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## A FORMAL SYNTHESIS OF (–)-KAINIC ACID BY MEANS OF SmI<sub>2</sub>-MEDIATED RADICAL CYCLIZATION

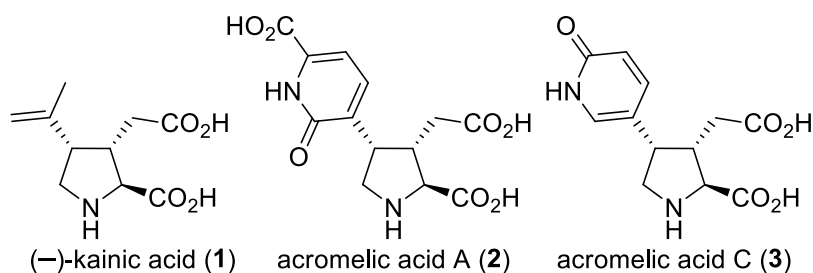
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**Abstract** – A formal synthesis of (–)-kainic acid (**1**) starting from the known D-serine derivative **9** has been established in 14 steps. Construction of all the stereogenic centers on the pyrrolidine core of **1** was successfully achieved by application of SmI<sub>2</sub>-mediated radical cyclization to the  $\alpha,\beta$ -unsaturated ester having an alkyne moiety, followed by hydroxy group directed diastereoselective hydrogenation over Wilkinson's catalyst.

### INTRODUCTION

The kainoid family is recognized to bind to glutamate receptors and to exhibit neuroexcitatory effects.<sup>1</sup> In particular, this class of alkaloids plays an important biological role as pharmacological probes to make models of neurodegenerative diseases such as Alzheimer's disease and Huntington's chorea.<sup>2</sup> Characteristic structural features of kainoids, represented by kainic acid (**1**),<sup>3,4</sup> acromelic acid A (**2**) and C (**3**), are based on two carboxylic acids at the C2 and C3 positions, and also alkenyl substituent at the C4 position of the pyrrolidine core as a common skeleton (Figure 1). Thus, the efforts to develop a novel methodology for constructing consecutive stereogenic centers at the C3 and C4 positions of the pyrrolidine ring have continued unabated. Kainic acid (**1**) is the simple kainoid with isopropenyl group at the C4 position.

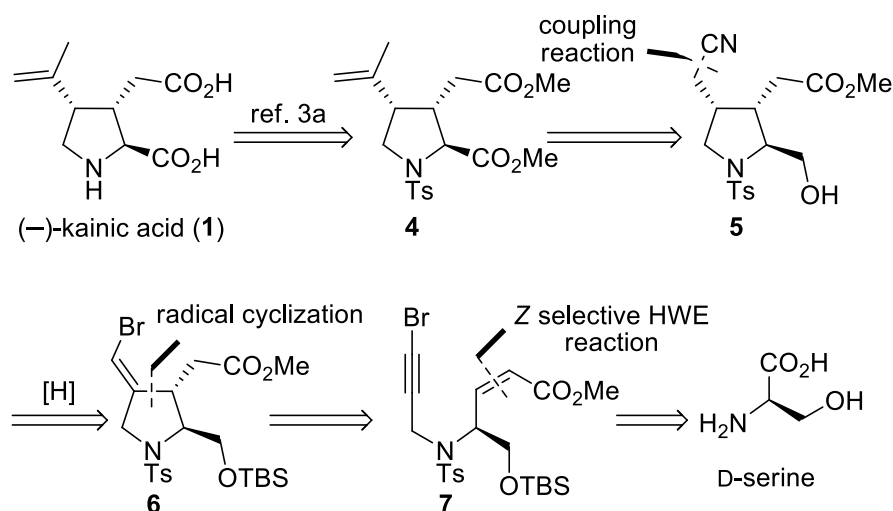


**Figure 1.** Structures of kainoid family

By establishing efficient synthetic method of kainic acid (**1**), the synthesis of other kainoids, such as acromelic acid A (**2**) and C (**3**), would also be possible by application of the strategy developed.

Previously, we reported SmI<sub>2</sub>-mediated intramolecular radical cyclization of (*Z*)- $\alpha,\beta$ -unsaturated esters having bromoalkyne functionalities in the same molecules providing 2,3-disubstituted pyrrolidines in high stereoselectivity.<sup>5</sup> Moreover, the resulting bromoalkenes were recognized to serve as the relevant precursors to introduce a variety of functional groups. Therefore, we decided to utilize the above-mentioned SmI<sub>2</sub>-mediated radical cyclization in the synthesis of (–)-kainic acid (**1**).

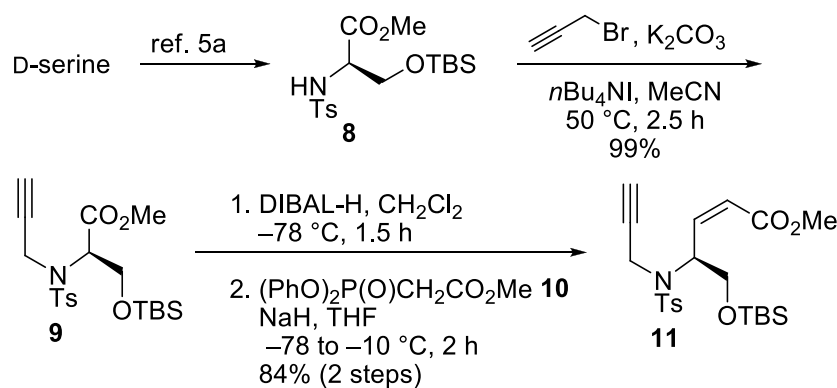
Herein, we describe a formal synthesis of **1**, possessing consecutive stereogenic centers at the C2, C3 and C4 positions on the pyrrolidine ring, by employing SmI<sub>2</sub>-mediated cyclization and subsequent diastereoselective hydrogenation as the key reactions.



