; Nakasugi, Y.; Yoshizawa, T.; Irino, N.; Hashimoto, F.; Kinjo, J.; Nohara, T.; Sakurada, S. *J. Nat. Prod.* **1999**, *62*, 1293–1294.
4. Chi, Y.-M.; Hashimoto, F.; Yan, W.-M.; Nohara, T.; Yamashita, M.; Marubayashi, N. *Chem. Pharm. Bull.* **1997**, *45*, 495–498.
5. Ichikawa, M.; Takahashi, M.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2004**, *126*, 16553–16558.
6. For an extensive review of synthetic application of intramolecular enone–olefin photocycloadditions, see: Crimmins, M. T. *Chem. Rev.* **1988**, *88*, 1453–1473.
7. For a review on 'three-component coupling', see: Noyori, R.; Suzuki, M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 847–876.
8. For a review of reduction with samarium(II) iodide, see: Molander, G. A. *Org. React.* **1994**, *46*, 211–367.
9. For cyclobutane ring opening with SmI_2, see: (a) Commins, D. L.; Zheng, X. *J. Chem. Soc., Chem. Commun.* **1994**, 2681–2682; (b) Commins, D. L.; Zhang, Y.-M.; Zheng, X. *Chem. Commun.* **1998**, 2509–2510; (c) Commins, D. L.; Zheng, X.; Goehring, R. R. *Org. Lett.* **2002**, *4*, 1611–1613; (d) Shipe, W. D.; Sorensen, E. J. *Org. Lett.* **2002**, *4*, 2063–2066.
10. For a review, see: Shintou, T.; Kikuchi, W.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1645–1667.