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Synthesis of α-conhydrine

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Abstract—A synthesis of α-conhydrine has been achieved from *trans*-(2*S*,4*R*)-4-hydroxyproline via diastereoselective Grignard addition, regioselective Baeyer–Villiger reaction, and ring-closing metathesis as the key steps.

1. Introduction

Based on the structural framework of *trans*-(2*S*,4*R*)-4-hydroxyproline, it possesses three functional groups that can be easily modified, and these are 1-amino, 2-carboxylate, and 4-hydroxy groups.[1] The skeleton represents the significant feature for producing a series of different carbon frameworks using an efficient modification technique.[2] Recently we have introduced a straightforward approach toward anisomycin,[2h] epibatidine,[2i] pancracine,[2j] and streptorubin B core[2k] employing *trans*-(2*S*,4*R*)-4-hydroxyproline as the starting material. To explore a new application, synthetic studies toward α-conhydrine were further investigated.

These alkaloids containing a 2-(1-hydroxyalkyl)piperidine unit with biological activities are abundant in nature.[3] Conhydrine is one of the alkaloids of the hemlock, isolated from the seeds and leaves of the poisonous alkaloids plant *Conium maculatum*, whose extracts were used in the ancient Greece for execution of criminals (Fig. 1).[4] Various methods for the asymmetric synthesis of α-conhydrine (**1a**) and β-conhydrine (**1b**) and mainly based on auxiliary-supported or chiral pool approaches have been documented in the literature.[5] In connection with our studies on the *trans*-(2*S*,4*R*)-4-hydroxyproline (**2**) as the chiral material, we are interested in developing a feasible and straightforward approach to α-conhydrine (**1a**) via diastereoselective Grignard addition, regioselective Baeyer–Villiger reaction, and ring-closing metathesis.

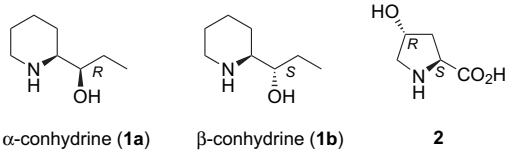
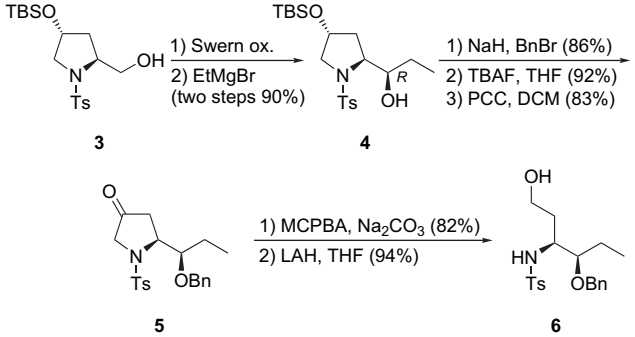


Figure 1.

2. Results and discussion

The synthesis of α-conhydrine (**1a**) began from prolinol **3** as illustrated in Scheme 1. The four-step preparation of compound **3** with 90% overall yield was reported from *trans*-(2*S*,4*R*)-4-hydroxyproline (**2**).[2i–k] First, prolinol **3** was treated with Swern oxidation and followed by Grignard addition to give compound **4** as a single isomer at −78 °C.[6] The diastereoselective addition occurred in favor of the *anti* isomer through a chelated intermediate.[5a,6] Subsequently, alcohol **4** was treated with O-benzylation, desilylation, and oxidation to afford ketone **5**. The relative *anti* configurations of compound **5** were based upon the single-crystal X-ray analysis (Fig. 2).[7]



Scheme 1.

Keywords: *trans*-(2*S*,4*R*)-4-Hydroxyproline; α-Conhydrine; Grignard addition; Regioselective Baeyer–Villiger reaction; Ring-closing metathesis.
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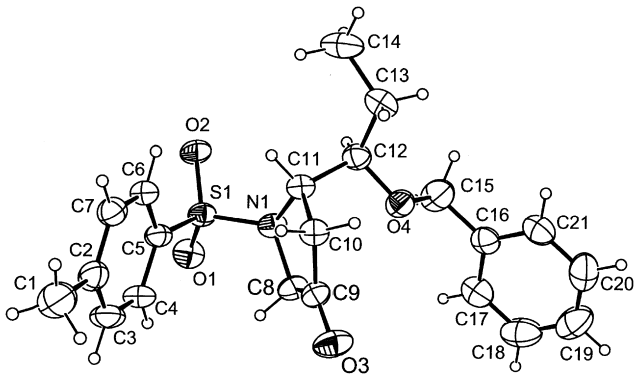
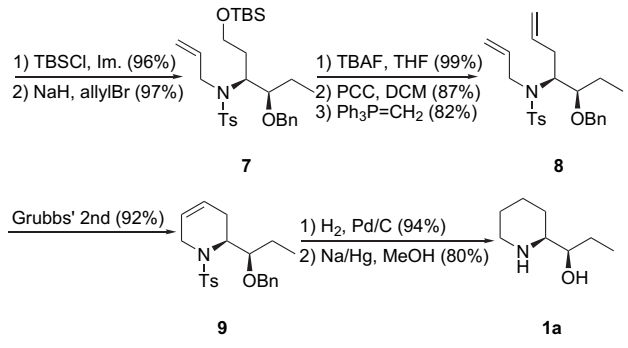


