SYNTHESIS OF PIPECOLIC ACID AND BAIKIAIN

Meng-Yang Chang,* Yung-Hua Kung, and Tsun-Cheng Wu

Department of Applied Chemistry, National University of Kaohsiung, Kaohsiung 811, Taiwan. Email: mychang@nuk.edu.tw

Abstract– A straightforward synthesis of pipecolic acid and baikaiain was achieved from trans-(2S,4R)-4-hydroxyproline via the key steps of regioselective Baeyer-Villiger reaction and ring-closing metathesis.

Based on the structural framework of trans-(2S,4R)-4-hydroxyproline, it possesses three functional groups that can be easily modified. The skeleton represents the significant feature for producing a series of different carbon framework using an efficient modification technique. Recently, we have introduced a facile approach toward anisomycin, epibatidine, pancracine, streptorubin B core, and vigabatrin employing trans-(2S,4R)-4-hydroxyproline as the starting material. Functionalized piperidines are among the most ubiquitous heterocyclic building blocks of natural and synthetic compounds with a wide range of pharmacological activity. Therefore, a huge amount of synthetic effort has been spent on the preparation of these systems. With respect to biological active target molecules, there is an increasing interest in the diastereo- and enantioselective preparation of substituted piperidines. Basically, the adopted strategies can be summarized in intramolecular nucleophilic substitution of an activated alcohol moiety by amines, ring-closing metathesis of unsaturated amines, direct base-induced α-functionalization of piperidines, ring-expansion of substituted prolinols, and chiral materials. In connection with our studies on the trans-(2S,4R)-4-hydroxyproline (1) as the chiral material, we are interested in developing a feasible and straightforward approach to pipecolic acid (2) and baikaiain (3) via two key approaches employing regioselective Baeyer-Villiger reaction and ring-closing metathesis (Figure 1).

Figure 1. Structures of trans-(2S,4R)-4-hydroxyproline (1), pipecolic acid (2) and baikaiain (3)
The synthesis of pipecolic acid (2) and baikiain (3) began from prolinol (4) as illustrated in Scheme 1. The four-step preparation with 90% overall yield was reported from \textit{trans}-(2S,4R)-4-hydroxyproline (1). First, ketone (5) was provided via \textit{O}-benzylaion of prolinol (4) with benzyl bromide and sodium hydride and followed by desilylation and subsequent oxidation of the corresponding secondary alcohol via Jones oxidation. With the results in hand, regioselective Baeyer-Villiger reaction of ketone (5) was next examined. While poring over the related literature, we found that Young’s group had developed the copper(II) acetate-mediated ring-expansion of 4-ketoprolines with \textit{m}-chloroperoxybenzoic acid. How is the regioselective Beayer-Villiger process initiated? The most likely explanation would be that it is controlled by involvement of the nitrogen lone pair on the substituted pyrrolidin-4-one. Therefore, regioselective Baeyer-Villiger reaction of ketone (5) was yielded a sole tetrahydro-1,3-oxazin-6-one ring skeleton with a rotamer of nearly 1:1 ratio at room temperature. In order to increase higher yields, other commercial available reagents and reaction conditions were tested. When the reaction was treated with the combination of sodium carbonate and \textit{m}-chloroperoxybenzoic acid, the yield was increased without other regioisomers. For the synthetic efficiency, sodium carbonate is better than copper(II) acetate in our cases during the regiospecific ring expansion. The difference between sodium carbonate and copper(II) acetate was not clear.

Scheme 1. Synthesis of pipecolic acid (2) and baikiain (3)
Reduction of the corresponding regioisomer was provided aminoalcohol (6). Compound (7) were synthesized via O-silylation of aminoalcohol (6) with t-butylidimethylsilyl chloride and imidazole and followed by N-allylation of the resultant product with sodium hydride and allyl bormide. Further, in order to achieve the synthesis of target compounds, we required the reasonable intermediate (8) for the synthetic manipulation. To this end, compound (7) was treated with desilylation, oxidation and Wittig olefination to afford diene (8). To build up the piperidine skeleton, diene (8) was subjected to a ring-closing metathesis employing Grubbs’ 2nd catalyst, the expected piperidine ring system (9) was generated. Synthesis of N-tosylpipecolic acid (10) and N-tosylbaikiain (11) was achieved via hydrogenation of compound (9) and Jones oxidation of the resulting alcohol, and debenzylation of compound (9) with boron tribromide and followed by Jones oxidation. The known compounds (10) and (11) were transformed to piceolic acid (2) and baikiain (3) by the reductive desulfonation with 6% sodium amalgam in methanol from the literature reference. In summary, we succeeded in accomplishing the synthesis of piceolic acid (2) and baikiain (3) from trans-(2S,4R)-4-hydroxyproline (1) in moderate yields via regioselective Baeyer-Villiger reaction and ring-closing metathesis as the key steps. Currently studies are in progress in this direction.