**Scheme 1.** Retrosynthetic analysis of (–)-kainic acid (**1**)

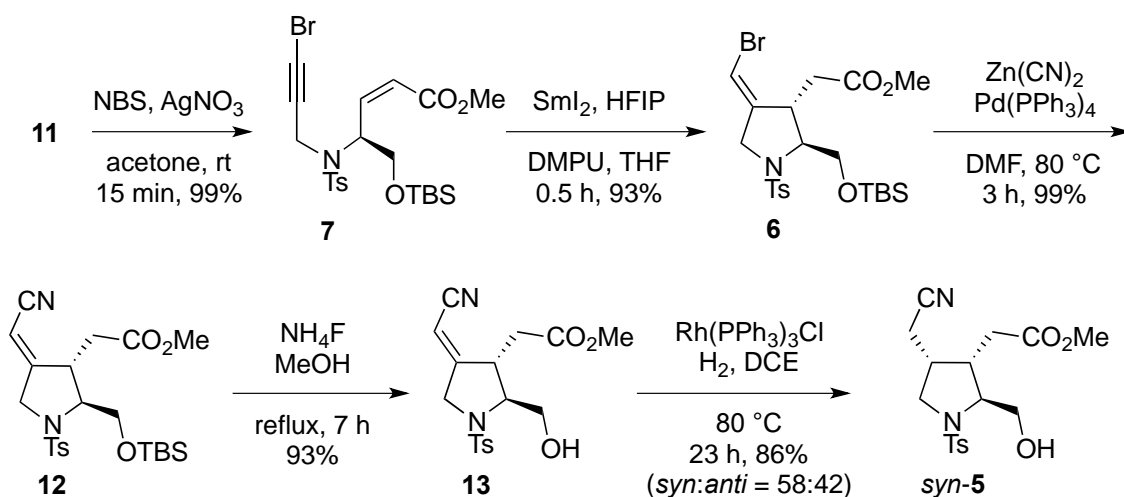
## RESULTS AND DISCUSSION

The retrosynthetic analysis is illustrated in Scheme 1. We planned to construct the substituent at the C4 position at the later stage of the synthesis. As can be seen in Scheme 1, the isopropenyl unit of Yoo's intermediate **4**<sup>3a</sup> would be derived from cyanoalkane **5**, in 7 steps, involving: 1) reduction of cyano group to the corresponding aldehyde, 2) methylenation at the  $\alpha$  position of the formyl group, 3) reduction of the formyl group, and 4) dehydroxylation of the corresponding allylic alcohol. The cyanoalkane **5** would be obtained by Pd-catalyzed coupling reaction of compound **6** with appropriate cyanides, and subsequent hydroxy group directed hydrogenation. The requisite bromoalkene **6** could be constructed by means of SmI<sub>2</sub>-mediated cyclization of compound **7**, which would easily be accessible from D-serine.



**Scheme 2.** Synthesis of (*Z*)- $\alpha,\beta$ -unsaturated ester **11**

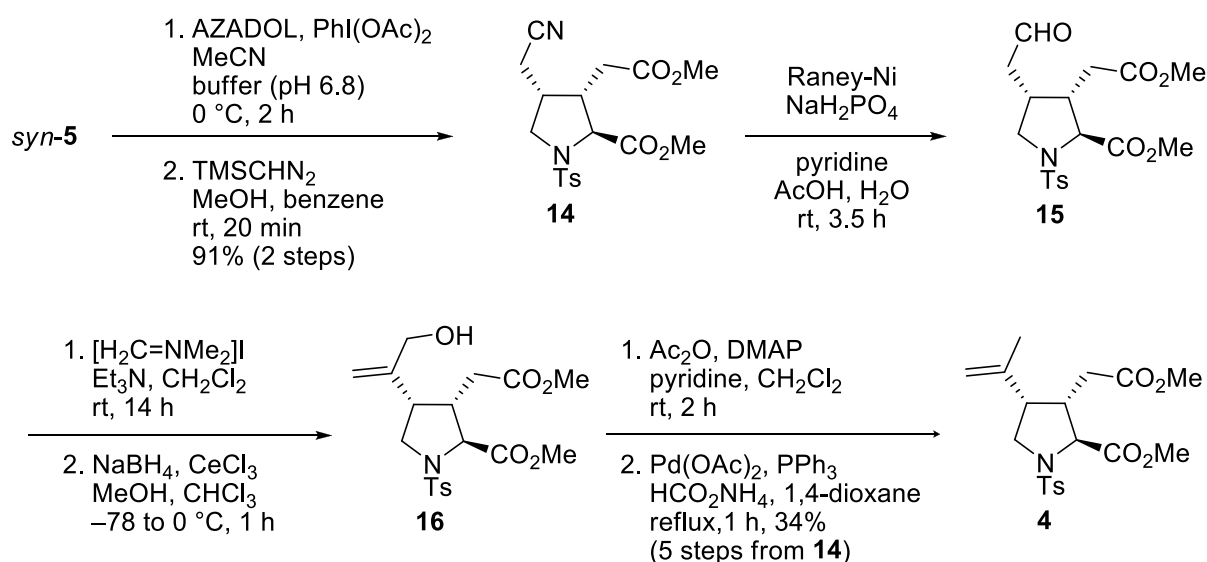
Alkylation of the known sulfonamide **8**, readily accessible from D-serine, with propargyl bromide in the presence of  $K_2CO_3$  gave alkyne **9**<sup>5a</sup> in 99% yield (Scheme 2). We note in advance that the similar  $SmI_2$ -mediated intramolecular cyclization of the (*E*)- $\alpha,\beta$ -unsaturated ester having a bromoalkyne moiety furnished *trans*-2,3-disubstituted pyrrolidine **6** in moderate stereoselectivity (*anti:syn* = 86:14).<sup>5a</sup> Thus, we decided to employ (*Z*)- $\alpha,\beta$ -unsaturated ester as a starting material in the synthesis of (–)-kainic acid. In order to synthesize the desired (*Z*)- $\alpha,\beta$ -unsaturated ester, reduction of **9** with DIBAL-H at  $-78\text{ }^\circ\text{C}$ , followed by *Z*-selective Ando's variant of Horner-Wadsworth-Emmons reaction<sup>6</sup> of the corresponding aldehyde with phosphate **10**<sup>6c</sup> was carried out to afford **11** in 84% yield over 2 steps.