Figure 2. X-ray crystallography of compound **5**.

With the result 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 expansion of 4-ketoprolines with *m*-chloroperoxybenzoic acid.[8] We believe that the nitrogen atom can play an important factor to initiate the regiospecific ring expansion.[8c] According to the reports, compound **5** was first treated with the combination of copper(II) acetate and *m*-chloroperoxybenzoic acid. The resulting tetrahydro-1,3-oxazin-6-one skeleton was provided in moderate (42%) yield. 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 *m*-chloroperoxybenzoic acid, the yield was increased to 82% yield 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. Next, reduction of the corresponding regioisomer provided aminoalcohol **6**.

As shown in Scheme 2, compound **7** was synthesized via silylation of compound **6** and N-allylation of the resultant product. Further, in order to achieve the synthesis of target compound **1a**, we required a 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' second catalyst, the expected piperidine ring **9** was generated.[9] Finally, synthesis of α-conhydrine (**1a**) was accomplished via hydrogenation and desulfonation.



Scheme 2.

3. Conclusion

In summary, we succeeded in accomplishing the synthesis of α-conhydrine (**1a**) from *trans*-(2*S*,4*R*)-4-hydroxyproline (**2**) in moderate yields (ca. 18%) via diastereoselective Grignard addition, regioselective Baeyer–Villiger reaction, and ring-closing metathesis as the key steps. Currently studies are in progress in this direction.

4. Experimental

4.1. General

Dichloromethane (DCM) and tetrahydrofuran (THF) were distilled prior to use. All other reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Products in organic solvents were dried with anhydrous magnesium sulfate before concentration in vacuo.

4.1.1. 2-(1-Hydroxypropyl)-4-(*tert*-butyldimethylsilanyloxy)-1-(4-methylphenylsulfonyl)pyrrolidine (4). A stirred solution of oxalyl chloride (400 mg, 3.15 mmol) in dichloromethane (20 mL) was mixed with dimethyl sulfoxide (400 mg, 5.1 mmol) at −78 °C. The solution was warmed to −40 °C for 15 min and recooled to −78 °C, and then a solution of prolinol **3** (385 mg, 1.0 mmol) in dichloromethane (10 mL) was added dropwise for 90 min followed by excess triethylamine (4 mL, 28.5 mmol) for 30 min. The reaction mixture was warmed to rt and poured into aqueous ammonium chloride solution (15%, 2 mL), and concentrated under reduced pressure. The residue was diluted with water (15 mL) and extracted with ethyl acetate (3×30 mL). The organic layer was washed with brine and water, dried, filtered, and concentrated under reduced pressure to produce crude aldehyde. Without further purification, a solution of ethylmagnesium bromide (1.0 M in tetrahydrofuran, 1.5 mL, 1.5 mmol) was added to a stirred solution of resulting aldehyde in tetrahydrofuran (20 mL) at −78 °C. The reaction mixture was stirred at rt for 2 h. Saturated sodium bicarbonate solution (1 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. Water (3 mL) and ethyl acetate (10 mL) was added to the residue and the mixture was filtered through a short plug of Celite. The filtrate was concentrated under reduced pressure. The residue was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexane/ethyl acetate=4/1) afforded alcohol **4** (372 mg, 90% of two steps). $[\alpha]_D^{29}$ −46.54 (*c* 0.104, $CHCl_3$); IR ($CHCl_3$) 3503, 2955, 1598, 1343, 1090, 836 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{36}NO_4SSi$ (M^++1) 414.2134, found 414.2133; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J*=8.0 Hz, 2H), 7.30 (d, *J*=8.0 Hz, 2H), 4.28–4.25 (m, 1H), 4.14–4.11 (m, 1H), 3.60 (dd, *J*=4.0, 11.5 Hz, 1H), 3.60–3.57 (m, 1H), 3.27 (ddd, *J*=2.0, 4.0, 11.5 Hz, 1H), 2.46 (d, *J*=4.0 Hz, 1H), 2.42 (s, 3H), 2.07–2.01 (m, 1H), 1.61–1.57 (m, 1H), 1.47–1.40 (m, 1H), 1.38–1.30 (m, 1H), 1.02 (t, *J*=7.0 Hz, 3H), 0.71 (s, 9H), −0.08 (s, 3H), −0.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.54, 133.84, 129.66 (2×), 127.83

