Methyl (S)-Lactate as a Chiral Auxiliary in the Asymmetric Synthesis of Bao Gong Teng A

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The asymmetric synthesis of Bao Gong Teng A, (−)-**1**, a natural product that shows strong antiglaucoma properties, is described. The synthesis begins with an asymmetric 1,3-dipolar cycloaddition of the acrylate of methyl (*S*)-lactate to the betaine of *N*-benzyl-3-hydroxypyridinium chloride giving cycloadduct **5a** as a major product. The crude cycloadduct was reduced by catalytic hydrogenation to produce **6** in 61% yield. The ketone **6** was reduced with $LiAl(OtBu)_3H$ to give *exo* alcohol **7b** in 62% yield. Protection of the alcohol group followed by replacement of the benzyl group on the nitrogen with a Boc group gave **12**, which was then hydrolyzed to the acid **13** in 91% yield for the three steps. The acid **13** was converted to the ketone **14** in 82% yield via the acid chloride. Baeyer–Villiger oxidation converted **14** to **15** in 52% yield. Optically pure Bao Gong Teng A was obtained in 9% overall yield by the removal of both the Boc and the TBDMS groups using 1% HCl–EtOH.

Bao Gong Teng A ((1*R*,2*S*,5*R*,6*S*)-6-(acetyloxy)-8-azabicyclo[3.2.1]octan-2-ol) is an optically active alkaloid isolated from the Chinese herb, *Erycible obtusifolia* (Convolvulaceae), which has been used to treat glaucoma.[1] Its absolute configuration, illustrated in Figure 1, has been proposed on the basis of CD and ORD studies.[1,2] An attractive strategy for the total synthesis of racemic **1** was presented by Jung *et al.* They constructed the basic carbon skeleton with appropriate functional groups and correct relative stereochemistry via a 1,3-dipolar cycloaddition of acrylonitrile to the betaine produced from *N*-benzyl-3-hydroxypyridinium bromide (Scheme 1).[1,3] The resulting racemic cycloadduct **2** was converted to racemic Bao Gong Teng A by a series of functional group transformations. A similar route to optically pure Bao Gong Teng A might be possible, if the 1,3-dipolar cycloaddition could be performed asymmetrically. Such a cycloaddition might also provide an asymmetric route to other alkaloids of this general class.

One possible way to accomplish an asymmetric 1,3-dipolar cycloaddition of a 3-hydroxypyridium betaine is to place a chiral auxiliary on the dipolarophile. The feasibility of such an asymmetric cycloaddition has been demonstrated by Koizumi *et al.* who reacted the chiral dipolarophile, (*R*)-(+)-*p*-tolyl vinyl sulfoxide, with *N*-methyl-3-hydroxypyridinium betaine, although the stereoselectivity of the cycloaddition was not good.[4] In search of a better chiral dipolarophile, we were attracted to the acrylates of alkyl (*S*)-lactate, especially the acrylate of methyl (*S*)-lactate, **3**, because it has been well studied in asymmetric Diels–Alder reactions. Cycloadditions of **3** have been shown to occur preferentially at the *re* face of the dienophile, and Lewis acids have not been required to achieve good stereoselectivity. 1,3-Dipolar cycloaddition of the betaine of *N*-alkyl-3-hydroxypyridinium salts are known to give 6-*exo* cycloadducts as shown in Scheme 1. Combining the *re* face reactivity of **3** with the 6-*exo* regio- and stereoselectivity would lead to a cycloadduct with the relative and absolute stereochemistry shown in structure **5a** (Scheme 2). This cycloadduct would have the appropriate absolute configuration for Bao Gong Teng A.

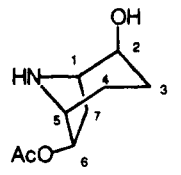
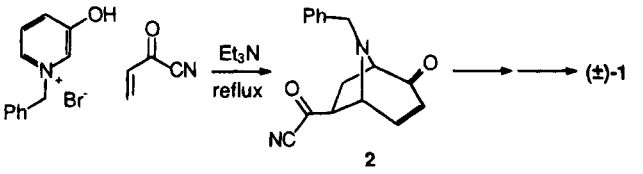
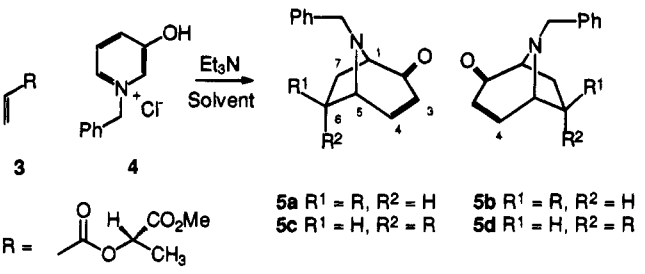


Figure 1. Absolute configuration of Bao Gong Teng A.

