JOC*Article*

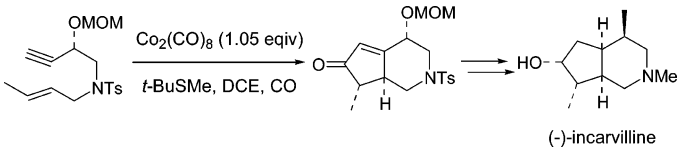
Diastereoselective Formal Synthesis of a Monoterpene Alkaloid, (−)-Incarvilline

Toshio Honda* and Kyosuke Kaneda

Faculty of Pharmaceutical Sciences, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142-8501, Japan

honda@hoshi.ac.jp

Received May 9, 2007



Diastereoselective formal synthesis of a monoterpene alkaloid, (−)-incarvilline, the key intermediate for the synthesis of (−)-incarvillateine, was achieved by using an intramolecular Pauson−Khand reaction of (*S*)-*N*-[(*E*)-2-butenyl]-*N*-(3-butynyl-2-methoxymethoxy)-*p*-toluenesulfonamide as a key step.

Introduction

Recent investigations of the plant *Incarvilla sinensis*,[1] which has been used to treat rheumatism and relieve pain as a traditional Chinese medicine, led to the isolation of a various types of monoterpene alkaloids with a wide range of structural and stereochemical features. Among them, incarvillateine **1** carrying a characteristic cyclobutane ring has been recognized to exhibit significant antinociceptive activity in a formalin-induced pain model in mice.[2] It is also suggested that the antinociceptive effect arose from the activation of μ- and κ-opioid receptors and adenosine receptor[3] (Figure 1).

Incarvillateine **1** was supposed to generate biosynthetically via dimerization of incarvine C **2**, a hydroxycinnamate derivative of a monoterpene alkaloid, incarvilline **3**. In fact, the first total synthesis of incarvillateine **1** using photochemical dimerization of a hydroxycinnamic acid derivative, followed by esterification with (+)-6-*epi*-incarvilline, was achieved by Kibayashi and co-workers.[4]

Thus, development of a new synthetic strategy for incarvilline **3**[5] would be an important research subject directed at searching potential antinociceptive compounds related to incarvillateine. To the best our knowledge, two total syntheses[4,6] and one synthetic approach[7] for **3** have been reported to date.

As part of our continuing effort to synthesize biologically active natural products, we are also interested in a diastereoselective synthesis of (−)-incarvilline. Our retrosynthetic analysis was depicted in Scheme 1, where we decided to exploit an intramolecular Pauson−Khand reaction[8] of (*S*)-*N*-[(*E*)-2-butenyl]-*N*-(3-butynyl-2-methoxymethoxy)-*p*-toluenesulfonamide as a key step, since the relative stereochemistry between the 7- and 7a-positions should be controlled by employing *E*-olefin as the starting material. The desired absolute configuration at the 7a-position should also be constructed, stereoselectively, with reflecting stereochemistry at the 4-position by assuming steric repulsion between the propargylic substituent and dicobalt−alkyne carbonyl complex generated in the intermediate of this

* Corresponding author. Tel: +81 (0)3 5498 5791. Fax: +81 (0)3 3787 0036.

(1) Chi, Y.; Yan, W.-M.; Li, J.-S. *Phytochemistry* **1990**, *29*, 2376−2378.

(2) 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.

(3) Chi, Y.; Nakamura, M.; Yoshizawa, T.; Zhao, X-Y.; Yan, W.-M.; Hashimoto, F.; Kinjo, J.; Nohara, T.; Sakurada, S. *Biol. Pharm. Bull*. **2005**, *28*, 1989−1991.

(4) Ichikawa, M.; Takahashi, M.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc*. **2004**, *126*, 16553−16558.

(5) (a) Chi, Y.-M.; Yan, W.-M.; Chen, D.-C.; Noguchi, H.; Iitaka, Y.; Sankawa, U. *Phytochemistry* **1992**, *31*, 2930−2932. (b) Chi, Y.-M.; Hashimoto, F.; Yan, W.-M.; Nohara, T.; Yamashita, M.; Marubayashi, N. *Chem. Pharm. Bull*. **1997**, *45*, 495−498.

(6) Ichikawa, M.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **2005**, *46*, 2327−2329.

(7) Hong, B.-C.; Gupta, A. K.; Wu, M.-F.; Liao, J.-H.; Lee. G.-H. *Org. Lett*. **2003**, *5*, 1689−1692.

(8) (a) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E. *J. Chem. Soc., Chem. Commun*. **1971**, 36. (b) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E.; Foreman, M. I. *J. Chem. Soc., Perkin Trans. 1* **1973**, 977−981. (c) Exon, C.; Magnus, P. *J. Am. Chem. Soc*. **1983**, *105*, 2477−2478. (d) Magnus, P.; Principe, L. M. *Tetrahedron Lett.* **1985**, *26*, 4851−4854. For recent reviews, see also: (e) Schore, N. E. *Org. React*. **1991**, *40*, 1−90. (f) Frühauf, H.-W. *Chem. Rev*. **1997**, *97*, 523−596. (g) Geis, O.; Schmalz, H.-G. *Angew. Chem., Int. Ed*. **1998**, *37*, 911−914. (h) Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263−3283. (i) Fletcher, A. J.; Christie, S. D. R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1657−1668. (j) Blanco-Urgoiti, J.; Anorbe, L.; Perez-Serrano, L.; Dominguez, G.; Perez-Castells, J. *Chem. Soc. Rev*. **2004**, *33*, 32−42. (k) Boñaga, L. V. R.; Krafft, M. E. *Tetrahedron* **2004**, *60*, 9795−9833.

10.1021/jo0709091 CCC: $37.00
Published on Web 07/21/2007

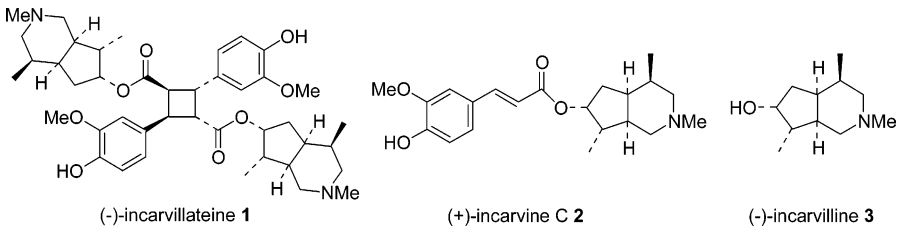
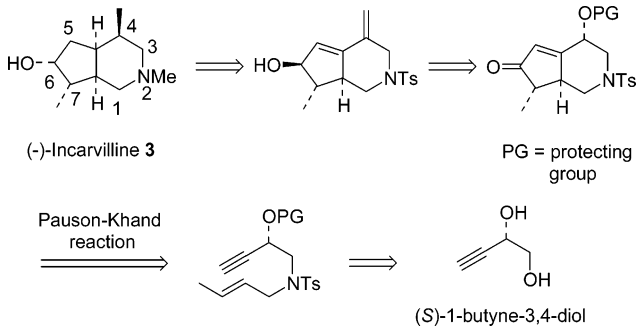
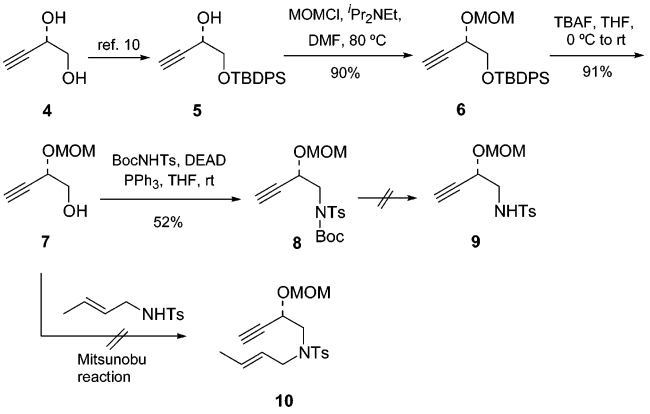


FIGURE 1. 1. Structure of typical alkaloids in *Incarvillea sinensis*.