EXPERIMENTAL

General. Tetrahydrofuran (THF) was distilled prior to use from a deep-blue solution of sodium-benzophenone ketyl. All other reagents were obtained from commercial sources and used without further purification. Reaction was routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Crude product was purified using column chromatography on SiO2 (MN Kieselgel 60, 70–230 mesh).

(2S)-2-Benzylxymethyl-1-(4-methylphenylsulfonyl)pyrrolidin-4-one (5).

A solution of prolinol (4) (7.7 g, 20.0 mmol) in THF (100 mL) was added to a rapidly stirred suspension of sodium hydride (1.60 g, 60%, 40.0 mmol) in THF (30 mL). After the reaction mixture was stirred at rt for 20 min, a solution of benzyl bromide (5.0 g, 29.0 mmol) in THF (100 mL) was added. The reaction mixture was stirred at refluxed temperature for 20 h. The resulting mixture was cooled to rt, quenched with aqueous NH4Cl (15%, 10 mL) and concentrated. The residue was extracted with AcOEt (3 x 150 mL) and the combined organic layers were washed with brine, dried, filtered and evaporated to afford the crude product. Without further purification, excess Jones reagent (50 mL) was added to a stirred solution of resulting benzyl compound in acetone (200 mL) at 0 °C. The mixture was stirred for 20 min and treated with 2-propanol (10 mL) to destroy the unreacted oxidation reagent. After the solvent was removed, the residue was diluted with water (10 mL) and extracted with Et2O (3 x 150 mL). The combined organic layers were dried, filtered and evaporated to afford crude product. Purification on silica gel
(hexane/AcOEt = 4/1) afforded compound (5) (5.9 g, two steps 82%). \([\alpha]^{25.4}_D +41.10^o \) (c 0.21, CHCl3); FAB-MS: C19H22NO4S m/z (%) = 91 (100), 155 (19), 224 (36), 238 (52), 360 (M+1, 17); HRMS (ESI, M+1) calcld for C19H22NO4S 360.1270, found 360.1272; 1H NMR (500 MHz, CDCl3) \(\delta\) 7.72 (d, \(J = 8.5\) Hz, 2H), 7.32-7.26 (m, 5H), 7.16 (d, \(J = 8.5\) Hz, 2H), 4.43 (d, \(J = 12.0\) Hz, 1H), 4.43-4.38 (m, 1H), 4.37 (d, \(J = 12.0\) Hz, 1H), 3.78 (dd, \(J = 3.5, 9.5\) Hz, 1H), 3.76 (s, 2H), 3.52 (dd, \(J = 3.5, 9.5\) Hz, 1H), 2.43 (s, 3H), 2.39-2.29 (m, 2H), 13C NMR (125 MHz, CDCl3) \(\delta\) 209.09, 144.08, 137.39, 135.36, 130.01 (2x), 128.41 (2x), 127.75, 127.31 (2x), 127.07 (2x), 73.37, 73.22, 56.84, 53.92, 40.47, 21.52; Anal. Calcld for C19H21NO4S: C, 63.49; H, 5.89; N, 3.90. Found: C, 63.41; H, 6.01; N, 3.71.

(2S)-N-(1-Benzoyloxymethyl-3-hydroxypropyl)-4-methylbenzenesulphonamide (6).