Scheme 1



Scheme 2



Results and Discussion

1,3-Dipolar cycloadditions of 3-hydroxypyridinium betaines have typically been carried out in neat dipolaro-

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(4) Takahashi, T.; Fujii, A.; Sugita, J.; Hagi, T.; Kitano, K.; Arai, Y.; Koizumi, T. *Tetrahedron Asymmetry* **1991**, *2*, 1379.
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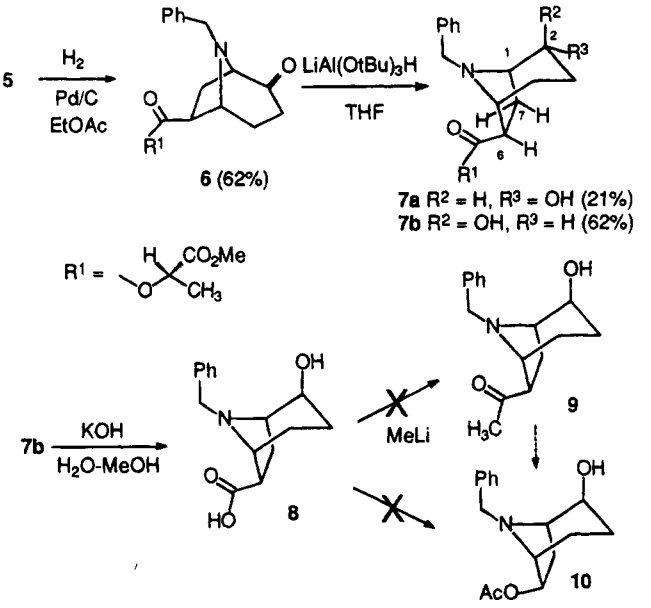
Table 1. Total Yields and Selectivity for the Major Isomer 5a in the Asymmetric 1,3-Dipolar Cycloaddition of the Acrylate of Methyl (S)-Lactate (3) with the Betaine of *N*-benzyl-3-hydroxypyridinium Hydrochloride

solvent	temperature	time	selectivity (% of **5a**)[a]	yield (%)
acetone	reflux	5 h	36	19
benzene	reflux	1 day	55	15
benzene	room	11 days	63	11
benzene	room	4 months	63	87
EtOAc	room	10 days	65	>90

[a] Estimated from NMR spectra.

phile at reflux temperature.[1,6-8] Although this method has been generally successful for readily available dipolarophiles, it would not be a practical method for an asymmetric cycloaddition using chiral dipolarophile **3**, since **3** is not available in large quantities. Initial attempts to add dipolarophile **3** to the betaine of **4** (see Scheme 2) were carried out using 1.5 equivalents of **3** in refluxing acetone solution. This resulted in a very low conversion to adducts (Table 1), and the NMR spectrum of the crude cycloadduct mixture exhibited four sets of double doublets at δ 6.90–7.20 ppm (H4) indicating that four different cycloadducts had been formed in nearly equal amounts. When the cycloaddition was performed in refluxing benzene, the conversion to products was still low but the selectivity was slightly better (Table 1). Lowering the temperature appeared to improve selectivity and at rt in benzene, 80% conversion was reached after four months. An investigation of the thermal stability of the cycloadducts showed that they were thermally unstable, reverting to the starting materials when heated. It appeared that good conversion of educts to cycloadducts was only possible at lower temperature where the higher entropy of the educts had less effect on the free energy of the reaction. When the cycloaddition was carried out in EtOAc at rt, the reaction time was shortened to 10 d with no loss in selectivity (Table 1). It was not possible to separate isomeric cycloadducts by column chromatography; however, a small amount of the major isomer was isolated by HPLC. The NMR of this isomer was compared to the NMR of cycloadducts from the work of Jung[1] and Katritzky.[6] Their NMR spectra of 6-*endo* cycloadducts, similar in structure to **5c** and **5d** (Scheme 2), exhibited H5 as a doublet of doublets and H6 as a triplet of doublets with a large coupling constant between the two protons ($J_{5,6}$ = >5 Hz). The 6-*exo* cycloadducts, similar in structure to **5a** and **5b**, exhibited H5 as a doublet and H6 as a double of doublets with no coupling between the two protons ($J_{5,6}$ = 0 Hz). The NMR analysis of the major cycloadduct of this work showed a coupling pattern similar to that of the 6-*exo* cycloadducts, indicating that it possessed structure **5a** or **5b**; however, the exact structure of the major cycloadduct could not be determined at this stage of the synthesis. Due to the thermal instability of the cycloadducts, they were hydrogenated at rt to a mixture of **6** and its isomers using 5% Pd/C in EtOAc (Scheme 3). The major ketone **6** was isolated by chromatography on silica gel and crystallized from 20% EtOAc in hexane to give **6** with a melting point of 87–88.5 °C. The overall yield of ketone **6** for the cycloaddition and reduction steps was 61%.

