Diastereoselective Formal Synthesis of a Monoterpene Alkaloid, \((-\)-incarvilline)

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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 \((S)-N-[(E)-2-butenyl]-N-(3-butyln-2-methoxymethoxy)\)-p-toluenesulfonamide as a key step.

Introduction

Recent investigations of the plant *Incarvillea 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 \(\mu\) and \(\kappa\)-opioid receptors and adenosine receptor\(^3\) (Figure 1).

Incarvillateine \(1\) was supposed to generate biosynthetically via dimerization of incarvone \(2\), a hydroxycinnaminate 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 \((+)-6\text{-}epi\text{-}incarvilline\), was achieved by Kibayashi and co-workers.\(^4\)

Thus, development of a new synthetic strategy for incarvilline \(3\) would be an important research subject directed at searching potential antinociceptive compounds related to incarvillateine.

To the best our knowledge, two total syntheses\(^5,6\) 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 \((S)-N-[(E)-2-butenyl]-N-(3-butyln-2-methoxymethoxy)\)-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

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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. Moreover, it has been known that the methyl group at the 4-position could be derived from the corresponding alkene by catalytic reduction, which could be available from the ketone as a precursor (Scheme 1). It is noteworthy that Schore and his colleagues reported a similar methodology in the synthesis of racemic tecomanine, 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.

**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. Moreover, it has been known that the methyl group at the 4-position could be derived from the corresponding alkene by catalytic reduction, which could be available from the ketone as a precursor (Scheme 1). It is noteworthy that Schore and his colleagues reported a similar methodology in the synthesis of racemic tecomanine, 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.

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**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, which was readily accessible via the known (S)-1-butyne-3,4-diol from D-(-)-mannitol. Methoxymethylation of (S)-4-tert-butyldimethylsiloxy-1-butyn-3-ol with chloromethyl methyl ether afforded methoxymethyl ether in good yield. Desilylation of methoxymethyl ether with tetrabutylammonium fluoride gave alcohol in 91% yield.

Introduction of butenylamino group was first attempted by treatment of alcohol with N-(2E)-2-butenyl-p-toluensulfonamide under the Mitsunobu reaction conditions. However, none of the desired product could be isolated, unfortunately. Although reaction of alcohol with N-(tert-butoxycarbonyl)-p-toluensulfonamide gave the desired tosylamide, subsequent deprotection of the tosylamide failed.

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**References**


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

| Entry | Promoter (equiv) | Solvent | Atom | Temperature (°C) | Time (h) | Yield (%)
|-------|------------------|---------|------|------------------|---------|----------
| 1     | None             | Toluene | Ar   | 110              | 2       | 54       |
| 2     | NMO (10)         | CHCl₃   | Ar   | rt               | 9       | 45       |
| 3     | n-BuSMe (3.5)    | DCE     | CO   | 83               | 24      | 58       |
| 4     | n-BuSMe (3.5)    | DCE     | CO   | 83               | 2.5     | 66       |
| 5     | t-BuSMe (3.5)    | DCE     | Ar   | 83               | 2.5     | 62       |
| 6     | t-BuSMe (3.5)    | DCE     | CO   | 83               | 2.5     | 73       |

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 for the best conditions for the intramolecular Pauson–Khand reaction. The stereochemistry of the minor product 13 was confirmed to have the desired stereochemistry and also 7-methyl and 7a-H as shown in Figure 2. Thus, 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.

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

Luche reduction<sup>16</sup> of 14 afforded \( \beta \)-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-diazabicycloundec-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,<sup>17</sup> Takai–Nozaki methylenation,<sup>18</sup> and olefination with Tobe reagent<sup>19</sup> 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 hydrogenolyis 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,<sup>4</sup> 27: \([\alpha]_D^{20} -30.0 (c = 0.61, \text{CHCl}_3)\) [lit.,<sup>4</sup> \([\alpha]_D^{20} -33.6 (c = 0.61, \text{CHCl}_3)\)] (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.
(5)-3-Butynyl-2-methoxyhex-1-ene (11). A solution of 7 (431 mg, 3.32 mmol) and sodium hydride (325 mg, 1.33 mmol) in DMF (26 mL) was stirred at room temperature for 10 min. 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 NaCl solution and extracted with EtOAc. The organic layer was washed with brine and dried over Na2SO4. 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 tosylylamide 9 (2.53 g, 68% from 11) as a colorless oil: [α]D20 +113.3° (c 1.00, CHCl3); IR cm⁻¹ 3275, 2945, 2895, 2120, 1599, 1330, 1160; 1H NMR (270 MHz, CDCl3) 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 (dd, J = 5.1, 2.0 Hz, 1H), 3.35 (s, 3H), 3.32 (dd, J = 13.2, 7.9, 4.3 Hz, 1H), 3.16 (dd, J = 13.2, 7.9, 5.1 Hz, 1H), 2.44 (d, J = 2.0 Hz, 1H), 2.43 (s, 3H); 13C NMR (67.8 MHz, CDCl3) 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 (CI) calculated for C13H14NO (M+H) 208.1073, found 208.1078.