**Scheme 3.** Synthesis of pyrrolidine derivative **5**

Bromination of terminal alkyne in **11** with NBS- $AgNO_3$  gave bromoalkyne **7** in 99% yield (Scheme 3).<sup>7</sup> Subsequently, the key reaction of **7** with  $SmI_2$ -DMPU<sup>5d</sup> proceeded smoothly to furnish bromoalkene **6** in 93% yield as a single stereoisomer. The stereochemistry of **6** was determined by NOE experiments. Since

construction of the basic pyrrolidine core of **1** with the desired stereochemistries at the 2- and 3-positions was thus successfully achieved, we focused our concentration on the installation of an isopropenyl group at the 3-position. Introduction of C1 unit to terminal alkene in **6** was conducted by utilizing Pd-catalyzed coupling reaction under various reaction conditions. A reductive carbonylation of **6** with *N*-formylsaccharin and Xantphos<sup>8</sup> was first investigated, however, none of the desired aldehyde was isolated, unfortunately. The major byproducts formed in this reaction were found to be debromination product of **6** and unsaturated carboxylic acid. Thus, we decided to convert the bromide to the corresponding cyanide. Although difficulties were initially encountered for a conversion of **6** to **12** by using Pd-catalyzed coupling reaction,<sup>9</sup> we found that **12** could be obtained by treatment of **6** with CuCN in *N*-methyl-2-pyrrolidone (NMP) at 200 °C in 68% yield.<sup>9c</sup> However, this conversion required rather harsh reaction conditions, and suffered from reproducibility and work-up for isolation, since the desired product **12** could not be separated both from **13** and desilylated product of **6** in this conversion. Finally, we are delighted to be able to find the best reaction conditions to prepare **12**, where Pd-catalyzed cyanation of **6** with Zn(CN)<sub>2</sub> in DMF at 80 °C for 3 h afforded the desired compound **12** in 99% yield.<sup>10</sup> Deprotection of the silyl group of **12** with NH<sub>4</sub>F gave **13** in 93% yield. Reduction of the *exo*-olefin in **13** was then subjected to a hydroxy group directed diastereoselective hydrogenation.<sup>11</sup> First, when the reaction was carried out using the Crabtree's catalyst, the undesired product *anti*-**5** was obtained as a major product (*syn:anti* = 38:62).



**Scheme 4.** The formal synthesis of Yoo's intermediate **4**

On the other hand, the reduction using Wilkinson's catalyst afforded the desired *syn*-**5** (*syn:anti* = 58:42), as the major product. Although no reasonable explanation could be provided, at present, for the observed

diastereoselectivity in this reduction, unfortunately, we assumed that the metal catalyst employed coordinated not only to OH group but also to CO<sub>2</sub>Me group. Since the obtained diastereoselectivity was not high enough, the reduction was attempted under the various reaction conditions to improve the diastereoselectivity, however, we could not increase the selectivity, unfortunately. The stereochemistries of *syn*- and *anti*-**5** were determined by conversion of *syn*-**5** to the target compound **4** as follows.

Oxidation of *syn*-**5** with AZADOL-PhI(OAc)<sub>2</sub>,<sup>12</sup> followed by esterification of the resulting carboxylic acid with TMSCHN<sub>2</sub> gave diester **14** in 91% yield over 2 steps (Scheme 4). Then, **14** was subjected to reduction with Raney Ni–NaH<sub>2</sub>PO<sub>4</sub><sup>13</sup> to furnish aldehyde **15**, which on treatment with Eschenmoser's salt,<sup>14</sup> and subsequent reduction of  $\alpha,\beta$ -unsaturated aldehyde with NaBH<sub>4</sub>-CeCl<sub>3</sub><sup>15</sup> provided allylic alcohol **16**. Deoxygenation of **16** was successfully achieved by employing Tsuji's procedure<sup>16</sup> as follows. Acetylation of **16** with acetic anhydride in pyridine in the presence of DMAP afforded the corresponding acetate, which, on treatment with Pd(OAc)<sub>2</sub> and ammonium formate provided Yoo's intermediate **4**, in 34% yield, over 5 steps. The spectroscopic data of the synthesized compound **4** were superimposable to those reported by Lautens.<sup>3b</sup>

In conclusion, we have accomplished the formal synthesis of (–)-kainic acid (**1**) by means of SmI<sub>2</sub>-mediated radical cyclization, followed by diastereoselective hydrogenation as key steps. Although the synthetic method for kainic acid developed here does not seem to be superior to the previously reports, in terms of the reaction steps and stereoselectivities, this strategy will be widely applicable to the synthesis of biologically active natural product having a pyrrolidine ring, and further synthetic work is under investigation in our laboratory.

## EXPERIMENTAL

Melting points were measured with a Yanaco MP-500P apparatus and are uncorrected. Optical rotations were measured with JASCO DIP-360 or P-2200. IR spectra were obtained using a JASCO FT/IR-4100 or IRPrestige-21 spectrophotometer. <sup>1</sup>H- and <sup>13</sup>C-NMR spectra were obtained on a Bruker AV III 400 (<sup>1</sup>H-NMR: 400 MHz, <sup>13</sup>C-NMR: 100 MHz) instrument for solutions in CDCl<sub>3</sub>, and chemical shifts are reported on the  $\delta$  scale using TMS as an internal standard of 0.00 for <sup>1</sup>H-NMR spectra and CDCl<sub>3</sub> as an internal standard of  $\delta$  77.00 for <sup>13</sup>C-NMR spectra, respectively. MS spectra were measured with a JEOL-600 spectrometer. Elemental analyses were performed on a Yanaco-MT5.

***N*-Tosyl-D-serine methyl ester.**<sup>17</sup> To a flask containing MeOH (20 mL) was added dropwise AcCl (2.00 mL, 28.2 mmol) at 0 °C under Ar. After stirring for 15 min at ambient temperature, D-serine (1.03 g, 9.81 mmol) was added to the mixture, and the whole was stirred for further 2 h at the same temperature. The volatile solvent was removed in vacuo, and the residue was used for the next step without further

purification. To a solution of the obtained D-serine methyl ester in  $\text{CHCl}_3$  (20 mL) were added  $\text{Et}_3\text{N}$  (6.64 mL, 47.7 mmol) and  $\text{TsCl}$  (2.13 g, 11.2 mmol) at 0 °C. After stirring for 20 h at ambient temperature, the reaction was quenched by addition of sat. aqueous  $\text{NaHCO}_3$  solution, and the mixture was extracted with  $\text{CHCl}_3$  ( $\times 2$ ). The extract was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated in vacuo. The residue was purified by column chromatography on silica gel using  $\text{AcOEt-CHCl}_3$  (6:4, v/v) as eluent to give *N*-tosyl-D-serine methyl ester (2.19 g, 82%) as a white solid.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ; 400 MHz)  $\delta$  7.75 (2H, d,  $J = 8.1$  Hz), 7.31 (2H, d,  $J = 8.1$  Hz), 5.39 (1H, d,  $J = 9.2$  Hz), 4.05 (1H, ddd,  $J = 9.2, 3.4, 2.9$  Hz), 3.97 (1H, dd,  $J = 9.9, 2.9$  Hz), 3.79 (1H, dd,  $J = 9.9, 3.4$  Hz), 3.57 (3H, s), 2.44 (3H, s), 0.84 (9H, s), 0.02 (3H, s), 0.01 (3H, s).