Scheme 3



In the next step of the synthesis, the ketone **6** was reduced to the 2-*exo* alcohol **7b** with the appropriate stereochemistry for Bao Gong Teng A. The reduction of ketone **6** using sodium borohydride in MeOH, following Jung's procedure for a similar ketone, produced a complicated mixture that could neither be separated nor analyzed as a whole. Using i-PrOH or EtOH as solvents produced similar results. Using THF as a solvent gave two products that could be separated by chromatography. These were identified as the 2-*endo* and 2-*exo* alcohols **7a** and **7b**, respectively, with **7a** being the major product. The alcohols **7a** and **7b** could be easily differentiated by IR due to the strong intramolecular hydrogen bonding in *exo* isomer **7b**.[1] In addition, NOE was observed between H2 and H7-*endo* in **7b** while no similar effect was found in **7a**, further confirming the above assignment. Reduction using the bulkier lithium tri-*tert*-butoxyaluminum hydride at −4 °C in THF gave predominantly the desired 2-*exo*-hydroxy compound **7b**.[9] After chromatography on silica gel, the crystalline **7b** (mp 73–74.5 °C), and **7a** as a light yellow oil, were obtained in yields of 62% and 21%, respectively. **7b** was hydrolyzed to the corresponding acid **8** and then treated with methyllithium to form to ketone **9**, an intermediate in the previously published racemic synthesis of Bao Gong Teng A (Scheme 3). However, the formation of ketone **9** was very irreproducible and an alternate route to Bao Gong Teng A from **7b** was investigated. Attempts to decarboxylate the acid **8** to directly produce the corresponding acetate **10** using lead tetraacetate were unsuccessful and we eventually chose a longer route to complete the synthesis (Scheme 4).

7b was converted to its TBDMS derivative **11** and debenzylated with simultaneous Boc protection (H_2 in MeOH, Pd/C, $(BOC)_2O$) to give N-t-BOC **12** (^1H and ^{13}C NMR spectra of the N-Boc protected intermediates were complicated by doubling of peaks due to the presence of carbamate rotamers).[10-12] The ester group was hydro-

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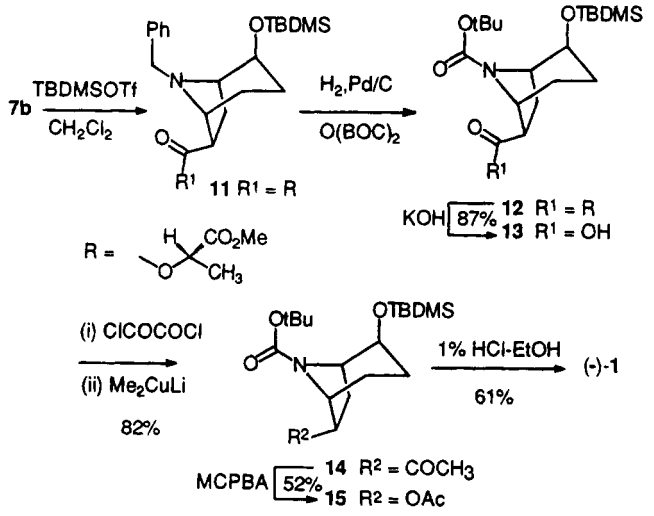
Scheme 4



lyzed to give the corresponding acid **13** in 91% yield from **11**. The acid **13** was converted to ketone **14** in 82% yield, via a conversion to the acid chloride followed by reaction with excess lithium dimethylcuprate.[12-14] The protected Bao Gong Teng A **15** was obtained by the Baeyer–Villiger oxidation of **14** using *m*-CPBA in a benzene–$CHCl_3$ mixture. **15** was obtained as a colorless oil in 52% yield after chromatography on silica gel. The appearance of two overlapping doublet of doublets at δ 5.00–5.10 and two singlets at 2.00–2.05 revealed the presence of the secondary acetate. Finally, the removal of both the Boc and the TBDMS groups from **15** using 1% HCl–MeOH produced Bao Gong Teng A, $[\alpha]^{22}_D$ −7.5° (*c* 0.34, H_2O) [lit.[15] $[\alpha]^{22}_D$ −7.21° (*c* 0.97, H_2O)]. The correct optical rotation of the newly synthesized Bao Gong Teng A confirmed that the asymmetric 1,3-dipolar cycloaddition of the acrylate of methyl (*S*)-lactate, **3**, to the betaine of **4** occurred at the *re* face of **3** as expected, and the major cycloadduct had structure **5a**. The NMR spectrum of Bao Gong Teng A from this work differs slightly from that reported by Jung *et al.* We observed H7-*exo* at 2.16 ppm as a doublet of doublets while Jung *et al.* did not report this resonance.[1]

Conclusion

The synthesis of optically pure Bao Gong Teng A was accomplished in 9% overall yield, via the asymmetric 1,3-dipolar cycloaddition of a chiral dipolarophile, the acrylate of methyl (*S*)-lactate, **3**, to the betaine of 3-hydroxypyridinium chloride. The 1,3-dipolar cycloaddition occurred at the *re* face of **3** with 6-*exo* regio and stereoselectivity to give the major cycloadduct **5a**. Boc protection of the nitrogen in the later stages of the synthesis was essential for alleviating problems of isolation and purification of intermediates.