SCHEME 1. Retrosynthetic Analysis for 3



SCHEME 2. Attempted Preparation of the Precursor for Pauson−Khand Reaction



reaction. Similar diastereoselectivity for an intramolecular Pauson−Khand reaction of enynes having a substituent at the propargylic position to construct a bicyclic cylopentenone system has been observed in previous works.[9] Moreover, it has been known that the methyl group at the 4-position could be derived from the corresponding alkene by catalytic reduction,[4] which could be available from the ketone as a precursor (Scheme 1). It is noteworthy that Schore and his colleauges reported a similar methodology in the synthesis of racemic tecomanine,[10] where they isolated the cycloaddition products in up to 16% yield with diastereoselectivity opposite to our assumption and also to the results of the previous works.[9]

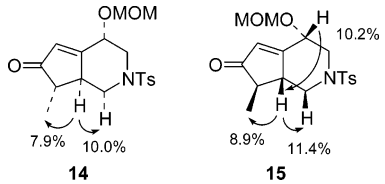


FIGURE 2. 2. Structure determination of **14** and **15** (observed NOEs are indicated by arrows).

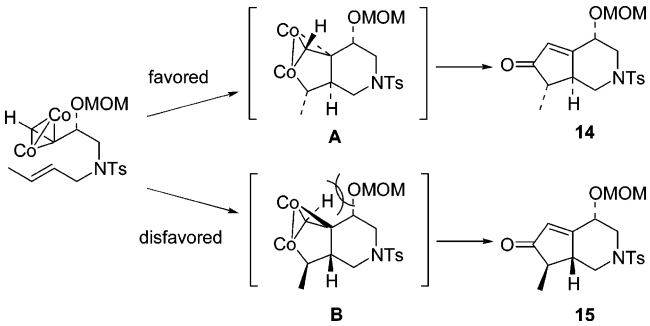


FIGURE 3. 3. Intermediates for Pauson−Khand reaction.

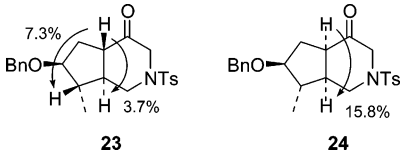


FIGURE 4. 4. Structure determination of **23** and **24** (observed NOEs are indicated by arrows).

Results and Discussion

Given these considerations, our synthesis of a monoterpene alkaloid, (−)-incarvilline, commenced with the synthesis of the known (*S*)-4-*tert*-butyldimethylsiloxy-1-butyn-3-ol **5**,[11] which was readily accessible via the known (*S*)-1-butyne-3,4-diol **4** from D-(−)-mannitol. Methoxymethylation of (*S*)-4-*tert*-butyldimethylsiloxy-1-butyn-3-ol **5** with chloromethyl methyl ether afforded methoxymethyl ether **6** in good yield. Desilylation of **6** with tetrabutylammonium fluoride gave alcohol **7** in 91% yield.

Introduction of butenylamino group was first attempted by treatment of **7** with *N*-(2*E*)-2-butenyl-*p*-toluenesulfonamide under the Mitsunobu reaction conditions.[12] However, none of the desired product **10** could be isolated, unfortunately. Although reaction of **7** with *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide gave the desired tosylamide **8**, subsequent deprotection of the

(9) (a) Jeong, N.; Lee, B. Y.; Lee, S. M.; Chung, Y. K.; Lee, S.-G. *Tetrahedron Lett.* **1993**, *34*, 4023−4026. (b) Clive, D. L. J.; Cole, D. C.; Tao, Y. *J. Org. Chem.* **1994**, *59*, 1396−1406. (c) Krafft, M. E.; Chirico, X. *Tetrahedron Lett.* **1994**, *35*, 4511−4514. (d) Mukai, C.; Uchiyama, M.; Sakamoto, S.; Hanaoka, M. *Tetrahedron Lett.* **1995**, *36*, 5761−5764. (e) Mukai, C.; Kim, J. S.; Uchiyama, M.; Hanaoka, M. *Tetrahedron Lett.* **1998**, *39*, 7909−7912. (f) Günter, M.; Gais, H.-J. *J. Org. Chem.* **2003**, *68*, 8037−8041. (g) Mukai, C.; Kozuka, T.; Suzuki, Y.; Kim, I. J. *Tetrahedron* **2004**, *60*, 2497−2507. (h) Nomura, I.; Mukai, C. *J. Org. Chem.* **2004**, *69*, 1803−1812.

(10) Ockey, D. A.; Lewis, M. A.; Schore, N. E. *Tetrahedron* **2003**, *59*, 5377−5381.

(11) Gooding, O. W.; Beard, C. C.; Jackson, D. Y.; Wren, D. L.; Cooper, G. F. *J. Org. Chem.* **1991**, *56*, 1083−1088.

(12) (a) Mitsunobu, O. *Synthesis* **1981**, 1−28. (b) Tsunoda, T.; Yamamiya, Y.; Ito, S. *Tetrahedron Lett.* **1993**, *34*, 1639−1642.

SCHEME 3. Preparation of the Precursor 10 for Pauson−Khand Reaction

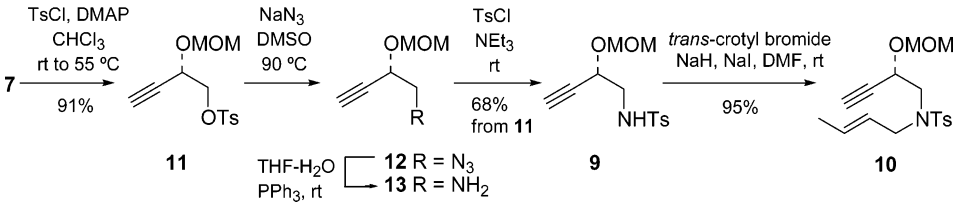
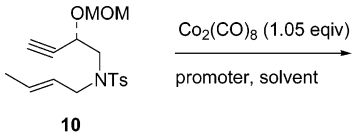
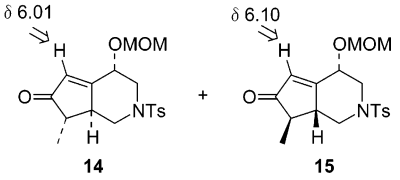


TABLE 1. Pauson−Khand Reaction of 10





						yield (%)	
entry	promoter (equiv)	solvent	atm	*T* (°C)	time (h)	**14**	**15**
1	none	toluene	Ar	110	2	54	7
2	NMO (10)	CH_2Cl_2	Ar	rt	9	45	5
3	*n*-BuSMe (3.5)	DCE	Ar	83	24	58	7
4	*n*-BuSMe (3.5)	DCE	CO	83	2.5	66	7
5	*t*-BuSMe (3.5)	DCE	Ar	83	2.5	62	6
6	*t*-BuSMe (3.5)	DCE	CO	83	2.5	73	8

Boc group did not provide the corresponding amide **9** under various reaction conditions (Scheme 2).