(2×), 72.92, 69.80, 63.62, 58.62, 35.08, 25.76, 25.65 (3×), 21.49, 17.94, 10.79, −4.93, −5.05; Anal. Calcd for $C_{20}H_{35}NO_4SSi$: C, 58.07; H, 8.53; N, 3.39. Found: C, 58.39; H, 8.21; N, 3.58.

4.1.2. 2-(1-Benzyloxypropyl)-1-(4-methylphenylsulfonyl) pyrrolidin-4-one (5). A solution of compound **4** (415 mg, 1.0 mmol) in tetrahydrofuran (5 mL) was added to a rapidly stirred suspension of sodium hydride (60%, 100 mg, 2.5 mmol) in tetrahydrofuran (10 mL). After the reaction mixture was stirred at rt for 10 min, a solution of benzyl bromide (200 mg, 1.16 mmol) in tetrahydrofuran (2 mL) was added. The reaction mixture was stirred at rt for 20 h, and poured into aqueous ammonium chloride solution (15%, 2 mL), and concentrated under reduced pressure. The residue was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexane/ethyl acetate=10/1) afforded benzyl product (432 mg, 86%). $[\alpha]_D^{28}$ −18.89 (*c* 0.01, $CHCl_3$); IR ($CHCl_3$) 2927, 1342, 1090, 755 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{27}H_{42}NO_4SSi$ (M^++1) 504.2604, found 504.2608; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J*=8.0 Hz, 2H), 7.38–7.26 (m, 7H), 4.81 (d, *J*=11.5 Hz, 1H), 4.72 (d, *J*=11.5 Hz, 1H), 4.39–4.35 (td, *J*=4.5, 10.0 Hz, 1H), 4.08 (t, *J*=7.0 Hz, 1H), 3.69 (t, *J*=7.0 Hz, 1H), 3.56 (dd, *J*=4.5, 10.0 Hz, 1H), 3.07 (dd, *J*=4.5, 10.0 Hz, 1H), 2.43 (s, 3H), 2.21–2.16 (m, 1H), 1.51–1.45 (m, 2H), 1.40–1.33 (m, 1H), 0.99 (t, *J*=7.5 Hz, 3H), 0.72 (s, 9H), −0.12 (s, 3H), −0.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.25, 139.21, 134.33, 129.60 (2×), 128.23 (2×), 127.82 (2×), 127.78 (2×), 127.36, 82.48, 74.38, 70.39, 62.62, 56.69, 34.74, 26.06, 25.72 (3×), 21.49, 18.03, 10.68, −5.01, −5.10; Anal. Calcd for $C_{27}H_{41}NO_4SSi$: C, 64.37; H, 8.20; N, 2.78. Found: C, 64.66; H, 8.08; N, 2.98. A solution of tetra-*n*-butylammonium fluoride (1.0 M in tetrahydrofuran, 1.2 mL, 1.2 mmol) in tetrahydrofuran (2 mL) was added to a solution of benzyl compound (400 mg, 0.8 mmol) in tetrahydrofuran (5 mL) at rt. The reaction mixture was stirred at rt for 2 h, and poured into aqueous ammonium chloride solution (15%, 2 mL), and concentrated under reduced pressure. The residue was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexane/ethyl acetate=2/1) afforded alcohol product (285 mg, 92%). $[\alpha]_D^{29}$ −32.35 (*c* 0.011, $CHCl_3$); IR ($CHCl_3$) 3501, 2933, 1338, 1156, 1090 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{21}H_{28}NO_4S$ (M^++1) 390.1739, found 390.1741; ^1H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J*=8.5 Hz, 2H), 7.35–7.26 (m, 7H), 4.79 (d, *J*=11.5 Hz, 1H), 4.71 (d, *J*=11.5 Hz, 1H), 4.33 (br s, 1H), 4.03 (ddd, *J*=2.0, 5.5, 8.0 Hz, 1H), 3.85 (td, *J*=2.0, 8.0 Hz, 1H), 3.48 (dd, *J*=4.0, 12.0 Hz, 1H), 3.36 (dt, *J*=2.0, 12.0 Hz, 1H), 2.43 (s, 3H), 2.25 (ddd, *J*=4.5, 7.0, 12.5 Hz, 1H), 1.69–1.64 (m, 1H), 1.51–1.32 (m, 2H), 1.13–1.11 (m, 1H), 0.96 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.65, 139.07, 134.69, 129.64 (2×), 128.29 (2×), 127.83 (2×), 127.75 (2×), 127.45, 82.35, 74.35, 70.61, 62.43, 56.95, 34.08, 25.82, 21.55, 10.61; Anal. Calcd for $C_{21}H_{27}NO_4S$: C, 64.75; H, 6.99; N, 3.60. Found: C, 64.58; H, 7.20; N, 3.88. A solution of alcohol product (390 mg, 1.0 mmol) in dichloromethane (5 mL) was added to a mixture of pyridinium chlorochromate (431 mg, 2.0 mmol) and Celite (1.0 g) in dichloromethane (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 compound. Purification on silica gel (hexane/ethyl acetate=5/1) afforded ketone **5** (320 mg, 83%). $[\alpha]_D^{29}$ +32.47 (*c* 0.023, $CHCl_3$); IR ($CHCl_3$) 2955, 1763, 1307, 1158, 1063, 697 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{21}H_{26}NO_4S$ (M^++1) 388.1583, found 388.1586; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J*=8.5 Hz, 2H), 7.34–7.25 (m, 5H), 7.18 (d, *J*=7.0 Hz, 2H), 4.60 (d, *J*=12.0 Hz, 1H), 4.44 (d, *J*=12.0 Hz, 1H), 4.29 (dt, *J*=2.0, 9.5 Hz, 1H), 3.81 (td, *J*=2.0, 7.0 Hz, 1H), 3.69 (d, *J*=17.5 Hz, 1H), 3.64 (d, *J*=17.5 Hz, 1H), 2.50 (d, *J*=17.5 Hz, 1H), 2.44 (s, 3H), 2.10 (dd, *J*=9.5, 17.0 Hz, 1H), 1.65–1.58 (m, 1H), 1.42–1.33 (m, 1H), 0.98 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.13, 144.16, 138.05, 135.31, 130.12 (2×), 128.38 (2×), 127.59, 127.13 (2×), 127.09 (2×), 84.11, 72.89, 59.87, 53.37, 37.10, 24.60, 21.55, 10.06; Anal. Calcd for $C_{21}H_{25}NO_4S$: C, 65.09; H, 6.50; N, 3.61. Found: C, 65.48; H, 6.78; N, 3.32. Single-crystal X-ray diagram: crystal of ketone **5** was grown by slow diffusion of ethyl acetate into a solution of ketone **5** in dichloromethane to yield colorless prism. The compound crystallizes in the monoclinic crystal system. space group *P*21(#4), *a*=7.9147(16) Å, *b*=6.1920(12) Å, *c*=21.110(4) Å, *V*=1033.5(4) $Å^3$, *Z*=2, d_{calcd}=1.245 mg/m^3, absorption coefficient=0.182 mm^{-1}, *F*(000)=412, 2θ range (1.93–26.00°).