Experimental Section

General Methods. The ^1H NMR spectra were recorded at 300 MHz using tetramethylsilane and 3-(trimethylsilyl)-propanesulfonic acid sodium salt (TSP) as internal standards in $CDCl_3$ and D_2O, respectively. ^{13}C NMR spectra were recorded at 75.47 MHz. Coupling constants for ring protons were assigned using an NMR simulation program.[16] The infrared (IR) spectra were recorded using solution cells. Melting points were measured on a hot stage instrument and are uncorrected. THF was distilled from sodium/benzophenone. Other solvents were reagent grade. *m*-CPBA[17] and CuI[14] were purified by recrystallization before use.

1-Benzyl-3-hydroxypyridinium Chloride (4). A mixture of 3-hydroxypyridine (10.4 g, 109 mmol) and benzyl chloride (15.5 g, 122 mmol) (90 mL) was refluxed overnight. The solvent was evaporated to leave a colorless solid which was recrystallized from acetonitrile to give crystalline **4** (18.2 g, 76%): mp 158–159 °C (lit.[3] mp 154–157 °C).

(*S*)-1-(Methoxycarbonyl)ethyl 8-Benzyl-2-oxo-8-azabicyclo[3.2.1]oct-3-ene-6-*exo*-carboxylate (5a). A mixture of the pyridinium salt **4** (8.79 g, 39.6 mmol), the acrylate of methyl (*S*)-lactate, **3**, (9.56 g, 60.4 mmol), triethylamine (15 mL), and a small amount of hydroquinone were stirred in EtOAc (200 mL) at rt under nitrogen for 10 d. The solid precipitate was filtered and washed with EtOAc (2 × 30 mL). The combined EtOAc was washed with aqueous $NaHCO_3$ (5%) and extracted with 3% HCl. The acid phase was made basic by adding solid $NaHCO_3$, and then it was extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and evaporated to give 13.0 g of crude product **5** (mixtures of **5a** and other isomers). A small amount of crude product was purified by HPLC (ODS-2, CH_3OH/H_2O 70:30) to give **5a** as an oil: ^1H NMR ($CDCl_3$) δ 7.20–7.34 (5H, m), 7.02 (1H, dd, J = 9.8, 5.1 Hz), 6.10 (1H, dd, J = 9.8, 1.5 Hz), 5.16 (1H, q, J = 7.1 Hz), 4.19 (1H, d, J = 5.0 Hz), 3.84 (1H, d, J = 13.5 Hz), 3.74 (1H, d, J = 13.5 Hz), 3.72 (3H, s), 3.65 (1H, d, J = 7.8 Hz), 3.03 (1H, dd, J = 9.4, 3.8 Hz), 2.86 (1H, ddd, J = 13.8, 7.8, 3.8 Hz), 1.94 (1H, dd, J = 13.8, 9.5 Hz), 1.52 (3H, d, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 16.9, 27.8, 47.0, 52.2, 52.3, 60.3, 68.6, 69.2, 127.2, 128.0, 128.3, 137.8, 147.7, 170.9, 172.0, 199.0.

(*S*)-1-(Methoxycarbonyl)ethyl 8-Benzyl-2-oxo-8-azabicyclo[3.2.1]octane-6-*exo*-carboxylate (6). A solution of **5** (13 g) in EtOAc and a catalytic amount of 5% Pd/C (110 mg) were stirred under hydrogen (1 atm) for 15 h at rt. The catalyst was filtered off and washed with EtOAc. The filtrate was evaporated to give a light yellow oil, which was crystallized from 20% EtOAc in hexane to give 8.41 g of **6** (61% for two steps): mp 87–88.5 °C; $[\alpha]^{23}_D$ −57.7° (*c* 0.14, $CHCl_3$); IR (CH_2Cl_2) 1744 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18–7.37 (5H, m), 5.16 (1H, q, J = 7.1 Hz), 3.89 (1H, br s), 3.83 (1H, d, J = 13.8 Hz), 3.72 (3H, s), 3.69 (1H, d, J = 13.8 Hz), 3.49 (1H, d, J = 7.3 Hz), 3.07 (1H, dd, J = 9.6, 5.8 Hz), 2.72 (1H, ddd, J =14.2, 7.3, 5.8 Hz), 2.34–2.42 (2H, m), 2.29 (1H, m), 2.08 (1H, dd, J = 14.2, 9.6 Hz), 1.91 (1H, m), 1.52 (3H, d, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 16.9, 29.5, 30.4, 32.9, 46.3, 52.3, 54.0, 61.2, 68.9, 70.2, 127.0, 128.2, 128.3, 138.2, 171.0, 174.0, 208.6; mass spectrum *m/z* (relative intensity) 317 (M^+ − CO, 25), 242 (9.8), 186 (22), 159 (21), 158 (42), 91 (100); exact mass calcd for $C_{18}H_{23}O_4N$ (M^+ − CO) 317.1627, found 317.1612.