For preparation of the requisite enyne amide **10**, alcohol **7** was converted to tosylate **11** in 91% yield. Treatment of **11** with sodium azide in DMSO gave azide **12**, which without further purification, was subjected to the Staudinger reaction[13] with triphenylphosphine in aqueous THF and subsequent tosylation of the resulting amine **13** with tosyl chlroride to provide tosylamide **9** in 68% yield from **11**. *N*-Alkylation of **9** with *trans*-crotyl bromide in the presence of NaH in DMF provided the desired amide **10** in 95% yield (Scheme 3).

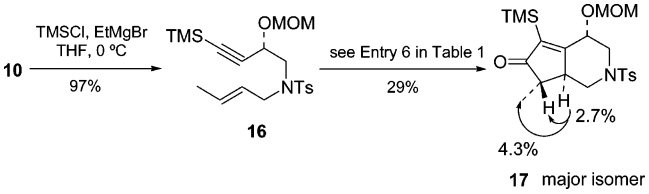
With the desired compound **10** in hand, a study was made for the best conditions for the intramolecular Pauson−Khand reaction, and the results obtained are summarized in Table 1.

First, enyne **10** was treated with 1.05 equiv of dicobalt octacarbonyl [$Co_2(CO)_8$] in toluene at 110 °C for 2 h under argon to furnish bicyclo compounds **14** and **15** in 54 and 7% yields, respectively (entry 1). The stereochemistry of the minor product **15** was assumed to have 7*R*-methyl and 7a*R*-hydrogen based on the analysis of its ^{1}H NMR and 2D-NMR spectral data, in which NOEs were observed between 4-H and 7a-H, and also 7-methyl and 7a-H as shown in Figure 2. Thus, the major product **14** was confirmed to have the desired stereochemistry for the synthesis of the target compound.

To improve the isolation yield and diastereoselectivity, the Pauson−Khand reaction was further investigated in the presence of a promoter.

When **10** was treated with 1.05 equiv of $Co_2(CO)_8$ in CH_2Cl_2 in the presence of 10 equiv of *N*-methylmorpholine oxide (NMO)[14] under argon, the reaction was found to proceed at ambient temperature; however, the yield was decreased to 50% with a formation of **14**/**15** in a ratio of 9:1 (entry 2).

SCHEME 4. Preparation and Attempted Pauson−Khand Reaction of 16



By changing a promoter to butyl methyl sulfides,[15] a similar reaction was carried out in refluxing dichloroethane (DCE) under argon to give **14** in slightly better yield (entries 3 and 5). The best result was obtained when the reaction was carried out by employing 1.05 equiv of $Co_2(CO)_8$ in refluxing DCE in the presence of 3.5 equiv of *tert*-butyl methyl sulfide as the promoter for 2.5 h under an atmosphere of CO to give **14** in 73% yield together with **15** in 8% yield (entry 6).

The diastereoselectivity can be rationalized by assuming that the cyclization would proceed through the sterically favored intermediate (**A**) leading to **14**, rather than the intermediate (**B**), in which the steric repulsion between MOM and dicobalt complex moieties was observed, as shown in Figure 3.

Similar diastereoselectivity was also observed by several groups.[9] In 1998, Mukai and his colleauges indicated that introduction of sterically bulky trimethylsilyl group at the terminal alkyne could improve the diastereoselectivity.[9e] However, they also noted that the yields were generally decreased and diastereoselectivities obtained were varied with the substitution patterns of the starting materials.

Thus, we prepared trimethylsilyl derivative **16** by silylation of **10** with trimethylsilyl chloride in the presence of ethylmagnesium bromide as the base in 97% yield to investigate its diastereoselectivity. Attempted intramolecular Pauson−Khand reaction of **16** under the same reaction conditions as entry 6 in Table 1 gave a mixture of diastereoisomers **17** in 29% yield in a ratio of 1:3. Although the observed diastereoselectivity was moderate, unfortunately, our results were not in agreement with their observations. The poor yield of cycloaddition was rationalized by the presence of steric repulsion between trimethylsilyl and methoxymethyloxy groups in the intermediate (Scheme 4).

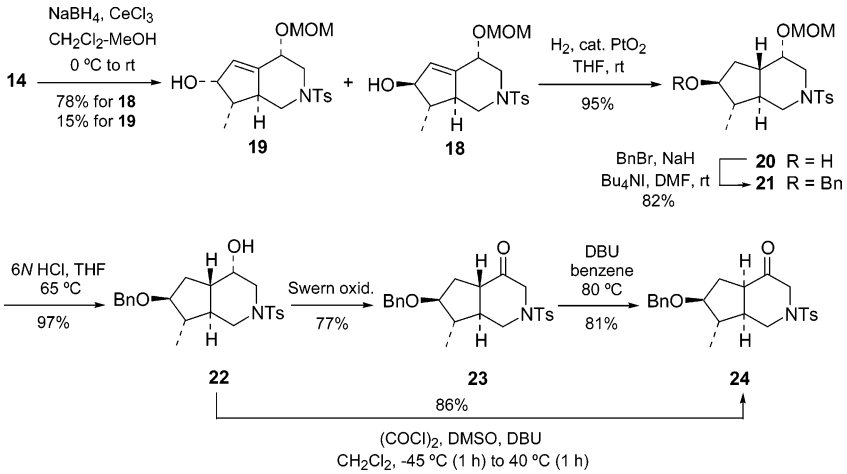
Since construction of a basic skeleton for the target compound was established diastereoselectively, our attention was focused on conversion of **14** to incarvilline.

(13) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635−646.

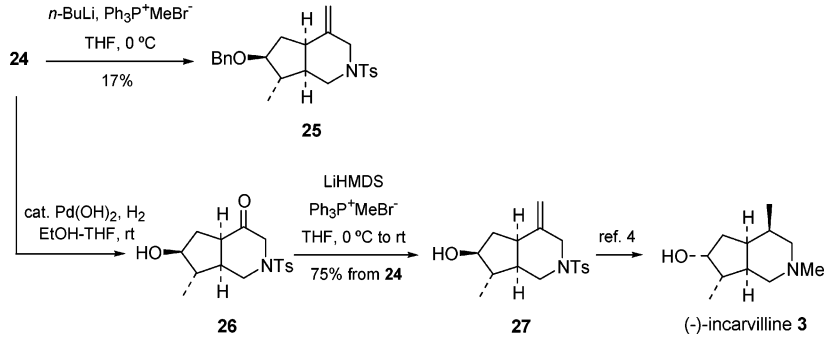
(14) Shambayati, S.; Crowe, W. E.; Schrieber, S. L. *Tetrahedron Lett.* **1990**, *31*, 5289−5292.

(15) (a) Sugihara, T.; Yamaguchi, M.; Nishizawa, M. *J. Synth. Org. Chem., Jpn* **1999**, *57*, 158−169. (b) Sugihara, T.; Yamada, M.; Yamaguchi, M.; Nishizawa, M. *Synlett* **1999**, 771−773.

SCHEME 5. Preparation of 24



SCHEME 6. Synthesis of a Key Intermediate for (−)-Incarvilline 3



Luche reduction[16] of **14** afforded β-alcohol **18** in 78% yield as a major compound together with its diastereoisomer **19** in 15% yield. Further reduction of the major compound **18** over platinum oxide gave *trans*-fused compound as the sole product **20** in 95% yield.