4.1.3. 4-Benzyloxy-3-(4-methylphenylsulfonylamino) hexan-1-ol (6). A solution of *m*-chloroperoxybenzoic acid (75%, 600 mg, 2.6 mmol) in dichloromethane (10 mL) was added to a solution of ketone **5** (390 mg, 1.0 mmol) and sodium carbonate (420 mg, 4.0 mmol) in dichloromethane (20 mL) at 0 °C. The reaction mixture was stirred at rt for 20 h. Saturated sodium carbonate solution (10 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexane/ethyl acetate=4/1 to 2/1) afforded lactone product (330 mg, 82%). $[\alpha]_D^{29}$ −102.74 (*c* 0.008, $CHCl_3$); IR ($CHCl_3$) 2923, 1764, 1352, 1156, 998 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{21}H_{26}NO_5S$ 404.1532, found 404.1538; ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J*=8.5 Hz, 2H), 7.39–7.31 (m, 7H), 5.79 (d, *J*=11.5 Hz, 1H), 5.17 (d, *J*=11.5 Hz, 1H), 4.76 (d, *J*=11.0 Hz, 1H), 4.67 (d, *J*=11.0 Hz, 1H), 3.97 (td, *J*=2.0, 7.0 Hz, 1H), 3.73 (ddd, *J*=2.0, 7.0, 10.0 Hz, 1H), 2.96 (dd, *J*=11.0, 16.0 Hz, 1H), 2.43 (s, 3H), 2.42 (dd, *J*=7.0, 16.0 Hz, 1H), 1.64–1.55 (m, 1H), 1.39–1.30 (m, 1H), 0.98 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.11, 144.94, 138.05, 134.53, 130.14 (2×), 128.55 (2×), 127.96, 127.93 (2×), 127.86 (2×), 83.47, 75.76, 74.32, 53.95, 28.19, 24.08, 21.64, 10.13; Anal. Calcd for $C_{21}H_{25}NO_5S$: C, 62.51; H, 6.25; N, 3.47. Found: C, 62.83; H, 6.58; N, 3.60. A solution of the resulting product (310 mg, 0.77 mmol) in tetrahydrofuran (10 mL) was added to a rapidly stirred suspension of lithium aluminum hydride (76 mg, 2.0 mmol) at 0 °C. The reaction mixture was stirred at rt for 2 h. Aqueous ammonium chloride solution (15%, 2 mL) was added to the reaction mixture