**(*R*)-Methyl 3-(*tert*-butyldimethylsilyloxy)-2-(4-methylphenylsulfonamido)propanoate (8).**<sup>31</sup> To a solution of *N*-tosyl-D-serine methyl ester (10.2 g, 37.4 mmol) in DMF (23 mL) were added imidazole (6.43 g, 94.6 mmol) and TBSCl (6.76 g, 44.9 mmol) at room temperature. After stirring for 2.5 h, the reaction mixture was treated with sat. aqueous  $\text{NaHCO}_3$  solution. After stirring for 50 min, the mixture was extracted with AcOEt. The extract was washed with brine, brine- $\text{H}_2\text{O}$  (1:1) ( $\times 3$ ), and brine. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , and concentrated in vacuo. The residue was purified by column chromatography on silica gel using  $\text{AcOEt-hexane-CHCl}_3$  (15:42.5:42.5, v/v) as eluent to give silyl ether **8** (13.1 g, 90%) as a white solid.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ; 400 MHz)  $\delta$  7.75 (2H, d,  $J = 8.1$  Hz), 7.31 (2H, d,  $J = 8.1$  Hz), 5.39 (1H, d,  $J = 9.2$  Hz), 4.05 (1H, ddd,  $J = 9.2, 3.4, 2.9$  Hz), 3.97 (1H, dd,  $J = 9.9, 2.9$  Hz), 3.79 (1H, dd,  $J = 9.9, 3.4$  Hz), 3.57 (3H, s), 2.44 (3H, s), 0.84 (9H, s), 0.02 (3H, s), 0.01 (3H, s).

**(*R*)-Methyl 3-(*tert*-butyldimethylsilyloxy)-2-(4-methyl-*N*-(prop-2-ynyl)phenylsulfonamido)propanoate (9).**<sup>5a</sup> To a solution of sulfonamide **8** (5.00 g, 12.9 mmol) in MeCN (100 mL) were added  $\text{K}_2\text{CO}_3$  (5.40 g, 39.1 mmol),  $n\text{Bu}_4\text{NI}$  (1.00 g, 2.71 mmol) and propargyl bromide (2.31 g, 19.4 mmol) at room temperature under Ar. After stirring for 2.5 h at 50 °C, the reaction mixture was cooled to room temperature, and insoluble materials were filtered off through a pad of Celite. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography on silica gel using hexane-AcOEt (8:2, v/v) as eluent to give alkyne **9** (5.48 g, 99%) as a pale yellow solid.  $[\alpha]_{\text{D}}^{22} +12.5$  ( $c$  1.0,  $\text{CHCl}_3$ ); IR  $\nu_{\text{max}}$  2123, 1752, 1161  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ; 400 MHz)  $\delta$  7.76 (2H, d,  $J = 8.3$  Hz), 7.27 (2H, d,  $J = 8.3$  Hz), 4.64 (1H, t,  $J = 4.6$  Hz), 4.31 (1H, d,  $J = 2.4$  Hz), 4.30 (1H, d,  $J = 2.4$  Hz), 4.09 (2H, d,  $J = 4.6$  Hz), 3.61 (3H, s), 2.42 (3H, s), 2.14 (1H, t,  $J = 2.4$  Hz), 0.84 (9H, s), 0.04 (3H, s), 0.01 (3H, s);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ ; 100 MHz)  $\delta$  169.52, 143.54, 136.73, 129.39 (2), 127.55 (2), 80.22, 71.55, 62.79, 60.65, 52.05, 35.39, 25.59 (3), 21.53, 18.03, -5.72, -5.95.

**(2Z,4S)-Methyl 5-(tert-butyldimethylsilyloxy)-4-{N-(prop-2-ynyl)-toluenesulfonamido}pent-2-enoate (11).** To a solution of alkyne **9** (4.97 g, 11.7 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (120 mL) was added dropwise DIBAL-H (1.02 M in hexane, 13.7 mL) at –78 °C under Ar. After stirring for 1.5 h at the same temperature, the reaction was quenched by addition of *i*PrOH at –78 °C. After stirring for 5 min, to the reaction mixture was added sat. aqueous Rochelle salt solution, and the whole were warmed up to room temperature. After stirring for 0.5 h, the mixture was diluted with AcOEt, and filtered through a pad of Ceilte to remove the insoluble materials. The filtrate was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo to give a residue, which was used for the next step without further purification. To a solution of methyl diphenylphosphonoacetate (**10**) (4.29 g, 14.0 mmol) in THF (40 mL) was added dropwise NaH (732 mg, 15.3 mmol) at 0 °C under Ar. After stirring for 0.5 h at the same temperature, the reaction mixture was cooled to –78 °C, and then added to the corresponding aldehyde in THF (20 mL). After stirring for 1 h at the same temperature, the mixture was warmed up to –10 °C over 1 h. The reaction was quenched with sat. aqueous NH<sub>4</sub>Cl solution, and extracted with AcOEt (×2). The extract was washed with H<sub>2</sub>O, brine-H<sub>2</sub>O (1:1) (×3), brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo to leave a residue, which was purified by column chromatography on silica gel using hexane-AcOEt (8:2) as eluent to give ester **11** (4.41 g, 84%) as a colorless oil.  $[\alpha]_D^{26}$  –32.9 (*c* 1.0, CHCl<sub>3</sub>); IR  $\nu_{\max}$  2120, 1721, 1339 and 1160 cm<sup>–1</sup>; <sup>1</sup>H-NMR (CDCl<sub>3</sub>; 400 MHz)  $\delta$  7.74 (2H, d, *J* = 8.3 Hz), 7.23 (2H, d, *J* = 8.3 Hz), 6.50 (1H, dd, *J* = 11.6, 8.9 Hz), 5.78 (1H, dd, *J* = 11.6, 1.1 Hz), 5.66-5.57 (1H, m), 4.45 (1H, dd, *J* = 18.5, 2.3 Hz), 4.27 (1H, dd, *J* = 18.5, 2.3 Hz), 3.90 (2H, d, *J* = 5.3 Hz), 3.72 (3H, s), 2.40 (3H, s), 2.20 (1H, t, *J* = 2.3 Hz), 0.82 (9H, s), 0.00 (3H, s), –0.01 (3H, s); <sup>13</sup>C-NMR (CDCl<sub>3</sub>; 100 MHz)  $\delta$  165.73, 144.74, 143.21, 137.32, 129.26 (2), 127.57 (2), 120.56, 80.02, 72.74, 64.06, 56.75, 51.41, 34.17, 25.68 (3), 21.47, 18.06, –5.57, –5.79; HRMS (ESI): Calcd for C<sub>22</sub>H<sub>34</sub>NO<sub>5</sub>SSi [M+H]<sup>+</sup>: 452.1927, Found: 452.1924.