Although the stereochemistry of **20** could not be determined at this stage, alcohol **20** was transformed to **22** via benzyl ether **21** by changing protecting groups in good yield. Swern oxidation of **22** gave ketone **23**, which on treatment with 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in benzene furnished the thermodynamically stable *cis*-fused compound **24** in 62% yield from **22**. It is noteworthy that conversion of **22** to **24** could be achieved in one step by changing the base from triethylamine to DBU in Swern oxidation of **22** in 86% yield (Scheme 5).

By measuring NOEs for compounds **23** and **24**, the stereochemistries of both compounds were unambiguously determined as depicted in Figure 4.

In order to introduce a methyl group at the 4-position, ketone **24** was subjected to the Wittig reaction on treatment with methyltriphenylphosphonium bromide in the presence of base under various reaction conditions; however, the desired olefin **25** was isolated in poor yield (up to 17%). Attempted Peterson olefination,[17] Takai−Nozaki methylenation,[18] and olefination with Tebbe reagent[19] for **24** were also found to be unsuccessful. Since we thought that the sterically bulky benzyl group might prevent the attack of reagents to **24** in these reactions, the benzyl group was removed prior to the Wittig reaction by hydrogenolysis with palladium hydroxide under hydrogen to give alcohol **26**.

Finally, Wittig reaction of **26** with 6 equiv of methyltriphenylphosphonium bromide in the presence of lithium hexamethyldisilazide afforded the known olefin **27** in 75% yield. The physicochemical properties of **27** including its specific optical rotation were identical to those reported in the literature.[4] **27**: $[\alpha]_D$ −30.0 (c = 0.61, $CHCl_3$) [lit.,[4] $[\alpha]_D$ −33.6 (c = 0.61, $CHCl_3$)] (Scheme 6).

Since this compound **27** was already transformed to (−)-incarvilline **3** in a few steps involving the reduction of olefin and the inversion of secondary hydroxyl group by Kibayashi, this synthesis constitutes its formal synthesis.

Conclusion

In summary, we have established diastereoselective formal synthesis of a monoterpene alkaloid, (−)-incarvilline, by employing an intramolecular Pauson−Khand reaction of the corresponding enyne amide as a key step. In this synthesis, the stereochemistry at the 7- and 7a-positions of the target compound was controlled with reflecting the stereochemistry at the 4-position providing the desired absolute configuration, by employing *E*-olefin as the starting material. We believe that the strategy developed here should be a useful tool for finding potential compounds that are biologically related to analgesic agent, incarvillateine.

(16) (a) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226−2227. (b) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454−5459.
(17) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780−784.
(18) Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc., Jpn.* **1980**, *53*, 1698−1702.
(19) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611−3613.

Experimental Section

(*S*)-3-Butynyl-2-methoxymethoxy-1-*p*-toluenesulfonate (11). A solution of **7** (431 mg, 3.32 mmol) and *p*-toluenesulfonyl chloride (1.26 g, 6.63 mmol) in $CHCl_3$ (13 mL) in the presence of Et_3N (1.38 mL, 9.95 mmol) was stirred at ambient temperature for 10 h. To this solution was added *N*,*N*-dimethylaminopyridine (40 mg, 0.33 mmol), and the resulting solution was stirred at 55 °C for 6 h. The mixture was treated with saturated NH_4Cl solution and extracted with $CHCl_3$. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane−EtOAc (3:1, v/v) gave tosylate **11** (853 mg, 91%) as a colorless oil: $[\alpha]^{28}_D$ +91.8 (*c* 1.00, $CHCl_3$); IR cm^{-1} 3280, 2960, 2895, 2119, 1599, 1360, 1178; ^1H NMR (270 MHz, $CDCl_3$) δ 7.83−7.78 (m, 2H), 7.37−7.34 (m, 2H), 4.84 (d, J = 6.9 Hz, 1H), 4.58 (d, J = 6.9 Hz, 1H), 4.56 (ddd, J = 7.3, 4.4, 2.1 Hz, 1H), 4.19 (dd, J = 10.5, 4.4 Hz, 1H), 4.13 (dd, J = 10.5, 7.3 Hz, 1H), 3.35 (s, 3H), 2.46 (s, 3H), 2.44 (d, J = 2.1 Hz, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 145.0, 132.7, 129.8, 127.9, 94.2, 77.6, 75.7, 70.4, 63.5, 55.7, 21.6; HRMS *m*/*z* (EI) calcd for $C_{13}H_{16}O_5S$ (M^+) 284.0718, found 284.0728.

(*S*)-*N*-(3-Butynyl-2-methoxymethoxy)-*p*-toluenesulfonamide (9). To a stirred solution of **11** (3.80 g, 13.38 mmol) in DMSO (45 mL) was added sodium azide (2.61 g, 40.14 mmol) at 90 °C, and the mixture was stirred for 2 h at the same temperature. After being cooled to room temperature, the mixture was treated with water and extracted with Et_2O. The ethereal solution was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave azide **12**, which without further purification was dissolved into THF−H_2O (1:1, 54 mL). After addition of triphenylphosphine (3.51 g, 13.38 mmol) to this solution, the mixture was stirred at ambient temperature for 1.5 h. To this mixture were successively added THF (27 mL), triethylamine (5.6 mL, 40.14 mmol), and *p*-toluenesulfonyl chloride (5.08 g, 26.76 mmol), and the whole was stirred at the same temperature for further 2 h. The mixture was treated with saturated NH_4Cl solution and extracted with Et_2O. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane−$CHCl_3$ (4:1, v/v) gave tosylamide **9** (2.53 g, 68% from **11**) as a colorless oil: $[\alpha]^{28}_D$ +115.3 (*c* 1.01 $CHCl_3$); IR cm^{-1} 3275, 2945, 2895, 2120, 1599, 1330, 1160; ^1H NMR (270 MHz, $CDCl_3$) δ 7.78−7.74 (m, 2H), 7.33−7.30 (m, 2H), 5.05−5.01 (m, 1H), 4.84 (d, J = 6.9 Hz, 1H), 4.56 (d, J = 6.9 Hz, 1H), 4.35 (ddd, J = 5.1, 4.3, 2.0 Hz, 1H), 3.35 (s, 3H), 3.32 (ddd, J = 13.2, 7.9, 4.3 Hz, 1H), 3.16 (ddd, J = 13.2, 7.9, 5.1 Hz, 1H), 2.44 (d, J = 2.0 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 143.6, 136.9, 129.7, 127.0, 94.4, 79.2, 75.4, 64.7, 56.0, 47.0, 21.5; HRMS *m*/*z* (EI) calcd for $C_{13}H_{17}NO_4S$ (M^+) 283.0878, found 283.0900.