and filtered through a short silica gel column. The filtrate was dried, filtered, and evaporated to yield crude compound. Purification on silica gel (hexane/ethyl acetate=5/1) afforded aminoalcohol **6** (273 mg, 94%). $[\alpha]_D^{29}$ −46.75 (*c* 0.015, $CHCl_3$); IR ($CHCl_3$) 3290, 2962, 1598, 1325, 1160, 815 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{20}H_{28}NO_4S$ 378.1739, found 378.1742; ^1H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, *J*=8.0 Hz, 2H), 7.41–7.34 (m, 4H), 7.25–7.22 (m, 3H), 4.89 (d, *J*=9.5 Hz, 1H), 4.55 (d, *J*=12.0 Hz, 1H), 4.18 (d, *J*=12.0 Hz, 1H), 3.88–3.82 (m, 1H), 3.69–3.64 (m, 1H), 3.49–3.43 (m, 1H), 2.89–2.86 (m, 1H), 2.64 (dd, *J*=6.0, 7.0 Hz, 1H), 2.42 (s, 3H), 1.74–1.67 (m, 1H), 1.65–1.55 (m, 2H), 1.38–1.29 (m, 1H), 0.70 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.39, 138.08, 137.38, 129.62 (2×), 128.70 (2×), 128.03, 127.76 (2×), 126.97 (2×), 81.57, 71.36, 58.18, 51.67, 30.38, 22.56, 21.51, 9.58; Anal. Calcd for $C_{20}H_{27}NO_4S$: C, 63.63; H, 7.21; N, 3.71. Found: C, 63.28; H, 7.56; N, 3.46.