(*S*)-1-(Methoxycarbonyl)ethyl 8-Benzyl-2-*exo*-hydroxy-8-azabicyclo[3.2.1]octane-6-*exo*-carboxylate (7b) and (*S*)-1-(Methoxycarbonyl)ethyl 8-Benzyl-2-*endo*-hydroxy-8-azabicyclo[3.2.1]octane-6-*exo*-carboxylate (7a). $LiAl(OtBu)_3H$ (9.19 g, 35.8 mmol) in THF (60 mL) was added to a solution of ketone **6** (5.80 g, 16.8 mmol) in THF (40 mL) at −4 °C under nitrogen, stirred for 3 h, and then quenched with 3% HCl (20 mL). Saturated $NaHCO_3$ was added, and the basic solution was extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and evaporated to leave a light yellow oil, which

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was chromatographed on silica gel, eluting with 3:7 EtOAc/hexane. Alcohol **7b** (3.60 g, 61.8%) was obtained as colorless crystals followed by **7a** as an oil (1.20 g, 20.6%).

Exo alcohol **7b**: mp 73–74.5 °C; $[\alpha]^{23}_D$ −106° (*c* 0.26, $CHCl_3$); IR (CH_2Cl_2) 3489, 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18–7.35 (5H, m), 5.14 (1H, q, *J* = 7.1 Hz), 3.80 (1H, br s), 3.68 (3H, s), 3.66 (1H, d, *J* = 13.4 Hz), 3.50 (1H, br s), 3.42 (1H, d, *J* = 13.4 Hz), 3.28 (1H, dd, *J* = 7.2, 3.8 Hz), 2.94 (1H, dd, *J* = 9.5, 5.9 Hz), 2.61 (1H, ddd, *J* = 14.1, 7.2, 5.9 Hz), 1.98 (1H, m), 1.81 (1H, dd, *J* = 14.1, 9.5 Hz), 1.46–1.62 (3H, m), 1.51 (3H, d, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 16.9, 24.8, 28.2, 29.4, 45.2, 52.3, 57.7, 65.3, 66.4, 68.2, 68.8, 127.0, 128.3, 128.7, 139.4, 171.0, 175.3; mass spectrum *m/z* (relative intensity) 347 (M^+, 7), 256 (23), 244 (13), 242 (17), 216 (28), 184 (20), 172 (16), 158 (17), 149 (24), 91 (100); exact mass calcd for $C_{19}H_{25}O_5N$ 347.1733, found 347.1721.

Endo alcohol **7a**: $[\alpha]^{23}_D$ −78.5° (*c* 0.37, $CHCl_3$); IR (CH_2Cl_2) 3606, 1739 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.16–7.38 (5H, m), 5.14 (1H, q, *J* = 7.1 Hz), 3.82 (1H, m), 3.73 (1H, br s), 3.72 (1H, d, *J* = 13.9 Hz), 3.68 (3H, s), 3.55 (1H, d, *J* = 13.9 Hz), 3.19 (1H, dd, *J* = 6.5, 3.7 Hz), 2.82 (1H, dd, *J* = 9.6, 6.2 Hz), 2.42 (1H, ddd, *J* = 13.8, 6.5, 6.2 Hz), 2.10 (1H, dd, *J* = 13.8, 9.6 Hz), 1.75–1.96 (2H, m), 1.61 (1H, m), 1.51 (3H, d, *J* = 7.1 Hz), 1.25 (1H, m); ^{13}C NMR ($CDCl_3$) δ 16.9, 25.0, 26.3, 30.7, 46.8, 52.2, 56.8, 64.1, 65.6, 68.7, 69.3, 126.7, 128.1, 128.5, 139.8, 171.2, 175.4; mass spectrum *m/z* (relative intensity) 347 (M^+, 5), 256 (10), 244 (6), 242 (6), 216 (13), 184 (9), 172 (9), 158 (10), 149 (20), 91 (65), 71 (100); exact mass calcd for $C_{19}H_{25}O_5N$ 347.1733, found 347.1738.

(*S*)-1-(Methoxycarbonyl)ethyl 8-Benzyl-2-*exo*-[(*tert*-butyldimethylsilyl)oxy]-8-azabicyclo[3.2.1]octane-6-*exo*-carboxylate (11). To a mixture of **7b** (2.17 g, 6.24 mmol) and triethylamine (3.70 mL) was added TBDMSOTf (2.20 mL, 9.58 mmol) over 3 min under nitrogen. TLC indicated that the reaction was complete. The reaction mixture was poured into saturated NaCl solution (40 mL) and then extracted with CH_2Cl_2 (4 × 20 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated to leave a dark yellow oil. This yellow oil was filtered through a short silica gel column with 3:7 EtOAc/hexane to provide **11** as a light yellow oil (2.77 g, 96%): $[\alpha]^{23}_D$ −68.7° (*c* 0.60, $CHCl_3$); IR (CH_2Cl_2) 1741 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46 (2H, d, *J* = 7.2 Hz), 7.14–7.32 (3H, m), 5.15 (1H, q, *J* = 7.1 Hz), 3.87 (1H, d, 14.9 Hz), 3.76 (1H, d, *J* = 14.9 Hz), 3.74 (1H, br s), 3.69 (3H, s), 3.62 (1H, br s), 3.28 (1H, dd, 7.0, 3.0 Hz), 2.92 (1H, dd, *J* = 9.4, 5.7 Hz), 2.51 (1H, ddd, *J* = 13.6, 7.0, 5.7 Hz), 2.19 (1H, dddd, *J* = 12.9, 12.9, 5.7, 2.7 Hz), 1.71 (1H, m), 1.70 (1H, dd, *J* = 13.6, 9.4 Hz), 1.56 (1H, m), 1.52 (3H, d, *J* = 7.1 Hz); 1.40 (1H, m), 0.92 (9H, s), 0.03 (3H, s), 0.00 (3H, s); ^{13}C NMR ($CDCl_3$) δ −5.0, −4.7, 16.9, 18.2, 25.8, 25.9, 26.6, 28.7, 45.4, 52.2, 55.9, 63.4, 65.4, 68.6, 70.2, 126.2, 127.8, 128.1, 140.5, 171.1, 175.5; mass spectrum *m/z* (relative intensity) 461 (M^+, 2), 370 (5), 356 (8.4), 330 (6.4), 300 (9.5), 266 (9.2), 210 (15), 91 (100); exact mass calcd for $C_{25}H_{39}O_5NSi$ 461.2598, found 461.2563.