(*S*)-*N*-[(*E*)-2-Butenyl]-*N*-(3-butynyl-2-methoxymethoxy)-*p*-toluenesulfonamide (10). A suspension of **9** (2.19 g, 7.74 mmol) and sodium hydride (325 mg, 8.13 mmol) in DMF (26 mL) was stirred at room temperature for 10 min under argon. To this mixture was added *trans*-crotyl bromide (1.03 mL, 8.51 mmol), and the whole was stirred for a further 10 min at the same temperature. The mixture was treated with saturated NH_4Cl solution and extracted with Et_2O. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane−EtOAc (3:1, v/v) gave enyne **10** (2.46 g, 95%) as a pale yellowish oil: $[\alpha]^{28}_D$ +108.1 (*c* 1.00, $CHCl_3$); IR cm^{-1} 3270, 2940, 2895, 2116, 1599, 1495, 1340, 1160; ^1H NMR (270 MHz, $CDCl_3$) δ 7.73−7.70 (m, 2H), 7.30 (d, J = 8.1 Hz, 2H), 5.68−5.53 (m, 1H), 5.25−5.15 (m, 1H), 4.87 (d, J = 6.8 Hz, 1H), 4.64−4.55 (m, 1H), 4.56 (d, J = 6.8 Hz, 1H), 4.05−3.81 (m, 2H), 3.44−3.36 (m, 2H), 3.33 (s, 3H), 2.45 (d, J = 2.1 Hz, 1H), 2.43 (s, 3H), 1.63 (dd, J = 6.3, 1.3 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 143.2, 137.3, 131.2, 130.0, 127.3, 125.0, 94.3, 75.0, 65.4, 55.8, 51.1, 50.0, 45.5, 21.5, 17.6; HRMS *m*/*z* (EI) calcd for $C_{17}H_{24}NO_4S$ (M^+ + H) 338.1426, found 338.1414.

(4*S*,7*S*,7a*S*)-4-Methoxymethoxy-7-methyl-2-(*p*-toluenesulfonyl)-1,2,3,4,7,7a-hexahydro-6*H*-cyclopenta[*c*]pyridin-6-one (14) and (4*S*,7*R*,7a*R*)-4-Methoxymethoxy-7-methyl-2-(*p*-toluenesulfonyl)-1,2,3,4,7,7a-hexahydro-6*H*-cyclopenta[*c*]pyridin-6-one (15). A solution of **10** (100 mg, 0.297 mmol) in dichloroethane (3 mL) in the presence of dicobalt octacarbonyl (107 mg, 0.312 mmol) was heated at 83 °C under an atmospheric pressure of CO. To this mixture was added *t*-BuSMe (0.13 mL, 1.04 mmol), and the whole was stirred at the same temperature for a further 2.5 h. After being cooled to room temperature, the mixture was filtered through Celite pad to remove the insoluble materials. The filtrate was concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane−EtOAc (1:1, v/v) gave **14** (79.1 mg, 73%) and **15** (8.7 mg, 8%) as colorless needles, respectively.

14: mp 149−151 °C; $[\alpha]^{32}_D$ −146.4 (*c* = 1.00, $CHCl_3$); IR cm^{-1} 2920, 1704, 1634, 1599, 1499, 1460, 1340, 1160; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 6.01 (d, J = 0.9 Hz, 1H), 4.70 (d, J = 7.2 Hz, 1H), 4.61 (d, J = 7.2 Hz, 1H), 4.60 (m, 1H), 4.26−4.23 (m, 2H), 3.40 (s, 3H), 2.95−2.92 (m, 1H), 2.52 (dd, J = 13.1, 1.8 Hz, 1H), 2.43 (s, 3H), 2.06 (t, J = 11.5 Hz, 1H), 1.91 (dq, J = 7.5, 2.7 Hz, 1H), 1.21 (d, J = 7.5 Hz, 3H); ^{13}C NMR (125.65 MHz, $CDCl_3$) δ 209.1, 172.0, 143.9, 133.8, 129.8, 129.2, 127.4, 94.5, 67.6, 55.9, 51.8, 50.7, 45.2, 44.6, 21.5, 14.7; HRMS *m*/*z* (CI) calcd for $C_{18}H_{24}NO_5S$ (M^+ + H) 366.1376, found 366.1375. Anal. Calcd for $C_{18}H_{23}NO_5S$: C, 59.16; H, 6.34; N, 3.82. Found: C, 59.02; H, 6.49; N, 3.76.

15: mp 122−124 °C; $[\alpha]^{27}_D$ +158.1 (*c* = 1.01, $CHCl_3$); IR cm^{-1} 2935, 1714, 1634, 1599, 1499, 1460, 1348, 1165; ^1H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.3 Hz, 2H), 6.10 (t, J = 1.3 Hz, 1H), 4.78 (d, J = 6.7 Hz, 1H), 4.74 (d, J = 6.7 Hz, 1H), 4.58−4.54 (m, 1H), 4.26 (ddd, J = 11.0, 6.4, 1.7 Hz, 1H), 4.20 (ddd, J = 11.3, 6.1, 1.7 Hz, 1H), 3.41 (s, 3H), 2.72−2.68 (m, 1H), 2.44 (s, 3H), 2.23 (t, J = 11.0 Hz, 1H), 2.00 (t, J = 11.3 Hz, 1H), 1.98 (dq, J = 7.3, 2.4 Hz, 1H), 1.22 (d, J = 7.3 Hz, 3H); ^{13}C NMR (125.65 MHz, $CDCl_3$) δ 208.2, 176.3, 144.2, 133.4, 130.0, 127.4, 125.8, 95.9, 72.3, 56.0, 51.4, 50.6, 48.0, 44.4, 21.6, 14.8; HRMS *m*/*z* (EI) calcd for $C_{18}H_{23}NO_5S$ (M^+) 365.1290, found 365.1297. Anal. Calcd for $C_{18}H_{23}NO_5S$: C, 59.16; H, 6.34; N, 3.82. Found: C, 59.12; H, 6.30; N, 3.83.

(*S*)-*N*-[(*E*)-2-Butenyl]-*N*-(3-butynyl-2-methoxymethoxy-4-trimethylsilyl)-*p*-toluenesulfonamide (16). To a stirred solution of **10** (250 mg, 0.742 mmol) in THF (74 mL) was added ethylmagnesium bromide in 0. 91 M THF solution (4.08 mL, 3.71 mmol) at 0 °C under argon. After being stirred for 45 min, trimethylsiliyl chloride (0.94 mL, 7.42 mmol) was added to the mixture, and the resulting mixture was stirred for a further 10 min at the same temperature. The mixture was treated with saturated NH_4Cl solution and extracted with Et_2O. The ethereal layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane−EtOAc (8:1, v/v) gave trimethylsilyl compound **16** (295 mg, 97%) as a pale yellowish oil: $[\alpha]^{28}_D$ +115.9 (*c* 1.00, $CHCl_3$); IR cm^{-1} 2960, 2895, 2175, 1595, 1340, 1160; ^1H NMR (270 MHz, $CDCl_3$) δ 7.75−7.70 (m, 2H), 7.31−7.2 (m, 2H), 5.65−5.52 (m, 1H), 5.25−5.13 (m, 1H), 4.86 (d, J = 6.8 Hz, 1H), 4.61−4.53 (m, 2H), 4.05−3.83 (m, 2H), 3.43−3.32 (m, 2H), 3.32 (s, 3H), 2.43 (s, 3H), 1.64−1.61 (m, 3H), 0.16 (s, 9H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 143.1, 137.6, 131.0, 129.5, 127.3, 125.1, 101.9, 94.2, 92.0, 66.0, 55.7, 51.0, 49.9, 21.5, 17.6, 0.0; HRMS *m*/*z* (CI) calcd for $C_{20}H_{32}NO_4SiS$ (M^+ + H) 410.1821, found 410.1798.