4.1.4. *N*-Allyl-*N*-{2-benzyloxy-1-[2-(*tert*-butyldimethylsilanyloxy)ethyl]butyl}-4-methylbenzenesulfonamide (7). *tert*-Butyldimethylsilyl chloride (150 mg, 1.0 mmol) and imidazole (136 mg, 2.0 mmol) were added to a stirred solution of compound **6** (300 mg, 0.8 mmol) in dimethylforamide (5 mL) at rt. The reaction mixture was stirred at rt for 2 h. The reaction mixture was concentrated under reduced pressure. The residue was diluted with water (10 mL) and the mixture was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with saturated sodium bicarbonate solution and brine, dried, filtered, and evaporated under reduced pressure to yield crude product. Purification on silica gel (hexane/ethyl acetate=5/1) afforded silyl product (375 mg, 96%). HRMS (ESI) *m/z* calcd for $C_{26}H_{42}NO_4SSi$ (M^++1) 492.2604, found 492.2606; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J*=8.0 Hz, 2H), 7.37–7.24 (m, 7H), 5.31 (d, *J*=7.5 Hz, 1H), 4.54 (d, *J*=11.5 Hz, 1H), 4.35 (d, *J*=11.5 Hz, 1H), 3.62–3.57 (m, 1H), 3.53–3.48 (m, 1H), 3.46–3.41 (m, 1H), 3.36–3.33 (m, 1H), 2.42 (s, 3H), 1.69–1.54 (m, 3H), 1.49–1.40 (m, 1H), 0.89 (s, 9H), 0.85 (t, *J*=7.5 Hz, 3H), 0.02 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.06, 138.54, 137.93, 129.52 (2×), 128.42 (2×), 127.65 (3×), 127.16 (2×), 81.88, 72.02, 60.21, 53.68, 31.03, 25.86 (3×), 23.08, 21.51, 18.11, 9.63, −5.49, −5.53; Anal. Calcd for $C_{26}H_{41}NO_4SSi$: C, 63.50; H, 8.40; N, 2.85. Found: C, 63.77; H, 8.22; N, 2.70. A solution of silyl compound (350 mg, 0.71 mmol) in dimethylforamide (2 mL) was added to a rapidly stirred suspension of sodium hydride (60%, 100 mg, 2.5 mmol) in dimethylforamide (3 mL). After the reaction mixture was stirred at ice bath for 5 min, allyl bromide (250 mg, 2.1 mmol) was added at ice bath. The resulting mixture was stirred at rt for 3 h. The reaction was quenched with 15% ammonium chloride solution (1 mL) and the mixture was concentrated under reduced pressure. The residue was diluted with water (10 mL) and the mixture was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with saturated sodium bicarbonate solution and brine, dried, filtered, and evaporated under reduced pressure to yield crude product. Purification on silica gel (hexane/ethyl acetate=10/1) afforded compound **7** (367 mg, 97%) as viscous oil. $[\alpha]_D^{29}$ −27.78 (*c* 0.011, $CHCl_3$); IR ($CHCl_3$) 2928, 1462, 1340, 1255, 1162, 1027, 835 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{29}H_{46}NO_4SSi$ (M^++1) 532.2917, found 532.2920; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J*=8.0 Hz, 2H), 7.34–7.25 (m, 7H), 5.81–5.73 (m, 1H), 5.10 (d, *J*=17.0 Hz, 1H), 5.02 (d, *J*=10.0 Hz, 1H), 4.55 (d, *J*=11.5 Hz, 1H), 4.36 (d, *J*=11.5 Hz, 1H), 4.02 (dd, *J*=6.5, 16.0 Hz, 1H), 3.97 (dt, *J*=4.0, 9.5 Hz, 1H), 3.89 (dd, *J*=6.5, 16.0 Hz, 1H), 3.49–3.46 (m, 1H), 3.44–3.40 (m, 1H), 3.36–3.31 (m, 1H), 2.42 (s, 3H), 1.88–1.82 (m, 1H), 1.80–1.73 (m, 1H), 1.70–1.63 (m, 1H), 1.60–1.52 (m, 1H), 0.94 (t, *J*=7.5 Hz, 3H), 0.87 (s, 9H), −0.01 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.94, 138.44, 138.33, 136.06, 129.41 (2×), 128.29 (2×), 127.50 (2×), 127.48, 127.45 (2×), 117.01, 84.10, 71.48, 60.50, 56.50, 47.32, 30.75, 25.88 (3×), 24.01, 21.49, 18.20, 9.78, −5.38, −5.42; Anal. Calcd for $C_{29}H_{45}NO_4SSi$: C, 65.49; H, 8.53; N, 2.63. Found: C, 65.83; H, 8.62; N, 2.44.