**(2Z,4S)-Methyl 4-{N-(3-bromoprop-2-ynyl)-4-methylphenylsulfonamido}-5-(tert-butyldimethylsilyloxy)pent-2-enoate (7).** To a solution of ester **11** (203 mg, 0.45 mmol) in acetone (2.5 mL) were added NBS (122 mg, 0.69 mmol) and AgNO<sub>3</sub> (25.7 mg, 0.15 mmol) at ambient temperature under Ar. After stirring for 15 min at the same temperature, the reaction was quenched with sat. aqueous NaHCO<sub>3</sub> solution. The volatile solvent was removed in vacuo. The residue was dissolved in AcOEt. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo to leave a residue, which was purified by column chromatography on silica gel using hexane-AcOEt (8:2, v/v) as eluent to give bromoalkyne **7** (235 mg, 99%) as a pale yellow oil.  $[\alpha]_D^{26}$  –30.7 (*c* 1.0, CHCl<sub>3</sub>); IR  $\nu_{\max}$  2219, 1721, 1348 and 1162 cm<sup>–1</sup>; <sup>1</sup>H-NMR (CDCl<sub>3</sub>; 400 MHz)  $\delta$  7.72 (2H, d, *J* = 8.3 Hz), 7.25 (2H, d, *J* = 8.3 Hz), 6.40 (1H, dd, *J* = 11.6, 8.9 Hz), 5.80 (1H, dd, *J* = 11.6, 1.1 Hz), 5.68-5.59 (1H, m), 4.46 (1H, d, *J* = 18.4 Hz),

4.32 (1H, d,  $J = 18.4$  Hz), 3.93-3.84 (2H, m), 3.73 (3H, s), 2.40 (3H, s), 0.82 (9H, s), 0.00 (3H, s),  $-0.01$  (3H, s);  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ ; 100 MHz)  $\delta$  165.71, 144.42, 143.26, 137.17, 129.23 (2), 127.56 (2), 120.57, 76.06, 64.53, 56.45, 51.42, 44.17, 35.39, 25.66 (3), 21.46, 18.04,  $-5.62$ ,  $-5.82$ ; HRMS (ESI): Calcd for  $\text{C}_{22}\text{H}_{32}\text{BrNNaO}_5\text{SSi}$   $[\text{M}+\text{Na}]^+$ : 552.0852, Found: 552.0848.

**Methyl 2-((2*S*,3*S*,4*E*)-4-(bromomethylene)-2-((*tert*-butyldimethylsilyloxy)methyl)-1-tosylpyrrolidin-3-yl)acetate<sup>5a</sup> (6).** To a flask were added 1,2-diiodoethane (3.45 g, 12.2 mmol) and metal Sm (2.25 g, 15.0 mmol). After the flask was flushed with Ar, THF (124 mL) was added to the reaction mixture at room temperature. After stirring for 2 h at the same temperature, a solution of bromoalkyne **7** (1.85 g, 3.49 mmol), HFIP (1.90 mL, 18.1 mmol), and DMPU (4.50 mL, 37.4 mmol) in THF (20 mL) was added dropwise to the above  $\text{SmI}_2$  in THF solution at  $0^\circ\text{C}$  under Ar. After stirring for 0.5 h at the same temperature, the reaction was quenched by addition of sat. aqueous  $\text{NaHCO}_3$  solution, and the precipitates formed were filtered off through a pad of Celite. The filtrate was concentrated in vacuo, and the residue was dissolved in AcOEt. The organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated in vacuo to leave a residue, which was purified by column chromatography on silica gel using hexane-AcOEt (8:2, v/v) as eluent to give bromoalkene **7** (1.72 g, 93%) as a white solid. Mp  $90.3$ – $90.9^\circ\text{C}$ ;  $[\alpha]_{\text{D}}^{25} -20.4$  ( $c$  1.0,  $\text{CHCl}_3$ ); IR  $\nu_{\text{max}}$  1738, 1350 and  $1165\text{ cm}^{-1}$ ;  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ ; 400 MHz)  $\delta$  7.74 (2H, d,  $J = 8.2$  Hz), 7.32 (2H, d,  $J = 8.2$  Hz), 6.02 (1H, dd,  $J = 3.2, 1.6$  Hz), 4.02 (1H, dd,  $J = 14.0, 1.6$  Hz), 3.94 (1H, dd,  $J = 14.0, 3.2$  Hz), 3.85 (1H, dd,  $J = 4.9, 2.8$  Hz), 3.75 (1H, dd,  $J = 10.3, 4.9$  Hz), 3.67 (1H, dd,  $J = 10.3, 2.8$  Hz), 3.63 (3H, s), 3.30-3.23 (1H, m), 2.43 (3H, s), 2.30 (1H, dd,  $J = 16.1, 3.9$  Hz), 1.59 (1H, dd,  $J = 16.1, 11.5$  Hz), 0.84 (9H, s), 0.03 (3H, s), 0.01 (3H, s);  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ ; 100 MHz)  $\delta$  171.54, 143.99, 143.83, 135.20, 129.83 (2), 127.23 (2), 99.69, 66.09, 65.99, 51.83, 51.79, 43.28, 34.87, 25.72 (3), 21.54, 18.08,  $-5.59$ ,  $-5.73$ ; HRMS (ESI): Calcd for  $\text{C}_{22}\text{H}_{35}\text{BrNO}_5\text{SSi}$   $[\text{M}+\text{H}]^+$ : 532.1189, Found: 532.1185.