A stirred solution of \(m\)-chloroperoxybenzoic acid (600 mg, 75%, 2.6 mmol) in CH2Cl2 (10 mL) was added to a solution of ketone (5) (360 mg, 1.0 mmol) and Na2CO3 (420 mg, 4.0 mmol) in CH2Cl2 (20 mL) at 0 °C. The reaction mixture was stirred at rt for 20 h. Aqueous Na2CO3 (10 mL) was added to the reaction mixture and the solvent was concentrated. The residue was extracted with AcOEt (3 x 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product. Without further purification, a solution of crude lactone product in THF (10 mL) was added to a rapidly stirred suspension of lithium aluminum hydride (76 mg, 2.0 mmol) in THF (10 mL) at 0 °C. The reaction mixture was stirred at rt for 2 h. Aqueous NH4Cl (15%, 2 mL) was added to the reaction mixture. After the solvent was removed, the residue was diluted with water (10 mL) and extracted with AcOEt (3 x 30 mL). The combined organic layers were dried, filtered and evaporated to afford crude product. Purification on silica gel (hexane/AcOEt = 5/1) afforded aminoalcohol (6) (270 mg, 77%). \([\alpha]^{30.8}_D -24.12^o \) (c 0.017, CHCl3); HRMS (ESI) m/z calcld for C18H24NO4S (M+1) 350.1426, found 350.1428; 1H NMR (500 MHz, CDCl3) \(\delta\) 7.68 (d, \(J = 8.5\) Hz, 2H), 7.34-7.30 (m, 3H), 7.27-7.20 (m, 4H), 4.98 (d, \(J = 8.5\) Hz, 1H), 4.40 (d, \(J = 12.0\) Hz, 1H), 4.31 (d, \(J = 12.0\) Hz, 1H), 3.88-3.83 (m, 1H), 3.68-3.64 (m, 1H), 3.60 (br s, 1H), 3.58-3.55 (m, 1H), 3.29 (dd, \(J = 1.8, 9.5\) Hz, 1H), 3.13 (dd, \(J = 4.5, 9.5\) Hz, 1H), 2.42 (s, 3H), 1.75-1.68 (m, 1H), 0.90-0.85 (m, 1H); 13C NMR (125 MHz, CDCl3) \(\delta\) 143.43, 137.42, 136.70, 129.68 (2x), 128.50 (2x), 127.96, 127.72 (2x), 126.98 (2x), 73.25, 71.26, 58.62, 50.52, 35.11, 21.54; Anal. Calcld for C18H23NO4S: C, 61.87; H, 6.63; N, 4.01. Found: C, 61.93; H, 6.82; N, 3.68.

(2S)-N-Allyl-N-[1-benzoyloxymethyl-3-(\(t\)-butyldimethylsilanyloxy)propyl]-4-methylbenzenesulphonamide (7).

t-Butyldimethylsilyl chloride (196 mg, 1.3 mmol) and imidazole (136 mg, 2.0 mmol) were added to a stirred solution of compound (6) (350 mg, 1.0 mmol) in DMF (5 mL) at rt. The reaction mixture was stirred at rt for 2 h. The reaction mixture was concentrated. The residue was diluted with water (10 mL) and the mixture was extracted with AcOEt (3 x 20 mL). The combined organic layers were washed with...
brine, dried, filtered and evaporated to yield crude product. Purification on silica gel (hexane/AcOEt = 5/1) afforded silyl product (440 mg, 95%). \([\alpha]^{31.4}_D -25.60^\circ (c 0.025, \text{CHCl}_3); \text{HRMS (ESI) } m/z \text{ calcd for } C_{24}H_{38}NO_4SSi (M^{++1}) 464.2291, \text{ found } 464.2295; \text{ } ^1\text{H NMR (500 MHz, CDCl}_3) \delta 7.73 (d, J = 8.0 Hz, 2H), 7.35-7.23 (m, 7H), 5.47 (d, J = 6.5 Hz, 1H), 4.42 (d, J = 12.0 Hz, 1H), 4.38 (d, J = 12.0 Hz, 1H), 3.65-3.61 (m, 1H), 3.53-3.49 (m, 3H), 3.38-3.35 (m, 1H), 2.42 (s, 3H), 1.71-1.68 (m, 2H), 0.88 (s, 9H), 0.01 (s, 6H); \text{ } ^13\text{C NMR (125 MHz, CDCl}_3) \delta 143.08, 137.84, 129.53 (2x), 128.39 (2x), 127.75 (2x), 127.66 (2x), 127.11 (2x), 73.16, 71.19, 60.09, 51.87, 33.79, 25.85 (3x), 21.50, 18.10, -5.55 (2x).