(4*S*,7*R*/*S*,7a*R*/*S*)-4-Methoxymethoxy-7-methyl-2-(*p*-toluenesulfonyl)-5-trimethylsilyl-1,2,3,4,7,7a-hexahydro-6*H*-cyclopenta-[*c*]pyridin-6-one (17). The intramolecular Pauson−Khand reaction for **16** (150 mg, 0.367 mmol) was carried out for 48 h by using the same reaction conditions as for the preparation of **15** to give **17** (46 mg, 29%) as an inseparable mixture of diastereoisomers. Data

for the major isomer of **17**: IR cm^{-1} 2960, 1760, 1695, 1600, 1490; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69−7.66 (m, 2H), 7.35−7.32 (m, 2H), 4.79−4.78 (m, 1H), 4.72 (d, *J*=7.1 Hz, 1H), 4.59 (d, *J*=7.1 Hz, 1H), 4.26−4.20 (m, 2H), 3.40 (s, 3H), 2.98−2.92 (m, 1H), 2.48−2.47 (m, 1H), 2.43 (s, 3H), 2.04 (t, *J*=11.4 Hz, 1H), 1.84−1.78 (m, 1H), 1.17 (d, *J*=7.4 Hz, 3H), 0.20 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 213.1, 177.5, 143.8, 140.9, 133.6, 129.7, 127.5, 94.0, 67.2, 55.7, 52.1, 50.6, 46.4, 44.5, 21.5, 14.5, −0.7; HRMS *m/z* (EI) calcd for $C_{21}H_{31}NO_5SiS$ (M^+) 437.1692, found 437.1691.

(4*S*,6*R*,7*S*,7a*S*)-4-Methoxymethoxy-7-methyl-2-(*p*-toluenesulfonyl)-2,3,4,6,7,7a-hexahydro-1*H*-cyclopenta[*c*]pyridin-6-ol (18) and (4*S*,6*S*,7*S*,7a*S*)-4-Methoxymethoxy-7-methyl-2-(*p*-toluenesulfonyl)-2,3,4,6,7,7a-hexahydro-1*H*-cyclopenta[*c*]pyridin-6-ol (19). To a stirred solution of **14** (620 mg, 1.70 mmol) in CH_2Cl_2−MeOH (1:1) (17 mL) containing cerium chloride (210 mg, 0.85 mmol) was added sodium tetrahydroborate (107 mg, 2.55 mmol) portionwise at 0 °C, and the resulting mixture was stirred at ambient temperature for a further 15 min. The mixture was treated with saturated NH_4Cl solution and extracted with CH_2Cl_2. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with acetone−CH_2Cl_2 (1:8, v/v) gave alcohol **18** (487 mg, 78%) as a colorless oil, together with its diastereoisomer **19** (92 mg, 15%) as colorless powder.

18: $[\alpha]^{26}_D$ +2.6 (*c* 1.01, $CHCl_3$); IR cm^{-1} 3450, 2890, 1599, 1338, 1165; ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.65 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.3 Hz, 2H), 5.66 (s, 1H), 4.60 (d, J = 7.0 Hz, 1H), 4.58 (d, J = 7.0 Hz, 1H), 4.45 (br d, J = 4.9 Hz, 1H), 4.29 (dd, J = 2.1, 1.8 Hz, 1H), 4.09 (ddd, J = 12.5, 2.1, 1.8 Hz, 1H), 4.03 (ddd, J = 11.1, 6.4, 1.8 Hz, 1H), 3.38 (s, 3H), 2.60−2.55 (m, 1H), 2.43 (dd, J = 12.5, 1.8 Hz, 1H), 2.43 (s, 3H), 1.99 (t, J = 11.1 Hz, 1H), 1.79 (m, 1H), 1.58−1.52 (m, 1H), 1.18 (d, J = 6.9 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 143.5, 141.2, 133.6, 131.3, 129.6, 127.5, 93.3, 83.7, 67.0, 55.5, 52.5, 50.9, 47.4, 47.0, 21.5, 17.1; HRMS *m/z* (EI) calcd for $C_{18}H_{25}NO_5S$ (M^+) 367.1453, found 367.1479.

19: mp 113−114 °C; $[\alpha]^{29}_D$ −91.1 (*c* 1.01, $CHCl_3$); IR cm^{-1} 3420, 2890, 1599, 1340, 1162; ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.66 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 5.84 (dd, J = 2.1, 1.8 Hz, 1H), 4.65 (d, J = 7.1 Hz, 1H), 4.62 (d, J = 7.1 Hz, 1H), 4.43 (br t, J = 6.1 Hz, 1H), 4.30 (dd, J = 2.1, 1.8 Hz, 1H), 4.18−4.14 (m, 1H), 4.09 (dt, J = 12.5, 1.8 Hz, 1H), 3.39 (s, 3H), 2.71−2.66 (m, 1H), 2.42 (s, 3H), 2.35 (dd, J = 12.5, 2.1 Hz, 1H), 1.86 (t, J = 11.2 Hz, 1H), 1.77−1.70 (m, 1H), 1.43 (br s, 1H), 1.11 (d, J = 7.2 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 144.4, 143.4, 133.9, 130.7, 129.6, 127.5, 93.7, 76.8, 67.6, 55.6, 52.3, 50.6, 45.7, 41.9, 21.5, 12.5; HRMS *m/z* (EI) calcd for $C_{18}H_{25}NO_5S$ (M^+) 367.1453, found 367.1483. Anal. Calcd for $C_{18}H_{25}NO_5S$: C, 58.83; H, 6.86; N, 3.81. Found: C, 58.93; H, 6.78; N, 3.75.

(4*S*,4a*S*,6*S*,7*S*,7a*S*)-4-Methoxymethoxy-7-methyl-2-(*p*-toluenesulfonyl)octahydro-1*H*-cyclopenta[*c*]pyridin-6-ol (20). A solution of **18** (102 mg, 0.278 mmol) in THF (5 mL) in the presence of PtO_2 (0.63 mg, 2.78×10^{-3} mmol) was stirred at room temperature for 4.5 h under hydrogen. After removal of the insoluble material by filtration through a Celite pad, the filtrate was concentrated to leave a residue, which was purified by column chromatography on silica gel. Elution with hexane/AcOEt (1:1, v/v) gave alcohol 20 (97 mg, 95%) as the sole product, as a colorless oil: $[\alpha]^{26}_D$ −57.5 (*c* 1.00, $CHCl_3$); IR cm^{-1} 3500, 2955, 2930, 2895, 1599, 1460, 1342, 1162; ^1H NMR (270 MHz, $CDCl_3$) δ 7.65 (d, J = 7.9 Hz, 2H), 7.32 (d, J = 7.9 Hz, 2H), 4.76 (d, J = 7.1 Hz, 1H), 4.62 (d, J = 7.1 Hz, 1H), 4.08−3.95 (m, 2H), 3.91−3.87 (m, 1H), 3.80 (m, 1H), 3.42 (s, 3H), 2.43 (s, 3H), 2.25 (dd, J = 12.6, 1.6 Hz, 1H), 2.05 (t, J = 10.6 Hz, 1H), 2.02−1.89 (m, 1H), 1.68−1.47 (m, 4H), 1.37−1.23 (m, 1H), 1.10 (d, J = 6.6 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 143.4, 133.6, 129.5, 127.4, 95.5, 79.3, 70.0, 55.7, 50.3, 49.2, 46.6, 45.2, 42.5, 34.9, 21.4, 16.2; HRMS *m/z* (CI) calcd for $C_{18}H_{28}NO_5S$ (M^+ + H) 370.1688, found 370.1713.