**Methyl 2-((2*S*,3*S*,*E*)-2-((*tert*-butyldimethylsilyloxy)methyl)-4-(cyanomethylene)-1-tosylpyrrolidin-3-yl)acetate (12).** To a flask were added bromoalkene **6** (2.00 g, 3.76 mmol),  $\text{Zn}(\text{CN})_2$  (880 mg, 7.52 mmol) and  $\text{Pd}(\text{PPh}_3)_4$  (217 mg, 0.19 mmol). After the flask was flushed with Ar, DMF (40 mL) was added at ambient temperature, and the resulting mixture was stirred for 3 h at  $80^\circ\text{C}$ , and extracted with AcOEt. The extract was washed with brine, brine- $\text{H}_2\text{O}$  (1:1) ( $\times 3$ ) and brine. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , and concentrated in vacuo to leave a residue, which was purified by column chromatography on silica gel using hexane-AcOEt (4:6, v/v) as eluent to give cyanoalkene **12** (1.79 g, 99%) as a colorless oil.  $[\alpha]_{\text{D}}^{24} -11.6$  ( $c$  1.4,  $\text{CHCl}_3$ ); IR  $\nu_{\text{max}}$  2222, 1739, 1350 and  $1163\text{ cm}^{-1}$ ;  $^1\text{H}$ -NMR



(CDCl<sub>3</sub>; 400 MHz)  $\delta$  7.72 (2H, d,  $J = 8.3$  Hz), 7.32 (2H, d,  $J = 8.3$  Hz), 5.23 (1H, dd,  $J = 3.7, 1.9$  Hz), 4.22 (1H, dd,  $J = 16.7, 3.7$  Hz), 4.16 (1H, dd,  $J = 16.7, 1.9$  Hz), 3.94-3.90 (1H, m), 3.79 (1H, dd,  $J = 10.5, 3.4$  Hz), 3.74 (1H, dd,  $J = 10.5, 2.3$  Hz), 3.67 (3H, s), 3.40-3.33 (1H, m), 2.44 (3H, s), 2.32 (1H, dd,  $J = 16.7, 4.2$  Hz), 1.83 (1H, dd,  $J = 16.7, 11.3$  Hz), 0.82 (9H, s), 0.02 (3H, s), -0.01 (3H, s); <sup>13</sup>C-NMR (CDCl<sub>3</sub>; 100 MHz)  $\delta$  170.79, 166.90, 144.11, 135.37, 129.93 (2), 127.08 (2), 115.06, 92.15, 66.46, 66.35, 52.71, 52.03, 43.80, 36.19, 25.66 (3), 21.52, 18.02, -5.75, -5.80; HRMS (ESI) Calcd for C<sub>23</sub>H<sub>34</sub>N<sub>2</sub>NaO<sub>5</sub>SSi [M+Na]<sup>+</sup>: 501.1855, Found: 501.1858.

**Methyl 2-(2*S*,3*S*,*E*)-4-(cyanomethylene)-2-(hydroxymethyl)-1-tosylpyrrolidin-3-yl)acetate (13).** To a solution of cyanoalkene **12** (367 mg, 0.77 mmol) in MeOH (15 mL) was added NH<sub>4</sub>F (287 mg, 7.76 mmol) at room temperature. After stirring for 7 h, the volatile solvent was removed in vacuo, and the residue was dissolved into CHCl<sub>3</sub>. The precipitates formed were filtered off through a pad of Celite. The filtrate was concentrated in vacuo to leave a residue, which was purified by column chromatography on silica gel using hexane-AcOEt (4:6, v/v) as eluent to give alcohol **13** (261 mg, 93%) as a white solid. Mp 92.7–95.5 °C;  $[\alpha]_D^{25} -33.9$  ( $c$  0.8, CHCl<sub>3</sub>); IR  $\nu_{\max}$  3525, 2223, 1737, 1345 and 1162 cm<sup>-1</sup>; <sup>1</sup>H-NMR (CDCl<sub>3</sub>; 400 MHz)  $\delta$  7.74 (2H, d,  $J = 8.3$  Hz), 7.36 (2H, d,  $J = 8.3$  Hz), 5.33 (1H, dd,  $J = 3.9, 1.9$  Hz), 4.25 (1H, dd,  $J = 16.8, 1.9$  Hz), 4.19 (1H, dd,  $J = 16.8, 3.9$  Hz), 3.81 (1H, ddd,  $J = 6.1, 4.5, 1.7$  Hz), 3.80 (1H, dd,  $J = 12.5, 4.5$  Hz), 3.69 (1H, dd,  $J = 12.5, 6.1$  Hz), 3.64 (3H, s), 3.36-3.29 (1H, m), 2.46 (3H, s), 2.31 (1H, dd,  $J = 17.0, 4.2$  Hz), 2.11 (1H, br s), 1.79 (1H, dd,  $J = 17.0, 10.6$  Hz); <sup>13</sup>C-NMR (CDCl<sub>3</sub>; 100 MHz)  $\delta$  170.63, 164.85, 144.59, 133.79, 130.03 (2), 127.30 (2), 114.92, 93.53, 66.48, 64.96, 52.67, 52.03, 43.08, 35.64, 21.52; HRMS (ESI): Calcd for C<sub>17</sub>H<sub>20</sub>N<sub>2</sub>NaO<sub>5</sub>S [M+Na]<sup>+</sup>: 387.0991, Found: 387.1019.

**Methyl (2*S*,3*S*)-4-(cyanomethyl)-2-(hydroxymethyl)-1-tosylpyrrolidin-3-yl)acetate (5).** To a flask were added **13** (310 mg, 0.85 mmol) and Rh(PPh<sub>3</sub>)<sub>3</sub>Cl (78.7 mg, 85.1  $\mu$ mol). After DCE (20 mL) was added to the reaction mixture, the flask was flushed with H<sub>2</sub>. After stirring for 23 h at 80 °C, the volatile solvent was removed in vacuo to leave a residue, which was purified by column chromatography on silica gel using AcOEt-Et<sub>2</sub>O (5:95, v/v) as eluent to give *anti*-**5** (49 mg, 16%), *syn*-**5** + *anti*-**5** (114 mg, 36%) and *syn*-**5** (106 mg, 34%) as a colorless oil.