A solution of silyl compound (465 mg, 1.0 mmol) in DMF (2 mL) was added to a rapidly stirred suspension of sodium hydride (60%, 100 mg, 2.5 mmol) in DMF (3 mL). After the reaction mixture was stirred at 0 °C for 5 min, allyl bromide (250 mg, 2.1 mmol) was added at 0 °C. The resulting mixture was stirred at rt for 3 h. The reaction was quenched with aqueous NH$_4$Cl (15%, 1 mL) and the mixture was concentrated. The residue was diluted with water (10 mL) and the mixture was extracted with AcOEt (3 x 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to yield crude product. Purification on silica gel (hexane/AcOEt = 10/1) afforded compound (7) (463 mg, 92%). \([\alpha]^{30.0}_D -10.00^\circ (c 0.008, \text{CHCl}_3); \text{HRMS (ESI) } m/z \text{ calcd for } C_{27}H_{42}NO_4SSi (M^{++1}) 504.2604, \text{ found } 504.2608; \text{ } ^1\text{H NMR (500 MHz, CDCl}_3) \delta 7.72 (d, J = 8.0 Hz, 2H), 7.34-7.27 (m, 3H), 7.21-7.17 (m, 4H), 5.84-5.76 (m, 1H), 5.13 (dd, J = 1.0, 17.0 Hz, 1H), 5.05 (dd, J = 1.0, 10.0 Hz, 1H), 4.40 (d, J = 12.0 Hz, 1H), 4.34 (d, J = 12.0 Hz, 1H), 4.18-4.13 (m, 1H), 3.86 (d, J = 6.5 Hz, 2H), 3.56-3.47 (m, 4H), 2.38 (s, 3H), 1.84-1.71 (m, 2H), 0.88 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); \text{ } ^13\text{C NMR (125 MHz, CDCl}_3) \delta 142.75, 138.29, 137.96, 136.06, 129.27 (2x), 128.27 (2x), 127.60 (2x), 127.56, 127.42 (2x), 117.07, 72.86, 71.36, 60.14, 55.09, 47.51, 33.69, 25.90 (3x), 21.47, 18.22, -5.38, -5.44; \text{Anal. Calcd for } C_{27}H_{41}NO_4SSi: C, 64.37; H, 8.20; N, 2.78. Found: C, 64.65; H, 8.45; N, 2.56.

(2S)-N-Allyl-N-(1-benzyloxymethyl-but-3-enyl)-4-methyl-benzenesulfonamide (8).
A solution of tetra-n-butylammonium fluoride (1.0 M in THF, 1.2 mL, 1.2 mmol) in THF (2 mL) was added to a solution of compound (7) (503 mg, 1.0 mmol) in THF (20 mL) at rt. The reaction mixture was stirred at rt for 2 h. Aqueous NH$_4$Cl (15%, 1 mL) was added to the mixture reaction and concentrated. The residue was extracted with AcOEt (3 x 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product. Purification on silica gel (hexane/AcOEt = 4/1) afforded product (371 mg, 95%). \([\alpha]^{31.0}_D -62.78^\circ (c 0.018, \text{CHCl}_3); \text{HRMS (ESI) } m/z \text{ calcd for } C_{21}H_{26}NO_4SSi (M^{++1}) 390.1739, \text{ found } 390.1741; \text{ } ^1\text{H NMR (500 MHz, CDCl}_3) \delta 7.71 (d, J = 8.5 Hz, 2H), 7.32-7.28 (m, 3H), 7.15 (d, J = 8.5 Hz, 2H), 7.11-7.09 (m, 2H), 5.83-5.75 (m, 1H), 5.10 (dd, J = 1.0, 17.0 Hz, 1H), 5.05 (dd, J = 1.0, 10.0 Hz, 1H), 4.32-4.28 (m, 1H), 4.29 (d, J = 12.0 Hz, 1H), 4.24 (d, J = 12.0 Hz, 2H), 4.17, 18.22, -5.38, -5.44; \text{Anal. Calcd for } C_{21}H_{28}NO_4SSi: C, 64.37; H, 8.20; N, 2.78. Found: C, 64.65; H, 8.45; N, 2.56.
A solution of alcohol product (390 mg, 1.0 mmol) in CH₂Cl₂ (5 mL) was added to a mixture of pyridinium chlorochromate (431 mg, 2.0 mmol) and Celite (1.0 g) in CH₂Cl₂ (20 mL). After being stirred at rt for 20 h, the mixture was filtered through a short silica gel column. The filtrate was dried, filtered and evaporated to yield crude product. Purification on silica gel (hexane/AcOEt = 5/1) afforded aldehyde product (338 mg, 87%). \([\alpha]^{30.1}_D -3.53^o\) (c 0.018, CHCl₃); HRMS (ESI) m/z calced for C₂₁H₂₆NO₄S (M⁺+1) 388.1583, found 388.1588; \(^1\)H NMR (500 MHz, CDCl₃) δ 9.59 (s, 1H), 7.70 (d, \(J = 8.5\) Hz, 2H), 7.34-7.28 (m, 3H), 7.23 (d, \(J = 8.5\) Hz, 2H), 7.18 (d, \(J = 7.0\) Hz, 2H), 5.82-5.74 (m, 1H), 5.16 (d, \(J = 17.0\) Hz, 1H), 5.11 (d, \(J = 10.0\) Hz, 1H), 4.57-4.52 (m, 1H), 4.39 (d, \(J = 12.0\) Hz, 1H), 4.34 (d, \(J = 12.0\) Hz, 1H), 3.89-3.82 (m, 2H), 3.56 (dd, \(J = 6.5, 10.0\) Hz, 1H), 3.47 (dd, \(J = 6.5, 10.0\) Hz, 1H), 2.78 (ddd, \(J = 1.0, 6.5, 17.0\) Hz, 1H), 2.69 (ddd, \(J = 1.0, 6.5, 17.0\) Hz, 1H), 2.40 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl₃) δ 199.44, 143.35, 137.58, 137.46, 135.38, 129.56 (2x), 128.28 (2x), 127.37 (2x), 127.27 (2x), 117.98, 73.03, 70.62, 52.55, 48.30, 45.31, 21.51.