(S)-N-(2-Butenyl)-N-(3-butynyl)-2-methoxyhexa-4,5-diene (10). A suspension of 9 (2.19 g, 7.74 mmol) and sodium hydride (325 mg, 1.33 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 NaCl solution and extracted with EtOAc. The organic layer was washed with brine and dried over Na2SO4. 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 yellow oil: [α]D20 +108.1° (c 1.00, CHCl3); IR cm⁻¹ 3270, 2940, 2895, 2116, 1599, 1495, 1340, 1160; 1H NMR (270 MHz, CDCl3) 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), 3.43−3.36 (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); 13C NMR (67.8 MHz, CDCl3) 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) calculated for C17H23NO4S (M+H) 338.1426, found 338.1414.

(S)-N-(2-Butenyl)-N-(3-butynyl)-2-methoxyhexa-4,5-diene (10). A 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, ethylmagnesium 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 NaCl solution and extracted with Et2O. The ether layer was washed with water and dried over Na2SO4. 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 trimethylsilylethyl compound 16 (295 mg, 97%) as a pale yellow oil: [α]D20 +115.9° (c 1.00, CHCl3); IR cm⁻¹ 2960, 2985, 1715, 1595, 1340, 1160; 1H NMR (270 MHz, CDCl3) 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, 3H); 13C NMR (67.8 MHz, CDCl3) δ 143.1, 137.6, 131.0, 129.5, 127.3, 125.1, 101.9, 94.2, 92.0, 66.0, 55.7, 50.9, 21.5, 17.6, 0.0; HRMS m/z (CI) calculated for C16H24NO2SiS (M+H) 410.1821, found 410.1798.

(S)-N-(2-Butenyl)-N-(3-butynyl)-2-methoxyhexa-4,5-diene (10). A suspension of 9 (2.19 g, 7.74 mmol) and sodium hydride (325 mg, 1.33 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 NaCl solution and extracted with EtOAc. The organic layer was washed with brine and dried over Na2SO4. 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 trimethylsilylethyl compound 16 (295 mg, 97%) as a pale yellow oil: [α]D20 +115.9° (c 1.00, CHCl3); IR cm⁻¹ 2960, 2985, 1715, 1595, 1340, 1160; 1H NMR (270 MHz, CDCl3) 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, 3H); 13C NMR (67.8 MHz, CDCl3) δ 143.1, 137.6, 131.0, 129.5, 127.3, 125.1, 101.9, 94.2, 92.0, 66.0, 55.7, 50.9, 21.5, 17.6, 0.0; HRMS m/z (CI) calculated for C16H24NO2SiS (M+H) 410.1821, found 410.1798.
for the major isomer of 17: IR cm⁻¹ 2960, 1760, 1695, 1600, 1490;
¹H NMR (400 MHz, CDCl₃) δ 7.69—7.66 (m, 2H), 7.35—7.32 (m, 2H), 4.70—4.77 (m, 1H), 2.35 (t, J = 7.1 Hz, 1H), 2.05 (t, J = 10.6 Hz, 2H), 2.02—1.89 (m, 1H), 1.68—1.48 (m, 4H), 1.37—1.23 (m, 1H), 1.10 (t, J = 6.6 Hz, 3H), 0.80 (m, 2H), 3.42 (s, 3H), 2.43 (s, 2H), 2.25 (dd, J = 12.6, 1.6 Hz, 1H), 1.05 (t, J = 10.6 Hz, 2H), 2.02—1.89 (m, 1H), 1.68—1.47 (m, 4H), 1.37—1.23 (m, 1H), 1.10 (t, J = 6.6 Hz, 3H).
¹³C NMR (70 MHz, CDCl₃) δ 176.6, 129.5, 121.4, 121.3, 49.2, 49.1, 41.3, 40.9, 34.9, 21.5, 14.9; HRMS m/z (EI) calcd for C₂₆H₂₂NO₃S (M⁺ + H) 370.1682, found 370.1713.