**Methyl 2-(2*S*,3*S*,4*R*)-4-(cyanomethyl)-2-(hydroxymethyl)-1-tosylpyrrolidin-3-yl)acetate (*syn*-**5**).**  $[\alpha]_D^{26} +0.5$  ( $c$  1.1, CHCl<sub>3</sub>); IR  $\nu_{\max}$  3509, 2249, 1731, 1341 and 1163 cm<sup>-1</sup>; <sup>1</sup>H-NMR (CDCl<sub>3</sub>; 400 MHz)  $\delta$  7.75 (2H, d,  $J = 8.3$  Hz), 7.38 (2H, d,  $J = 8.3$  Hz), 3.87 (1H, dd,  $J = 11.8, 4.3$  Hz), 3.72 (1H, dd,  $J = 11.8, 4.3$  Hz), 3.67 (1H, dd,  $J = 10.8, 6.3$  Hz), 3.65 (3H, s), 3.35 (1H, dd,  $J = 9.1, 4.3$  Hz), 3.19 (1H, dd,  $J = 10.8, 6.7$  Hz), 2.83-2.73 (1H, m), 2.72-2.63 (1H, m), 2.46 (3H, s), 2.18 (1H, dd,  $J = 16.7, 6.4$  Hz), 2.10

(1H, br s), 2.02 (1H, dd,  $J = 16.4, 7.5$  Hz), 1.76 (1H, dd,  $J = 16.4, 8.1$  Hz), 1.71 (1H, dd,  $J = 16.7, 9.3$  Hz);  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ ; 100 MHz)  $\delta$  171.33, 144.53, 133.25, 130.10 (2), 127.48 (2), 117.49, 65.54, 64.66, 52.22, 52.09, 39.90, 36.34, 31.77, 21.59, 16.23; HRMS (ESI): Calcd for  $\text{C}_{17}\text{H}_{22}\text{N}_2\text{NaO}_5\text{S}$   $[\text{M}+\text{Na}]^+$ : 389.1147, Found: 389.1161.

**Methyl 2-(2*S*,3*S*,4*S*)-4-(cyanomethyl)-2-(hydroxymethyl)-1-tosylpyrrolidin-3-yl)acetate (anti-5).**  $[\alpha]_{\text{D}}^{22} -15.0$  ( $c$  0.9,  $\text{CHCl}_3$ ); IR  $\nu_{\text{max}}$  3523, 2250, 1734, 1343 and 1161  $\text{cm}^{-1}$ ;  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ ; 400 MHz)  $\delta$  7.73 (2H, d,  $J = 8.3$  Hz), 7.38 (2H, d,  $J = 8.3$  Hz), 3.93 (1H, dd,  $J = 11.9, 3.5$  Hz), 3.70 (1H, dd,  $J = 11.9, 4.4$  Hz), 3.69 (1H, dd,  $J = 11.9, 7.4$  Hz), 3.64 (3H, s), 3.35 (1H, ddd,  $J = 6.9, 4.4, 3.5$  Hz), 3.26 (1H, dd,  $J = 11.9, 8.6$  Hz), 2.53 (1H, dd,  $J = 17.1, 5.7$  Hz), 2.47 (3H, s), 2.42 (1H, dd,  $J = 17.1, 7.8$  Hz), 2.35-2.22 (3H, m), 2.07 (1H, br s), 1.77-1.66 (1H, m);  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ ; 100 MHz)  $\delta$  171.42, 144.47, 133.60, 130.08 (2), 127.56 (2), 117.38, 66.92, 63.82, 53.35, 52.01, 42.50, 39.33, 36.40, 21.60, 19.36; HRMS (ESI): Calcd for  $\text{C}_{17}\text{H}_{22}\text{N}_2\text{NaO}_5\text{S}$   $[\text{M}+\text{Na}]^+$ : 389.1147, Found: 389.1160.

**(2*S*,3*S*,4*R*)-Methyl 4-(cyanomethyl)-3-(2-methoxy-2-oxoethyl)-1-tosylpyrrolidine-2-carboxylate (14).**

To a solution of alcohol *syn*-5 (104 mg, 0.28 mmol) in MeCN (2 mL) was added 1 M phosphate buffer (pH = 6.8, 2 mL) at room temperature. To the mixture were added AZADOL<sup>®</sup> (9.0 mg, 58.8  $\mu\text{mol}$ ) and  $\text{PhI}(\text{OAc})_2$  (272 mg, 0.85 mmol) at 0  $^\circ\text{C}$ , and the resulting mixture were further stirred at room temperature for 2 h. The reaction was quenched with sat. aqueous  $\text{Na}_2\text{S}_2\text{O}_3$  solution, and the whole was stirred for 0.5 h at ambient temperature. The mixture was treated with brine, and extracted with  $\text{CHCl}_3$ -MeOH (9:1, v/v) ( $\times 3$ ). The extract was washed with brine, and concentrated in vacuo to leave a residue, which was used for the next step without further purification. To a solution of the corresponding carboxylic acid in benzene-MeOH (4 mL, 1:1) was added dropwise  $\text{TMSCHN}_2$  (0.6 M in hexane, 0.95 mL) at room temperature. After stirring for 10 min at the same temperature, the volatile solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel using hexane-AcOEt (4:6, v/v) as eluent to give ester 14 (102 mg, 91%) as a white solid. Mp 114.3–118.1  $^\circ\text{C}$ ;  $[\alpha]_{\text{D}}^{23} -17.1$  ( $c$  1.0,  $\text{CHCl}_3$ ); IR  $\nu_{\text{max}}$  2252, 1739, 1733, 1348, 1211 and 1165  $\text{cm}^{-1}$ ;  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ ; 400 MHz)  $\delta$  7.76 (2H, d,  $J = 8.2$  Hz), 7.35 (2H, d,  $J = 8.2$  Hz), 4.05 (1H, d,  $J = 5.6$  Hz), 3.74 (3H, s), 3.68 (3H, s), 3.66 (1H, dd,  $J = 10.6, 6.1$  Hz), 3.35 (1H, dd,  $J = 10.6, 4.9$  Hz), 2.91-2.77 (2H, m), 2.44 (3H, s), 2.27 (2H, d,  $J = 5.9$  Hz), 2.25 (1H, dd,  $J = 16.7, 5.9$  Hz), 1.90 (1H, dd,  $J = 16.7, 9.0$  Hz);  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ ; 100 MHz)  $\delta$  171.19, 170.92, 144.34, 134.73, 129.95 (2), 127.46 (2), 63.95, 52.88, 52.30, 51.26, 42.41, 37.36, 31.85, 21.63, 16.19; HRMS (ESI): Calcd for  $\text{C}_{17}\text{H}_{22}\text{N}_2\text{NaO}_5\text{S}$   $[\text{M}+\text{Na}]^+$ : 417.1096, Found: 417.1100.