\(n\)-Butyllithium (1.0 mL, 1.6 M in hexane, 1.6 mmol) was added to a stirred solution of methyl triphenylphosphonium iodide (808 mg, 2.0 mmol) in THF (20 mL) at −78 °C. The orange red colored mixture was stirred at −78 °C for 1 h. A solution of aldehyde product (194 mg, 0.5 mmol) in THF (5 mL) was added to the reaction mixture at −78 °C via a syringe and further stirred at −78 °C for 2 h. The reaction was quenched with aqueous NH₄Cl (15%, 10 mL) and the mixture was extracted with Et₂O (3 x 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product. Purification on silica gel (hexane/EtOAc = 2/1) afforded compound (8) (154 mg, 80%). \([\alpha]^{32.1}_D -14.41^o\) (c 0.011, CHCl₃); HRMS (ESI) m/z calced for C₂₂H₂₈NO₃S (M⁺+1) 386.1790, found 386.1794; \(^1\)H NMR (500 MHz, CDCl₃) δ 7.71 (d, \(J = 8.5\) Hz, 2H), 7.36-7.27 (m, 3H), 7.21-7.17 (m, 4H), 5.84-5.76 (m, 1H), 5.67-5.59 (m, 1H), 5.13 (dd, \(J = 1.5, 17.5\) Hz, 1H), 5.05 (dd, \(J = 1.5, 10.5\) Hz, 1H), 5.02 (dd, \(J = 1.5, 16.5\) Hz, 1H), 4.98 (d, \(J = 10.0\) Hz, 1H), 4.40 (d, \(J = 12.0\) Hz, 1H), 4.34 (d, \(J = 12.0\) Hz, 1H), 4.14-4.07 (m, 1H), 3.88 (dd, \(J = 7.0, 16.5\) Hz, 1H), 3.82 (dd, \(J = 6.0, 16.5\) Hz, 1H), 3.51 (dd, \(J = 7.0, 10.0\) Hz, 1H), 3.45 (dd, \(J = 5.5, 10.0\) Hz, 1H), 2.42-2.35 (m, 1H), 2.38 (s, 3H), 2.31-2.26 (m, 1H); \(^{13}\)C NMR (125 MHz, CDCl₃) δ 142.80, 138.17, 137.85, 136.21, 134.60, 129.23 (2x), 128.28 (2x), 127.62 (2x), 127.60, 127.44 (2x), 117.46, 117.95, 72.91, 70.68, 57.63, 47.17, 35.27, 21.47; Anal. Calcd for C₂₂H₂₈NO₃S: C, 68.54; H, 7.06; N, 3.63. Found: C, 68.33; H, 7.40; N, 3.95.
(2S)-2-Benzylxoyethyl-1-(4-methylphenylsulfonyl)-1,2,3,6-tetrahydropyridine (9).