(4S,6aS,7aS,5aS)-7-Octahydropyrido[1,2-a]pyridine-6(1H)-carboxylic acid (22). A solution of 22 (87 mg, 0.49 mmol) in DMF (1.2 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 NH₄Cl solution and extracted with EtOAc. The organic layer was washed with brine and dried over Na₂SO₄. 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 Ref 22 (93 mg, 82%) as a colorless oil: [α]²⁰D +30.0 (c 1.00, CHCl₃); IR cm⁻¹ 2952, 2950, 2940, 1599, 1549, 1449, 1381, 1345, 1246; H NMR (270 MHz, CDCl₃) δ 7.65 (d, J = 8.2 Hz, 2H), 7.30—7.11 (m, 7H), 4.57 (d, J = 6.9 Hz, 1H), 4.66 (d, J = 6.9 Hz, 1H), 4.43 (d, J = 6.9 Hz, 1H), 3.96 (d, J = 6.9 Hz, 1H), 3.84 (m, 3H), 3.68 (m, 3H), 3.52 (m, 3H), 2.42—2.37 (m, 4H), 2.10—1.90 (m, 3H), 1.90—1.67 (m, 3H), 1.60—1.38 (m, 3H), 1.29—1.07 (m, 3H), 0.89 (m, 3H); ¹H NMR (67.8 MHz, CDCl₃) δ 143.7, 138.4, 133.4, 129.7, 125.7, 125.8, 127.5, 127.58, 127.51, 127.48, 86.1, 71.4, 64.9, 52.6, 50.7, 46.1, 43.4, 42.1, 31.7, 21.5, 17.0; HRMS m/z (EI) calcd for C₂₆H₂₂NO₃S (M⁺ + H) 416.1895, found 416.1872. Anal. Calcd for C₂₆H₂₂NO₃S: C, 66.48; H, 7.03; N, 3.39. Found: C, 66.27; H, 6.59; N, 3.36.
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$^{13}$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$_4$S (M$^+$) 413.1661, found 413.1677. Anal. Calcd for C$_{23}$H$_{27}$NO$_4$S: C 66.80; H 6.58; N 3.39. Found: C 66.80; H 6.58; N 3.39.

**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$_4$Cl solution and extracted with CHCl$_3$. The organic layer was washed with brine and dried over Na$_2$SO$_4$. Evaporation of the solvent gave a residue, which was recrystallized from EtOAc−Et$_2$O to give cis-compound 24 (178 mg, 81%) as colorless needles.

**Method B (One Pot Procedure).** To a stirred solution of oxaly chloride (76 µL, 0.89 mmol) in CH$_2$Cl$_2$ (3 mL) was added a solution of methyltriphenylphosphonium bromide (553 mg, 1.55 mmol) at 0 °C and stirred for 1 h. A solution of LiHMDS in 1.0 M THF solution (0.94 mL, 0.94 mmol) was added to the mixture, 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$_4$Cl solution and extracted with CHCl$_3$. The organic layer was washed with brine and dried over Na$_2$SO$_4$. 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:

$^{1}$H NMR (500 MHz, CDCl$_3$) δ 4.43 (d, J = 12.8 Hz, 1H), 3.79 (d, J = 12.2, 6.4 Hz, 1H), 2.77 (dd, J = 12.1, 4.2 Hz, 1H), 2.70 (dd, J = 12.1, 4.2 Hz, 1H), 1.98−1.80 (m, 1H), 1.04 (d, J = 7.0 Hz, 3H); $^{13}$C NMR (125.67 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, 34.3, 31.4, 21.6, 17.2; HRMS m/z (EI) calcd for C$_{23}$H$_{27}$NO$_4$S (M$^+$) 413.1661, found 413.1652. Anal. Calcd for C$_{23}$H$_{27}$NO$_4$S: C 66.80; H 6.58; N 3.39. Found: C 66.77; H, 6.48; N, 3.44.

The organic layer was washed with brine and dried over Na$_2$SO$_4$. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane−EtOAc (99:1, v/v) gave ketone 24 (242 mg, 86%) as colorless needles.

**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.

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.

$^{1}$H NMR (67.8 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), 3.53−3.48 (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, 4.2 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$_{23}$H$_{27}$NO$_4$S (M$^+$) 411.1868, found 411.1840.

(4aR,6S,7S,7aS)-6-Benzoxyl-7-methyl-2-(p-toluenesulfonyl)-octahydro-4H-cyclopenta[c]pyridin-4-one (27). A solution of 24 (77 mg, 0.187 mmol) in THF (5 mL) and EtOH (10 mL) in the presence of palladium hydroyde 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 methyltritylphosphonium 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$_4$Cl solution and extracted with Et$_2$O. The organic layer was washed with brine and dried over Na$_2$SO$_4$. 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:

$^{1}$H NMR (67.8 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), 3.53−3.48 (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, 4.2 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$_{23}$H$_{27}$NO$_4$S (M$^+$) 411.1868, found 411.1840.

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.

JOC0709091