(*S*)-1-(Methoxycarbonyl)ethyl 8-(*tert*-Butoxycarbonyl)-2-*exo*-[(*tert*-butyldimethylsilyl)oxy]-8-azabicyclo[3.2.1]-octane-6-*exo*-carboxylate (12). Di-*tert*-butyl dicarbonate (1.15 g, 5.26 mmol) was added to a solution of **11** (1.33 g, 2.89 mmol) in MeOH (70 mL) followed by 5% Pd/C (150 mg). The resulting suspension was hydrogenated (1 atm) for 15 h and then filtered. The catalyst was thoroughly washed with MeOH, and the combined filtrates were evaporated to leave a colorless oil with di-*tert*-butyl dicarbonate as a contaminant. A small amount of the crude product was pumped under high vacuum for 2 weeks to obtain a sample of solid **12** for characterization purposes (the bulk of the crude product was used in the next step without further purification): mp 53–55 °C; $[\alpha]^{23}_D$ −14.0° (*c* 0.47, $CHCl_3$); IR (CH_2Cl_2) 1744, 1691 cm^{-1}; ^1H NMR ($CDCl_3$), mixture of two rotamers, δ 5.06 (1H, q, *J* = 7.1 Hz), 4.52 and 4.63 (1H, br s), 4.22 and 4.27 (1H, m), 3.71 and 3.72 (3H, s), 3.62 and 3.65 (1H, br s), 2.82 (1H, m), 2.26 (1H, m), 2.04 (1H, m), 1.57–1.84 (2H, m), 1.45 (3H, d, *J* = 7.1 Hz), 1.41 (9H, s), 1.30–1.57 (2H, m), 0.86 and 0.87 (9H, s), 0.05 (3H, s), 0.02 (3H, s); ^{13}C NMR ($CDCl_3$), mixture of two rotamers, δ −5.1 and −5.0, −4.9 and −4.7, 16.8, 18.1 and 18.1, 25.5, 25.8 and 25.9, 26.7 and 26.9, 28.4, 29.8 and 30.4, 44.7 and 45.2, 52.2 and 52.3, 56.3 and 57.0, 58.0 and 59.3, 68.5 and 68.8, 68.9 and 69.0, 78.5 and 78.8, 152.6 and 153.2, 171.0 and 171.1, 173.9 and 174.0; mass spectrum *m/z* (relative intensity) 398 (M^+ − OtBu, 3.1), 370 (6.6), 358 (31), 314 (85), 83 (49), 73 (49), 57 (100); exact mass calcd for $C_{19}H_{32}O_6NSi$ (M^+ − OtBu) 398.1999, found 398.2018.

8-(*tert*-Butoxycarbonyl)-2-*exo*-[(*tert*-butyldimethylsilyl)oxy]-8-azabicyclo[3.2.1]octane-6-*exo*-carboxylic Acid (13). KOH (2.43 g, 43.3 mmol) in H_2O (30 mL) was added to a solution of crude **12** from the previous procedure in MeOH (60 mL), and the resulting mixture was stirred at rt for 15 h. Most of the MeOH was then evaporated. The resulting aqueous solution was adjusted to pH 3 with 7M H_3PO_4 and then extracted with $CHCl_3$. The organic phase was dried ($MgSO_4$) and evaporated to give the acid **13** as a colorless solid (1.05 g, 94.3% for the two steps): mp 131.5–133.5 °C; $[\alpha]^{23}_D$ +1.4° (*c* 1.0, $CHCl_3$); IR (CH_2Cl_2) 1713, 1695, 1643 cm^{-1}; ^1H NMR ($CDCl_3$), mixture of two rotamers, δ 11.29 (1H, br s), 4.44 and 4.63 (1H, br s), 4.18 and 4.26 (1H, m), 3.60 (1H, s), 2.74 (1H, m), 2.23 (1H, m), 2.01 (1H, m), 1.55–1.68 (2H, m), 1.37 (9H, s), 1.32–1.60 (2H, m), 0.84 (9H, s), 0.02 (3H, s), −0.01 (3H, s); ^{13}C NMR ($CDCl_3$), mixture of two rotamers, δ −5.1 and −4.9, −4.9 and −4.8, 18.1, 25.4, 25.9, 26.6 and 26.9, 28.4, 29.9 and 30.0, 44.8 and 45.4, 56.9 and 57.2, 58.1 and 59.6, 68.8 and 68.9, 78.8 and 79.8, 153.1 and 154.4, 177.9 and 179.9; mass spectrum *m/z* (relative intensity) 312 (M^+ − OtBu, 2.6), 272 (28), 228 (100), 210 (48), 114 (48), 108 (46), 82 (45), 75 (69), 73 (64), 69 (49), 57 (80); exact mass calcd for $C_{15}H_{26}O_4NSi$ (M^+ − OtBu) 312.1631, found 312.1642. Anal. Calcd for $C_9H_{35}O_5NSi$: C, 59.19; H, 9.15; N, 3.63. Found: C, 59.1; H, 9.31; N, 3.60.