Grubbs’ 2nd generation catalyst (30 mg) was added to a solution of compound (8) (78 mg, 0.2 mmol) in CH₂Cl₂ (50 mL) at rt. The reaction mixture was refluxed under nitrogen atmosphere for 2 h. The mixture was concentrated and purified by flash column chromatography (hexane/AcOEt = 4/1) to afford compound (9) (63 mg, 88%). [α]³¹⁹⁺ D -13.85° (c 0.013, CHCl₃); HRMS (ESI) m/z calcd for C₂₀H₂₄NO₃S (M⁺+1) 358.1477, found 358.1480; ¹H NMR (300 MHz, CDCl₃) δ 7.69 (d, J = 8.1 Hz, 2H), 7.33-7.19 (m, 7H), 5.66-5.55 (m, 2H), 4.47 (d, J = 12.0 Hz, 1H), 4.39-4.35 (m, 1H), 4.37 (d, J = 12.0 Hz, 1H), 4.08 (d, J = 18.3 Hz, 1H), 3.57-3.36 (m, 3H), 2.39 (s, 3H), 2.22-2.05 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 143.23, 138.25, 137.83, 129.71 (2x), 128.60 (2x), 127.87 (2x), 127.84, 127.32 (2x), 123.66, 122.67, 73.13, 68.91, 49.66, 41.12, 25.47, 21.73; Anal. Calcd for C₂₀H₂₃NO₃S: C, 67.20; H, 6.49; N, 3.92. Found: C, 67.36; H, 6.61; N, 3.59.

(2S)-1-(4-Methylphenylsulfonyl)piperidine-2-carboxylic acid (N-tosylpipecolic acid, 10).

Compound (9) (54 mg, 0.15 mmol) was dissolved in MeOH (20 mL) and 10% Pd/C (10 mg) as catalyst was added. Then hydrogen was bubbled into the mixture for 10 min, and stirring occurred at rt for 10 h. The mixture was filtered through a short silica gel column. The filtrate was dried, filtered and evaporated to yield crude product. Purification on silica gel (hexane/AcOEt = 5/1) afforded alcohol product (37 mg, 92%). HRMS (ESI) m/z calcd for C₁₃H₂₀NO₃S (M⁺+1) 270.1164, found 270.1166; ¹H NMR (300 MHz, CDCl₃) δ 7.73 (d, J = 8.1 Hz, 2H), 7.28 (J = 8.1 Hz, 2H), 4.02-3.97 (m, 1H), 3.81 (t, J = 11.1 Hz, 1H), 3.83-3.75 (m, 1H), 3.55 (dd, J = 5.7, 11.1 Hz, 1H), 3.08 (td, J = 2.4, 12.3 Hz, 1H), 2.41 (s, 3H), 2.13 (br s, 1H), 1.60-1.19 (m, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 143.47, 138.36, 19.99 (2x), 127.23 (2x), 60.91, 54.92, 41.64, 25.02, 24.44, 21.73, 19.38.

Excess Jones reagent (2 mL) was added to a solution of alcohol compound (27 mg, 0.1 mmol) in acetone (10 mL) at rt. The mixture was stirred for 20 min and treated with 2-propanol (1 mL) to destroy the unreacted oxidation reagent. After the solvent was removed, the residue was diluted with water (5 mL) and extracted with Et₂O (4 x 10 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product. Purification on silica gel (hexane/AcOEt = 1/1) afforded product (10) (25 mg, 89%). [α]²⁷⁺ D +82.86° (c 0.007, CHCl₃); HRMS (ESI) m/z calcd for C₁₃H₁₈NO₄S (M⁺+1) 284.0957, found 284.0961; ¹H NMR (300 MHz, CDCl₃) δ 7.69 (d, J = 8.1 Hz, 2H), 7.27 (J = 8.1 Hz, 2H), 4.77 (d, J = 5.1 Hz, 1H), 3.75 (d, J = 12.3 Hz, 1H), 3.19 (dt, J = 2.4, 12.3 Hz, 1H), 2.50 (br s, 1H), 2.42 (s, 3H), 2.16 (d, J = 12.3 Hz, 1H), 1.74-1.67 (m, 3H), 1.47-1.25 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 175.91, 143.61, 137.20, 129.75 (2x), 127.41 (2x), 54.99, 42.80, 27.66, 24.68, 21.76, 20.35.