4.1.5. *N*-Allyl-*N*-[1-(1-benzyloxypropyl)but-3-enyl]-4-methylbenzenesulfonamide (8). A solution of tetra-*n*-butylammonium fluoride (1.0 M in tetrahydrofuran, 1.2 mL, 1.2 mmol) in tetrahydrofuran (2 mL) was added to a solution of compound **7** (530 mg, 1.0 mmol) in tetrahydrofuran (20 mL) at rt. The reaction mixture was stirred at rt for 2 h, and poured into aqueous ammonium chloride solution (15%, 2 mL), and concentrated under reduced pressure. The residue was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexane/ethyl acetate=4/1) afforded alcohol product (410 mg, 99%). HRMS (ESI) *m/z* calcd for $C_{23}H_{32}NO_4S$ (M^++1) 418.2052, found 418.2055; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J*=8.5 Hz, 2H), 7.34–7.24 (m, 7H), 5.88–5.80 (m, 1H), 5.09 (dd, *J*=1.5, 17.5 Hz, 1H), 5.05 (dd, *J*=1.0, 10.0 Hz, 1H), 4.54 (d, *J*=11.5 Hz, 1H), 4.27 (d, *J*=11.5 Hz, 1H), 4.06 (dd, *J*=7.5, 16.0 Hz, 1H), 3.96 (dt, *J*=3.5, 10.0 Hz, 1H), 3.92 (dd, *J*=10.0, 16.0 Hz, 1H), 3.71–3.65 (m, 1H), 3.64–3.58 (m, 1H), 3.19 (dt, *J*=4.5, 8.5 Hz, 1H), 2.56 (dd, *J*=5.0, 7.5 Hz, 1H), 2.44 (s, 3H), 1.89–1.77 (m, 2H), 1.61–1.53 (m, 1H), 1.16–1.37 (m, 1H), 0.48 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.37, 138.02, 137.97, 136.02, 129.60 (2×), 128.37 (2×), 127.66, 127.51 (2×), 127.29 (2×), 117.43, 82.91, 71.00, 58.59, 55.95, 47.29, 29.58, 23.56, 21.53, 9.80; Anal. Calcd for $C_{23}H_{31}NO_4S$: C, 66.16; H, 7.48; N, 3.35. Found: C, 66.39; H, 7.62; N, 3.71. A solution of alcohol product (420 mg, 1.0 mmol) in dichloromethane (5 mL) was added to a mixture of pyridinium chlorochromate (431 mg, 2.0 mmol) and Celite (1.0 g) in dichloromethane (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 compound. Purification on silica gel (hexane/ethyl acetate=5/1) afforded aldehyde product (364 mg, 87%). $[\alpha]_D^{28}$ −35.20 (*c* 0.013, $CHCl_3$); IR ($CHCl_3$) 3029, 2927, 2733, 1722, 1598, 1398, 1089 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{23}H_{30}NO_4S$ (M^++1) 416.1896, found 416.1899; ^1H NMR (500 MHz, $CDCl_3$) δ 9.45 (dd, *J*=1.0, 2.5 Hz, 1H), 7.71 (d, *J*=8.0 Hz, 2H), 7.33–7.24 (m, 7H), 5.79–5.71 (m, 1H), 5.10 (d, *J*=9.0 Hz, 1H), 5.09 (d, *J*=18.0 Hz, 1H), 4.53 (d, *J*=11.5 Hz, 1H), 4.42 (dt, *J*=5.0, 8.0 Hz, 1H), 4.33 (d, *J*=11.5 Hz, 1H), 3.94 (dd, *J*=6.0, 16.5 Hz, 1H), 3.65 (dd, *J*=7.0, 16.5 Hz, 1H), 3.55 (dt, *J*=5.0, 7.5 Hz, 1H), 2.61 (dd, *J*=3.0, 8.5, 16.5 Hz, 1H), 2.42 (s, 3H), 2.23 (dd,

J=5.0, 16.5 Hz, 1H), 1.73–1.62 (m, 2H), 0.95 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.68, 143.67, 137.58, 137.21, 135.18, 129.77 (2×), 128.39 (2×), 127.92 (2×), 127.79, 127.32 (2×), 118.01, 80.92, 71.66, 55.12, 48.26, 43.94, 22.70, 21.51, 8.36; Anal. Calcd for $C_{23}H_{29}NO_4S$: C, 66.48; H, 7.03; N, 3.37. Found: C, 66.69; H, 7.09; N, 3.49. *n*-Butyllithium (1.6 M in hexane, 1.0 mL, 1.6 mmol) was added to a stirred solution of methyl triphenylphosphonium iodide (808 mg, 2.0 mmol) in tetrahydrofuran (20 mL) at −78 °C. The orange red colored mixture was stirred at −78 °C for 1 h. A solution of aldehyde product (290 mg, 0.7 mmol) in tetrahydrofuran (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 saturated ammonium chloride (10 mL) and the mixture was extracted with diethyl ether (3×20 mL) and the combined organic layers were washed with brine, dried, filtered, and evaporated. Purification on silica gel (hexane/ethyl acetate=2/1) afforded compound **8** (237 mg, 82%). $[\alpha]_D^{28}$ +3.33 (*c* 0.009, $CHCl_3$); IR ($CHCl_3$) 2925, 1455, 1337, 1090, 662 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{24}H_{32}NO_3S$ (M^++1) 414.2103, found 414.2104; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, J=8.5 Hz, 2H), 7.33–7.26 (m, 7H), 5.95–5.77 (m, 1H), 5.52–5.44 (m, 1H), 5.10 (dd, J=1.5, 17.5 Hz, 1H), 5.04 (dd, J=1.5, 10.0 Hz, 1H), 4.92 (dd, J=1.5, 17.5 Hz, 1H), 4.81 (d, J=10.0 Hz, 1H), 4.56 (d, J=11.0 Hz, 1H), 4.38 (d, J=11.0 Hz, 1H), 3.99 (dd, J=6.0, 16.5 Hz, 1H), 3.92 (td, J=5.0, 10.0 Hz, 1H), 3.80 (dd, J=6.5, 16.5 Hz, 1H), 3.47 (dd, J=5.5, 11.5 Hz, 1H), 2.49–2.42 (m, 1H), 2.43 (s, 3H), 2.35–2.28 (m, 1H), 1.71–1.59 (m, 2H), 0.96 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.03, 138.35, 138.16, 136.15, 135.69, 129.32 (2×), 128.33 (2×), 127.60 (2×), 127.55, 127.54 (2×), 116.98, 116.78, 83.20, 71.62, 60.12, 47.39, 32.39, 23.90, 21.49, 9.65; Anal. Calcd for $C_{24}H_{31}NO_3S$: C, 69.70; H, 7.56; N, 3.39. Found: C, 66.91; H, 7.82; N, 3.58.