6-*exo*-Acetyl-8-(*tert*-butoxycarbonyl)-2-*exo*-[(*tert*-butyldimethylsilyl)oxy]-8-azabicyclo[3.2.1]octane (14). Oxalyl chloride (0.71 mL, 8 mmol) was added to a solution of acid **13** (1.05 g, 2.72 mmol) and a catalytic amount of DMF (5 drops) in benzene (40 mL), and the resulting solution was stirred for 2 h and then evaporated to dryness. A solution of Me_2CuLi (11.6 mmol) in Et_2O/THF (1:4.9, 48.3 mL) was cannulated into the solution of the crude acid chloride in THF (30 mL) at −78 °C under nitrogen. After stirring at −78 °C for 15 min, the reaction mixture was quenched by addition of MeOH (15 mL) and allowed to warm to rt. The reaction mixture was poured into 0.5 M KOH (40 mL) and extracted with $CHCl_3$. The organic phase was dried ($MgSO_4$) and evaporated to leave the ketone **14** as a light yellow oil (0.851 g, 81.5%): $[\alpha]^{23}_D$ +16.2° (*c* 0.79, $CHCl_3$); IR (CH_2Cl_2) 1713, 1691 cm^{-1}; ^1H NMR ($CDCl_3$), mixture of two rotamers, δ 4.36 and 4.52 (1H, s), 4.21 and 4.30 (1H, m), 3.65 and 3.68 (1H, s), 2.84 (1H, m), 2.32 and 2.17 (1H, m), 2.15 and 2.20 (3H, s), 2.13 (1H, m), 1.64–1.82 (2H, m), 1.50–1.64 (2H, m), 1.43 (9H, s), 0.88 and 0.89 (9H, s), 0.07 (3H, s), 0.05 (3H, s); ^{13}C NMR ($CDCl_3$), mixture of two rotamers, δ −5.1 and −5.0, −4.9 and −4.7, 18.1, 25.5, 25.8 and 25.9, 26.9 and 27.1, 27.3 and 27.9, 28.1, 28.4 and 28.5, 53.0 and 53.7, 55.5 and 55.9, 58.1 and 59.6, 68.8 and 69.0, 78.7 and 79.2, 152.6 and 153.8, 207.5 and 207.6; mass spectrum *m/z* (relative intensity) 310 (M^+ − OtBu, 0.4), 270 (21), 226 (69), 73 (66), 57 (100); exact mass calcd for $C_{16}H_{28}O_3NSi$ (M^+ − OtBu) 310.1838, found 310.1846.

6-*exo*-Acetyl-8-(*tert*-butoxycarbonyl)-2-*exo*-[(*tert*-butyldimethylsilyl)oxy]-8-azabicyclo[3.2.1]octane (15). To a solution of ketone **14** (0.658 g, 1.71 mmol) was added *m*-CPBA (1.044 g, 6.05 mmol) in 1:2 benzene/$CHCl_3$ (60 mL). After stirring for 7 d the solution was washed with 5% $NaHCO_3$ (2 × 20 mL) to remove *m*-chlorobenzoic acid, back extracting with $CHCl_3$. The organic phase was dried ($MgSO_4$) and further *m*-CPBA (0.406 g, 2.36 mmol) added. Stirring was continued for another 2 d. The reaction mixture was washed with aqueous $NaHCO_3$ (5%) and then with aqueous Na_2SO_3 (10%) to destroy the excess peracid and again with aqueous $NaHCO_3$ (5%). The organic phase was dried ($MgSO_4$) and evaporated to give the crude acetate **15** as a light yellow oil (0.672 g, 98.0%). Column chromatography using 15% EtOAc in hexane gave a colorless oil (0.35 g, 52.0%): $[\alpha]^{23}_D$ −14.9° (*c* 0.74, $CHCl_3$); IR (CH_2Cl_2) 1734, 1692 cm^{-1}; ^1H NMR ($CDCl_3$), mixture of two rotamers, δ 5.03 (1H, m), 4.25 and 4.33 (1H, m), 4.07 and 4.29 (1H, s), 3.61 and 3.64 (1H, m), 1.95–2.12