(4*S*,4a*S*,6*S*,7*S*,7a*S*)-6-Benzyloxy-4-methoxymethoxy-7-methyl-2-(*p*-toluenesulfonyl)octahydro-1*H*-cyclopenta[*c*]pyridine (21). A solution of **20** (910 mg, 2.47 mmol), tetrabutylammonium iodide (182 mg, 0.49 mmol), and benzyl bromide (0.61 mL, 5.43 mmol) in DMF (12.3 mL) in the presence of sodium hydride (296 mg, 7.40 mmol) was stirred at ambient temperature for 7 h. The mixture was treated with saturated NH_4Cl solution and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane−EtOAc (3:1, v/v) gave benzyl ether **21** (934 mg, 82%) as a colorless oil: $[\alpha]^{26}_D$ −30.0 (*c* 1.00, $CHCl_3$); IR cm^{-1} 2952, 2928, 2892, 1599, 1494, 1456, 1345, 1165; ^1H NMR (270 MHz, $CDCl_3$) δ 7.64 (d, J = 8.2 Hz, 2H), 7.31−7.21 (m, 7H), 4.76 (d, J = 6.9 Hz, 1H), 4.61 (d, J = 6.9 Hz, 1H), 4.48 (d, J = 11.8 Hz, 1H), 4.39 (d, J = 11.8 Hz, 1H), 4.06 (d, J = 12.5 Hz, 1H), 3.99 (dd, J = 10.6, 3.2 Hz, 1H), 3.81 (br s, 1H), 3.59 (br t, J = 5.0 Hz, 1H), 3.41 (s, 3H), 2.40 (s, 3H), 2.23 (d, J = 12.5 Hz, 1H), 2.04 (t, J = 10.6 Hz, 1H), 1.44−1.97 (m, 5H), 1.09 (d, J = 6.4 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 143.2, 138.3, 133.5, 129.4, 128.2, 128.2, 127.4, 127.3, 95.4, 86.1, 71.2, 69.9, 55.6, 50.3, 49.1, 45.2, 44.2, 42.3, 31.5, 21.3, 16.8; HRMS *m/z* (EI) calcd for $C_{25}H_{33}NO_5S$ (M^+) 459.2079, found 459.2079.

(4*S*,4a*S*,6*S*,7*S*,7a*S*)-6-Benzyloxy-7-methyl-2-(*p*-toluenesulfonyl)octahydro-1*H*-cyclopenta[*c*]pyridin-4-ol (22). A solution of **21** (454 mg, 0.99 mmol) in THF (10 mL) and 6 N HCl (2 mL) was heated at 65 °C for 2 h. After being cooled to 0 °C, the solution was treated with saturated sodium hydrogen carbonate solution and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane−EtOAc (2:1, v/v) gave alcohol **22** (397 mg, 97%) as colorless needles: mp 135−136 °C; $[\alpha]^{25}_D$ −43.5 (*c* 1.00, $CHCl_3$); IR cm^{-1} 3450, 2951, 2940, 2898, 2870, 1599, 1494, 1460, 1345, 1163; ^1H NMR (270 MHz, $CDCl_3$) δ 7.65 (d, J = 8.2 Hz, 2H), 7.34−7.25 (m, 7H), 4.49 (d, J = 11.7 Hz, 1H), 4.39 (d, J = 11.7 Hz, 1H), 4.01−3.87 (m, 3H), 3.61−3.57 (m, 1H), 2.43 (s, 3H), 2.38 (dd, J = 12.3, 1.4 Hz, 1H), 2.16 (t, J = 7.9 Hz, 1H), 2.06 (t, J = 10.4 Hz, 1H), 1.87−1.68 (m, 2H), 1.55−1.50 (m, 3H), 1.11 (d, J = 6.1 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 143.7, 138.4, 133.4, 129.7, 128.3, 127.58, 127.51, 127.48, 86.1, 71.4, 64.9, 52.6, 50.7, 46.1, 44.3, 42.1, 31.7, 21.5, 17.0; HRMS *m/z* (CI) calcd for $C_{23}H_{30}NO_4S$ (M^+ + H) 416.1895, found 416.1872. Anal. Calcd for $C_{23}H_{29}NO_4S$: C, 66.48; H, 7.03; N, 3.39. Found: C, 66.27; H, 6.59; N, 3.36.

(4a*S*,6*S*,7*S*,7a*S*)-6-Benzyloxy-7-methyl-2-(*p*-toluenesulfonyl)-octahydro-4*H*-cyclopenta[*c*]pyridin-4-one (23). To a stirred solution of oxalyl chloride (80 μL, 0.90 mmol) in CH_2Cl_2 (3 mL) was added a solution of DMSO (98 μL, 1.38 mmol) in CH_2Cl_2 (1 mL) at −78 °C under argon, and the resulting solution was stirred at the same temperature for 10 min. A solution of **22** (287 mg, 0.69 mmol) in CH_2Cl_2 (3 mL) was added to the solution, and the whole was stirred at −45 °C for a further 1 h. The mixture was treated with triethylamine (0.39 mL, 2.77 mmol), and warmed to room temperature over a period of 20 min. The solution was treated with saturated NH_4Cl solution and extracted with $CHCl_3$. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane−acetone (3:1, v/v) gave ketone (**23**) (221 mg, 77%) as colorless needles: mp 113−115 °C; $[\alpha]^{25}_D$ +36.5 (*c* 1.00, $CHCl_3$); IR cm^{-1} 2960, 2878, 1732, 1599, 1458, 1494, 1345, 1162; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, J = 8.2 Hz, 2H), 7.36−7.27 (m, 7H), 4.51 (d, J = 11.8 Hz, 1H), 4.38 (d, J = 11.8 Hz, 1H), 3.86 (dd, J = 10.8, 5.2 Hz, 1H), 3.84 (d, J = 15.5 Hz, 1H), 3.56 (ddd, J = 8.1, 5.8, 2.7 Hz, 1H), 3.44 (d, J = 15.5 Hz, 1H), 2.85 (t, J = 10.8 Hz, 1H), 2.56 (ddd, J = 13.1, 10.4, 7.9 Hz, 1H), 2.44 (s, 3H), 1.97 (ddd, J = 14.2, 10.4, 8.1 Hz, 1H), 1.85 (ddd, J = 14.2, 7.9, 2.7 Hz, 1H), 1.82−1.75 (m, 1H), 1.50−1.42 (m, 1H), 1.10 (d, J = 6.7 Hz, 3H);

^{13}C NMR (67.8 MHz, $CDCl_3$) δ:202.6, 144.1, 134.0, 133.0, 129.9, 128.4, 127.7, 127.6, 127.5, 85.2, 71.6, 54.3, 52.9, 48.7, 47.3, 45.6, 28.7, 21.5, 16.6; HRMS *m*/*z* (EI) calcd for $C_{23}H_{27}NO_4S$ (M^+) 413.1661, found 413.1677. Anal. Calcd for $C_{23}H_{27}NO_4S$: C, 66.80; H, 6.58; N, 3.39. Found: C, 66.77; H, 6.48; N, 3.44.

(4a*R*,6*S*,7*S*,7a*S*)-6-Benzyloxy-7-methyl-2-(*p*-toluenesulfonyl)-octahydro-4*H*-cyclopenta[*c*]pyridin-4-one (24). Method A. A solution of **23** (220 mg, 0.53 mmol) and DBU (119 μL, 0.80 mmol) in benzene (5.3 mL) was heated at 80 °C for 30 min. After being cooled to room temperature, the mixture was treated with saturated NH_4Cl solution and extracted with $CHCl_3$. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a solid, which was recrystallized from EtOAc−Et_2O to give *cis*-compound **24** (178 mg, 81%) as colorless needles.