4.1.6. 2-(1-Benzyloxypropyl)-1-(4-methylphenylsulfonyl)-1,2,3,6-tetrahydropyridine (9). Grubbs' second generation catalyst (30 mg) was added to a solution of compound **8** (210 mg, 0.51 mmol) in dichloromethane (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/ethyl acetate=4/1) to yield compound **9** (180 mg, 92%). $[\alpha]_D^{28}$ −56.00 (*c* 0.005, $CHCl_3$); IR ($CHCl_3$) 2924, 1598, 1342, 1091, 754 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{28}NO_3S$ (M^++1) 386.1790, found 386.1795; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, J=9.0 Hz, 2H), 7.34–7.24 (m, 7H), 5.55–5.52 (m, 2H), 4.59 (d, J=11.5 Hz, 1H), 4.35 (d, J=11.5 Hz, 1H), 4.17 (19.0 Hz, 1H), 4.05 (dd, J=6.5, 9.5 Hz, 1H), 3.60 (dt, J=3.0, 19.0 Hz, 1H), 3.52–3.48 (m, 1H), 2.41 (s, 3H), 2.25 (d, J=18.0 Hz, 1H), 1.89–1.82 (m, 1H), 1.80–1.75 (m, 1H), 1.72–1.63 (m, 1H), 1.04 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.08, 138.26, 137.86, 129.54 (2×), 128.36 (2×), 127.66 (2×), 127.62, 126.93 (2×), 124.22, 122.38, 77.66, 72.21, 51.96, 41.31, 23.01, 22.99, 21.50, 8.26; Anal. Calcd for $C_{22}H_{27}NO_3S$: C, 68.54; H, 7.06; N, 3.63. Found: C, 68.78; H, 6.91; N, 3.44.

4.1.7. 1-Piperidin-2-yl-propan-1-ol (α-conhydrine, 1a). Compound **9** (80 mg, 0.21 mmol) was dissolved in ethanol (20 mL) and 10% palladium on activated carbon (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 compound. Purification on silica gel (hexane/ethyl acetate=5/1) afforded alcohol product (58 mg, 94%). $[\alpha]_D^{28}$ −33.21 (*c* 0.026, $CHCl_3$); IR ($CHCl_3$) 3516, 2935, 1455, 1332, 1092, 933, 658 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{23}NO_3S$ (M^++1) 298.1477, found 298.1481; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, J=8.5 Hz, 2H), 7.30 (d, J=8.5 Hz, 2H), 3.85–3.74 (m, 3H), 3.03 (ddd, J=3.0, 13.0, 14.5 Hz, 1H), 2.43 (s, 3H), 1.94–1.91 (m, 1H), 1.82–1.79 (m, 1H), 1.59–1.50 (m, 1H), 1.46–1.37 (m, 3H), 1.26–1.16 (m, 1H), 1.14–1.05 (m, 1H), 1.01 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.97, 138.75, 129.69 (2×), 126.99 (2×), 71.12, 57.14, 42.34, 27.04, 23.42, 23.03, 21.51, 18.84, 10.85; Anal. Calcd for $C_{15}H_{23}NO_3S$: C, 60.58; H, 7.79; N, 4.71. Found: C, 60.68; H, 7.94; N, 4.69. Sodium amalgam (Na/Hg, 0.5 g, 6%) and sodium phosphate (71 mg, 0.5 mmol) were added to a stirred solution of *N*-tosylconhydrine (30 mg, 0.1 mmol) in methanol (10 mL), and vigorously stirred for 5 h at rt. The residue was filtered and washed with methanol (2×10 mL) and the combined organic layers were evaporated to afford the crude products. Purification on silica gel (hexane/ethyl acetate=1/1 to 1/2) afforded α-conhydrine (**1a**) (12 mg, 80%). The NMR spectral data of α-conhydrine (**1a**) were in accordance with those reported in the literature.[5g]

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Supplementary data

Photocopies of NMR (^{1}H and ^{13}C) spectral data for new compounds were supported. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.09.004.

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