(2H, m), 2.02 and 2.03 (3H, s), 1.85 (1H, m), 1.59 (1H, m), 1.38–1.56 (2H, m), 1.45 and 1.47 (9H, s), 0.88 and 0.89 (9H, s), 0.07 and 0.08 (3H, s), 0.04 (3H, s); ^{13}C NMR ($CDCl_3$), mixture of two rotamers, δ −5.1 and −5.0, −4.9 and −4.6, 18.1 and 18.2, 21.1 and 21.2, 23.9 and 23.9, 25.5 and 25.6, 25.8 and 25.9, 28.5 and 28.5, 34.9 and 35.8, 58.0 and 58.5, 59.2 and 59.8, 68.7 and 68.8, 76.3 and 77.2, 78.7 and 79.1, 153.5 and 154.1, 170.9 and 170.9; mass spectrum *m/z* (relative intensity) 326 (M^+ − OtBu, 3.1), 286 (40), 242 (95), 182 (63), 75 (77), 73 (78), 57 (100); exact mass calcd for $C_{16}H_{28}O_4NSi$ (M^+ − OtBu) 326.1788, found 326.1797.

Bao Gong Teng A [(−)1]. The pure acetate **15** (35.7 mg, 0.089 mmol) was stirred in a solution of 1% HCl in EtOH (5 mL) for 2 h. The EtOH was evaporated by rotary evaporation at 70 °C, dissolved in $CHCl_3$, and washed with aqueous K_3PO_4 (2 M). The organic phase was passed through filter paper to remove H_2O and evaporated to yield Bao Gong Teng A (10.1 mg, 61.3%): $[\alpha]^{23}_D$ −7.5° (*c* 0.34, H_2O) [lit.[15] −7.2° (*c* 0.97, H_2O)]; IR (CH_2Cl_2) 1732, 1623 cm^{-1}; ^1H NMR ($CDCl_3$), δ 5.12 (1H, dd, J = 6.9, 2.1 Hz), 3.54 (1H, br s), 3.52 (1H, s br), 3.28 (1H, br s), 2.16 (1H, dd, J = 14.7, 6.9 Hz), 2.05–2.14 (2H, exchangeable, br s), 2.04 (3H, s), 1.70–1.94 (2H, m), 1.44–1.63 (3H, m) (lit.[1]); ^{13}C NMR ($CDCl_3$), δ 21.3, 24.8, 25.0, 37.2, 60.6, 61.1, 67.5, 78.1, 170.7; mass spectrum *m/z* (relative intensity) 185 (M^+, 7.0), 149 (52), 142 (18), 126 (48), 99 (76), 82 (68), 81 (45), 80 (100), 68 (47); exact mass calcd for $C_9H_{15}O_3N$ 185.1052, found 185.1037.

8-Benzyl-2-*exo*-hydroxy-8-azabicyclo[3.2.1]octane-6-*exo*-carboxylic Acid (8). KOH (405 mg, 7.21 mmol) in H_2O (6 mL) was added to a solution of **7b** (336 mg, 96.8 mmol) in MeOH (12 mL), and the resulting mixture was stirred at rt for 20 h. Most of the MeOH was then evaporated. The resulting aqueous solution was adjusted to pH 2 by adding 3% HCl and then was slowly poured onto an acidic (pH 2) ion exchange column (Dowex 50W-X8, hydrogen form). The column was rinsed with aqueous HCl (pH 2, 100 mL) and then H_2O until no more chloride ion was eluted. The acid **8** was eluted with 1 L of aqueous NH_3 (pH 11), and the solvent was evaporated to give a colorless solid. The solid was dissolved in H_2O (20 mL) and then frozen and lyophilized under high vacuum overnight. The resulting acid **8** (186 mg, 73.5%) appeared as flaky, colorless solid: $[\alpha]^{23}_D$ −9.6° (*c* 0.10, H_2O); ^1H NMR (D_2O), δ 7.40–7.53 (5H, m), 4.39 (1H, d, J = 13.4 Hz), 4.36 (1H, s), 4.00 (1H, s), 3.92 (1H, d, J = 13.4), 3.66 (1H, m), 3.16 (1H, dd, J = 10.5, 5.6 Hz), 2.65 (1H, ddd, J = 15.2, 7.1, 5.6 Hz), 2.33 (1H, m), 2.23 (3H, dd, J = 10.5, 15.2 Hz), 1.78–2.00 (2H, m), 1.68 (1H, m); ^{13}C NMR ($CDCl_3$), δ 22.7, 26.6, 26.8, 45.5, 56.0, 66.1, 67.8, 68.5, 129.9, 130.2, 130.9, 131.0, 179.9; mass spectrum *m/z* (relative intensity) 261 (7.1), 170 (30.6), 149 (18.8), 91 (100), 69 (51.6), 57 (47.5), 55 (42.1); exact mass calcd for $C_{15}H_{19}O_3N$ 261.1365, found 261.1364.

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Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra of all compounds; a table of chemical shifts and coupling constants obtained from NMR simulations (37 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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