Method B (One Pot Procedure). To a stirred solution of oxalyl chloride (76 μL, 0.89 mmol) in CH_2Cl_2 (3 mL) was added a solution of DMSO (97 μL, 1.37 mmol) in CH_2Cl_2 (2 mL) at −78 °C under argon, and the resulting solution was stirred at the same temperature for 10 min. A solution of **22** (284 mg, 0.68 mmol) in CH_2Cl_2 (2 mL) was added to the solution, and the whole was stirred at −45 °C for a further 1 h. The mixture was treated with DBU (0.42 mL, 2.74 mmol) and stirred at room temperature for 2 h and also at 40 °C for 1 h. The solution was treated with saturated NH_4Cl solution and extracted with $CHCl_3$. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with $CHCl_3$−EtOAc (99:1, v/v) gave ketone **24** (242 mg, 86%) as colorless needles, which was identical with the authentic sample obtained by method A: mp 150−151 °C; $[\alpha]^{21}_D$ −14.8 (*c* 1.00, $CHCl_3$); IR cm^{-1} 2952, 2870, 1718, 1599, 1494, 1458, 1348, 1162; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, J = 8.2 Hz, 2H), 7.34−7.24 (m, 7H), 4.50 (d, J = 11.8 Hz, 1H), 4.36 (d, J = 11.8 Hz, 1H), 3.73 (dd, J = 17.1, 1.2 Hz, 1H), 3.53−3.46 (m, 3H), 2.83−2.75 (m, 2H), 2.44 (s, 3H), 2.36−2.29 (m, 1H), 2.22 (dt, J = 13.4, 5.9 Hz, 1H), 2.11−2.05 (m, 1H), 1.86−1.80 (m, 1H), 1.04 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125.65 MHz, $CDCl_3$) δ 205.8, 144.1, 138.3, 132.7, 129.9, 128.3, 127.68, 127.54, 127.50, 84.8, 70.9, 55.7, 47.8, 46.9, 44.2, 43.3, 31.4, 21.6, 17.2; HRMS *m*/*z* (EI) calcd for $C_{23}H_{27}NO_4S$ (M^+) 413.1661, found 413.1652. Anal. Calcd for $C_{23}H_{27}NO_4S$: C, 66.80; H, 6.58; N, 3.39. Found: C, 66.94; H, 6.65; N, 3.32.

(4a*R*,6*S*,7*S*,7a*R*)-6-Benzyloxy-7-methyl-4-methylene-2-(*p*-toluenesulfonyl)octahydro-1*H*-cyclopenta[*c*]pyridine (25). To a stirred solution of methyltriphenylphosphonium bromide (553 mg, 1.55 mmol) in THF (5 mL) was added *n*-BuLi in 1.59 M THF solution (0.65 mL, 1.03 mmol) at 0 °C under argon, and the resulting solution was stirred at the same temperature for 1 h. A solution of **24** (213 mg, 0.52 mmol) in THF (5 mL) was added to the mixture, and the whole was stirred at the same temperature for further 30 min. The mixture was treated with water and extracted with $CHCl_3$. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane−tOAc (7:1, v/v) gave the recovered starting material **24** (151 mg, 71%) and the desired olefin **25** (35 mg, 17%), respectively.

25: $[\alpha]^{26}_D$ −2.28 (*c* 1.00, $CHCl_3$); IR cm^{-1} 2926, 2955, 2869, 1650, 1596, 1494, 1454,1348, 1162; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.68−7.65 (m, 2H), 7.35−7.24 (m, 7H), 4.93 (s, 1H), 4.89 (s, 1H), 4.49 (d, J = 11.8 Hz, 1H), 4.43 (d, J = 11.8 Hz, 1H), 3.75 (d, J = 12.9 Hz, 1H), 3.55−3.48 (m, 1H), 3.48 (d, J = 12.9 Hz, 1H), 3.34 (dd, J = 12.1, 4.2 Hz, 1H), 2.77 (dd, J = 12.1, 8.4 Hz, 1H), 2.69−2.63 (m, 1H), 2.43 (s, 3H), 2.11−2.01 (m, 1H), 1.85−1.62 (m, 3H), 1.05 (d, J = 6.6 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 141.7, 138.5, 133.7, 129.7, 128.3, 127.61, 127.51, 127.47, 112.8, 100.5, 86.2, 71.6, 49.8, 46.3, 45.0, 42.3, 40.4, 35.1, 21.5, 18.3; HRMS *m*/*z* (EI) calcd for $C_{24}H_{29}NO_3S$ (M^+) 411.1868, found 411.1840.

(4a*R*,6*S*,7*S*,7a*R*)-7-Methyl-4-methylene-2-(*p*-toluenesulfonyl)-octahydro-1*H*-cyclopenta[*c*]pyridin-6-ol (27). A solution of **24** (77 mg, 0.187 mmol) in THF (5 mL) and EtOH (10 mL) in the presence of palladium hyroxide on carbon (6.5 mg, 5 mol %) was hydrogenated under an atmospheric pressure of hydrogen at ambient temperature for 24 h. After removal of the insoluble material, the filtrate was concentrated to give alcohol **26**, which without further purification, was used in the next reaction. To a stirred solution of methyltriphenylphosphonium bromide (401 mg, 1.12 mmol) in THF (6 mL) was added LiHMDS in 1.0 M THF solution (0.94 mL, 0.94 mmol) at 0 °C under argon, and the resulting solution was stirred at the same temperature for 30 min. A solution of **26** obtained above in THF (4 mL) was added to the mixture, and the whole was warmed to room temperature over the period of 6 h. The mixture was treated with saturated NH_4Cl solution and extracted with Et_2O. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane−EtOAc (1:1, v/v) gave the desired olefin **27** (45 mg, 75%) as a colorless oil: $[\alpha]^{20}_D$ −30.0 (*c* 0.61, $CHCl_3$); IR cm^{-1} 3500, 2955, 2927, 2870, 2257, 1650, 1595, 1495, 1456, 1345, 1162; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.66 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 4.92 (s, 1H), 4.90 (s, 1H), 3.79 (d, J = 12.8 Hz, 1H), 3.71 (q, J = 7.4 Hz, 1H), 3.54 (d, J = 12.8 Hz, 1H), 3.11 (dd, J = 12.2, 4.8 Hz, 1H), 3.00 (dd, J = 12.2, 6.4 Hz, 1H), 2.63 (q, J = 8.3 Hz, 1H), 2.43 (3H, s), 2.10−2.00 (m, 1H), 1.83−1.57 (m, 3H), 1.06 (d, J = 6.8 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 143.4, 142.0, 133.6, 129.6, 127.4, 112.6, 79.0, 50.3, 46.0, 44.7, 44.3, 39.6, 37.6, 21.4, 16.8; HRMS *m*/*z* (EI) calcd for $C_{17}H_{24}NO_3S$ (M^+) 321.1398, found 321.1388. The spectroscopic data were identical with those reported in the literature.

Acknowledgment. We are grateful to Prof. S. Aoyagi, School of Pharmacy, Tokyo University of Pharmacy and Life Science, for his generous gifts of ^{1}H and ^{13}C NMR spectra of the related compounds. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan and also by The Open Research Project.

Supporting Information Available: Experimental procedures and product characterization for new compounds and selected ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0709091