**(2*S*,3*S*,4*S*)-Methyl 3-(2-methoxy-2-oxoethyl)-4-(propen-2-yl)-1-tosylpyrrolidine-2-carboxylate (4).**

To a solution of ester **14** (60.5 mg, 154  $\mu\text{mol}$ ) in pyridine-H<sub>2</sub>O-AcOH (2:1:1, 4 mL) were added NaH<sub>2</sub>PO<sub>2</sub>·H<sub>2</sub>O (163 mg, 1.54 mmol) and Raney Ni (280 mg, 4.75 mmol) at ambient temperature. After stirring for 1.5 h at the same temperature, NaH<sub>2</sub>PO<sub>2</sub>·H<sub>2</sub>O (163 mg, 1.54 mmol) and Raney Ni (272 mg, 4.61 mmol) were further added to the above mixture. After stirring for 1.5 h at the same temperature, NaH<sub>2</sub>PO<sub>2</sub>·H<sub>2</sub>O (162 mg, 1.53 mmol) and Raney Ni (285 mg, 4.83 mmol) were further added to the above mixture. After stirring for 1.5 h, the reaction mixture was poured into sat. aqueous NaHCO<sub>3</sub> solution, and extracted with AcOEt ( $\times 2$ ). The extract was washed with brine, sat. aqueous KHSO<sub>4</sub> solution ( $\times 2$ ), brine, sat. aqueous NaHCO<sub>3</sub> solution and brine. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo, and the residue was used for the next step without further purification. To a solution of the corresponding aldehyde **15** in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) were added Et<sub>3</sub>N (65  $\mu\text{L}$ , 462  $\mu\text{mol}$ ) and Eschenmoser's salt (57.6 mg, 311  $\mu\text{mol}$ ) under Ar. After stirring for 14 h at room temperature, the reaction mixture was poured into sat. aqueous NH<sub>4</sub>Cl solution and extracted with AcOEt ( $\times 2$ ). The extract was washed with sat. aqueous NH<sub>4</sub>Cl solution and brine, and dried over Na<sub>2</sub>SO<sub>4</sub>. Evaporation of the solvent gave a residue, which was used for the next step without further purification. To a solution of the corresponding  $\alpha,\beta$ -unsaturated aldehyde in CHCl<sub>3</sub>-MeOH (5 mL, 4:1) containing CeCl<sub>3</sub>·7H<sub>2</sub>O (172 mg, 462  $\mu\text{mol}$ ), was added portionwise NaBH<sub>4</sub> (12.5 mg, 329  $\mu\text{mol}$ ) at  $-78$  °C. After stirring for 15 min at the same temperature, the reaction mixture was warmed up to 0 °C over 1 h, and treated with H<sub>2</sub>O. The mixture was extracted with AcOEt ( $\times 3$ ), and the extract was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo to give a crude alcohol **16**. To a solution of the crude alcohol **16** in CH<sub>2</sub>Cl<sub>2</sub> (6 mL) were added DMAP (3.9 mg, 32.0  $\mu\text{mol}$ ), pyridine (62  $\mu\text{L}$ , 0.77 mmol), and Ac<sub>2</sub>O (80  $\mu\text{L}$ , 0.85 mmol) at ambient temperature under Ar, and stirred for 2 h at the same temperature. The mixture was poured into sat. aqueous KHSO<sub>4</sub> solution, and extracted with AcOEt ( $\times 2$ ). The extract was washed with brine, sat. aqueous NaHCO<sub>3</sub> solution and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated to give crude acetate. To a solution of the crude acetate in 1,4-dioxane (5 mL) were added HCO<sub>2</sub>NH<sub>4</sub> (19.6 mg, 0.31 mmol), Pd(OAc)<sub>2</sub> (3.6 mg, 16.0  $\mu\text{mol}$ ) and PPh<sub>3</sub> (16.3 mg, 62.2  $\mu\text{mol}$ ) under Ar. After stirring for 1 h at reflux, the reaction mixture was poured into sat. aqueous NaHCO<sub>3</sub> solution. The volatile solvent was removed in vacuo to leave a residue, which was extracted with AcOEt ( $\times 3$ ). The extract was washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel using hexane-AcOEt (6:4, v/v) as eluent to give Yoo's intermediate **4** (20.5 mg, 34%) as a yellow solid.  $[\alpha]_{\text{D}}^{23} -47.1$  ( $c$  0.6, CHCl<sub>3</sub>), [lit:  $[\alpha]_{\text{D}}^{25} -45.1$  ( $c$  1.3, CHCl<sub>3</sub>)]; <sup>1</sup>H-NMR (CDCl<sub>3</sub>; 400 MHz)  $\delta$  7.77 (2H, d,  $J = 8.3$  Hz), 7.32 (2H, d,  $J = 8.3$  Hz), 4.88 (1H, s), 4.58 (1H, s), 4.29 (1H, s), 3.76 (3H, s), 3.65 (3H, s), 3.55 (1H, dd,  $J = 8.9, 7.2$  Hz), 3.24 (1H, t,  $J = 9.6$  Hz), 3.13-3.04 (1H,

m), 2.85-2.76 (1H, m), 2.43 (3H, s), 2.06 (1H, dd,  $J = 16.8, 4.0$  Hz), 1.64 (3H, s), 1.56 (1H, dd,  $J = 16.8, 10.8$  Hz);  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ ; 100 MHz)  $\delta$  171.98, 171.69, 143.80, 140.05, 134.85, 129.62 (2), 127.44 (2), 113.19, 65.04, 52.65, 51.82, 48.28, 46.09, 41.39, 31.73, 22.57, 21.53; HRMS (ESI): Calcd for  $\text{C}_{19}\text{H}_{26}\text{NO}_6\text{S}$   $[\text{M}+\text{H}]^+$ : 396.1481, Found: 396.1495.

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