(2S)-Piperidine-2-carboxylic acid (pipecolic acid, 2).
6% Sodium amalgam (Na/Hg, 0.5 g) and sodium phosphate (71 mg, 0.5 mmol) were added to a stirred solution of N-tosylpipecolic acid (10) (20 mg, 0.07 mmol) in MeOH (10 mL), and vigorously stirred for 5 h at rt. The residue was filtered and washed with water (2 x 5 mL) and the combined layers were evaporated to afford the crude products. Purification by ion exchange chromatography afforded pipecolic acid (2) (7.3 mg, 80%). The NMR spectral data of pipecolic acid (2) were in accordance with those reported in the literature.\(^{4}\)

(2S)-1-(4-Methylphenylsulfonyl)-1,2,3,6-tetrahydropyridine-2-carboxylic acid (N-tosylbaikiain, 11).\(^{5b-i}\)

A solution of boron tribromide (1.0 mL, 1.0 M in CH\(_2\)Cl\(_2\), 1.0 mmol) was added to a solution of compound (9) (54 mg, 0.15 mmol) in CH\(_2\)Cl\(_2\) (10 mL) at -78 °C. The mixture was stirred for 3 h at -78 °C and treated with aqueous NH\(_4\)Cl (15%, 5 mL) to destroy the unreacted reagent. After the solvent was removed, the residue was diluted with water (5 mL) and extracted with AcOEt (4 x 10 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product. Purification on silica gel (hexane/AcOEt = 2/1) afforded alcohol product (35 mg, 87%). HRMS (ESI) m/z calcd for C\(_{13}\)H\(_{18}\)NO\(_3\)S (M\(^{+}\)+1) 268.1007, found 268.1013; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.70 (d, \(J = 8.1\) Hz, 2H), 7.26 (d, \(J = 8.1\) Hz, 2H), 5.63-5.54 (m, 2H), 4.16-4.08 (m, 2H), 3.73-3.61 (m, 2H), 3.51-3.45 (m, 1H), 2.40 (s, 3H), 2.24 (br s, 1H), 2.10-2.02 (m, 1H), 1.91-1.84 (m, 1H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 143.63, 137.62, 129.92 (2x), 127.22 (2x), 123.57, 122.64, 61.81, 52.45, 40.82, 24.72, 21.75.

Excess Jones reagent (2 mL) was added to a solution of alcohol compound (30 mg, 0.11 mmol) in acetone (10 mL) at rt. The mixture was stirred for 20 min and treated with 2-propanol (1 mL) to destroy the unreacted oxidation reagent. After the solvent was removed, the residue was diluted with water (5 mL) and extracted with Et\(_2\)O (4 x 10 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product. Purification on silica gel (hexane/AcOEt = 1/1) afforded product (11) (27 mg, 85%). \([\alpha]^{27.1}_D\) -5.39\(^o\) (c 0.087, CHCl\(_3\)); HRMS (ESI) m/z calcd for C\(_{13}\)H\(_{16}\)NO\(_4\)S (M\(^{+}\)+1) 282.0800, found 282.0805; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.67 (d, \(J = 8.1\) Hz, 2H), 7.27 (d, \(J = 8.1\) Hz, 2H), 6.45 (br s, 1H), 5.72-5.62 (m, 2H), 4.87 (dd, \(J = 3.3, 5.1\) Hz, 1H), 4.02 (d, \(J = 17.4\) Hz, 1H), 3.84 (d, \(J = 17.4\) Hz, 1H), 2.53 (br s, 2H), 2.41 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 176.05, 143.80, 136.44, 129.77 (2x), 127.43 (2x), 123.72, 122.41, 52.56, 42.24, 27.66, 21.75.

(2S)-1,2,3,6-Tetrahydropyridine-2-carboxylic acid (baikiain, 3).

6% Sodium amalgam (Na/Hg, 0.5 g) and sodium phosphate (71 mg, 0.5 mmol) were added to a stirred solution of N-tosylbaikiain (11) (26 mg, 0.09 mmol) in MeOH (10 mL), and vigorously stirred for 5 h at rt. The residue was filtered and washed with water (2 x 10 mL) and the combined layers were evaporated
to afford the crude products. Purification by ion exchange chromatography afforded baikiain (3) (8.5 mg, 72%). The NMR spectral data of baikiain (3) were in accordance with those reported in the literature.\textsuperscript{5b-i}

**ACKNOWLEDGEMENTS**

The authors would like to thank the National Science Council (NSC-95-2113-M-390-003-MY2) of the Republic of China for financial support.

**REFERENCES AND NOTES**


