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TETRAHEDRON: *ASYMMETRY*

Efficient stereospecific synthesis of (*S*,*S*)-3-methoxy-4-methylaminopyrrolidine

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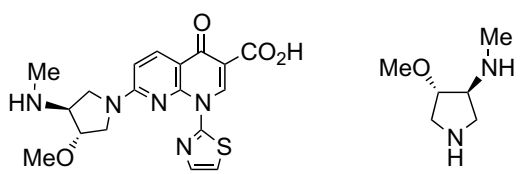
Abstract—Efficient stereospecific synthesis of (*S*,*S*)-3-methoxy-4-methylaminopyrrolidine, an important intermediate for a novel quinolone antitumor agent AG-7352 is presented. Starting from either D- or L-tartaric acid, a stereospecific synthesis of the chiral pyrrolidine was achieved via two S_N2 displacement reactions. From the results of this synthetic study, the absolute structure of AG-7352 was chemically determined.

1. Introduction

Chiral, non-racemic pyrrolidines are common structural subunits found in many natural and unnatural products with interesting and important biological activity.[1] One such compound is AG-7352 (+)-**1**, which is a novel anti-tumor agent created at our laboratories and is now under development. It shows anti-tumor activities equal or superior to those of cisplatin and etoposide against human breast, ovarian and colon cancers implanted in mice.[2] It has recently been reported that some quinolone-related compounds show anti-tumor activity with inhibition of eukaryotic topoisomerase II.[3] While those reported compounds have in common a quinolone structure as basic frame, the basic structure of (+)-**1** is 4-oxo-1,8-naphthyridine-3-carboxylic acid. Thus, (+)-**1** is structurally a new type of antitumor agent.

In addition to the naphthyridine ring, (+)-**1** has a 3-methoxy-4-methylaminopyrrolidinyl group at C(7) (see Fig. 1).



AG-7352 ((+)-1) **2**

Figure 1.

We needed to prepare the (+)-enantiomer of 3-methoxy-4-methylaminopyrrolidine **2** for a synthesis of (+)-**1**. While a synthesis of (±)-**2** is known,[4] a synthesis of optically active **2** has not been reported to date. Our original synthesis of optically active **2** was carried out from 3-pyrroline through an optically active intermediate obtained by optical resolution,[2b] and the absolute configuration of (+)-**2** could not be confirmed by this method. Therefore, we developed a new stereospecific synthesis of the chiral pyrrolidine to determine its absolute configuration without optical resolution of the racemate. Herein, we describe that an efficient stereospecific synthesis of (+)-enantiomer **2** could be achieved from commercially available D-(*S*,*S*)-tartaric acid via two S_N2 displacement reactions. Furthermore, starting from L-(*R*,*R*)-tartaric acid, another stereospecific synthesis of the same chiral pyrrolidine could be also achieved. The result allowed us to determine the absolute structure of (+)-**2** as (3*S*,4*S*) and the absolute structure of (+)-**1** was deduced as (3′*S*,4′*S*).

2. Results and discussion

The synthesis of (+)-**2** requires the stereospecific construction of two stereogenic centers on the pyrrolidine ring. The retrosynthetic analysis outlined in Scheme 1 suggests the use of tartaric acid, an extremely useful and versatile chiral building block, as the starting material. The efficient differentiation of the two adjacent hydroxyl groups could be attained by this synthetic route with tartaric acid. Starting from tartaric acid, the route includes a key intermediate ((*R*,*R*)-**3** or (*S*,*S*)-**3**) which has a hydroxyl function protected by a bulky

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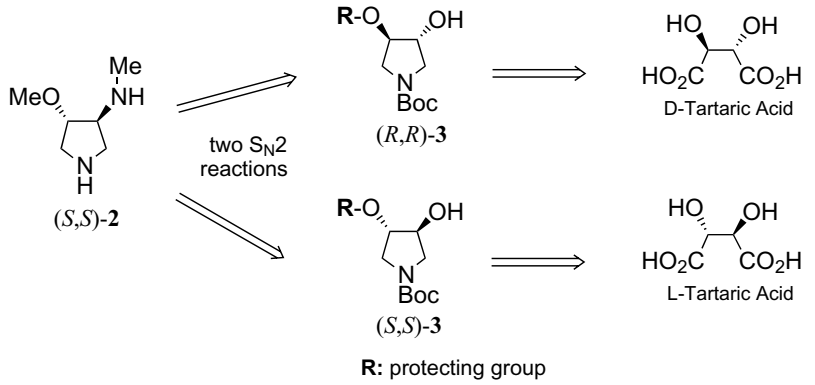
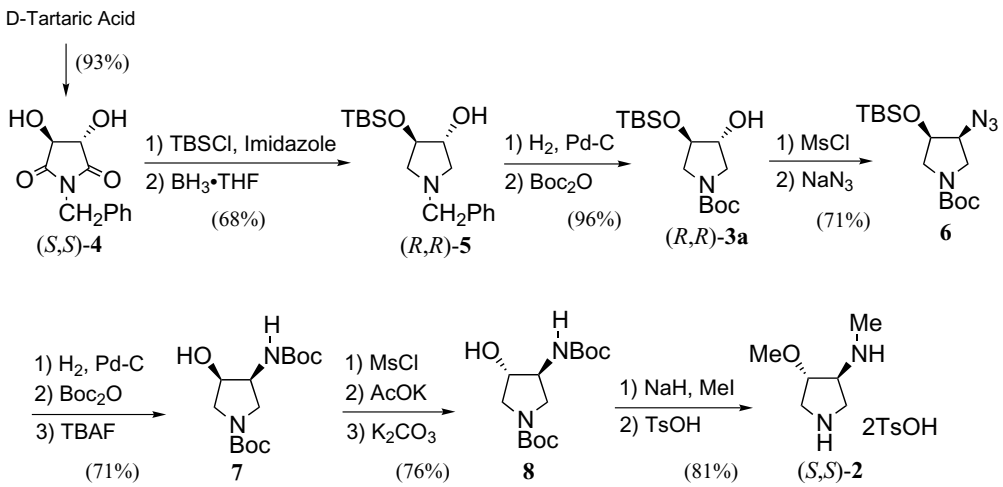


Scheme 1.

tert-butyldimethylsilyl residue. By this simple protection, the two functional groups on the pyrrolidine ring could be clearly distinguished. The intermediate ((*R*,*R*)-**3**) from D-tartaric acid would be converted into (*S*,*S*)-**2** via two S_N2 displacement reactions with inversion of configuration. (*S*,*S*)-**2** could also be synthesized via two S_N2 displacement reactions through the pyrrolidine derivative (*S*,*S*)-**3** from L-tartaric acid. Another enantiomer (*R*,*R*)-**2** could be synthesized by the same strategy with opposite starting materials.

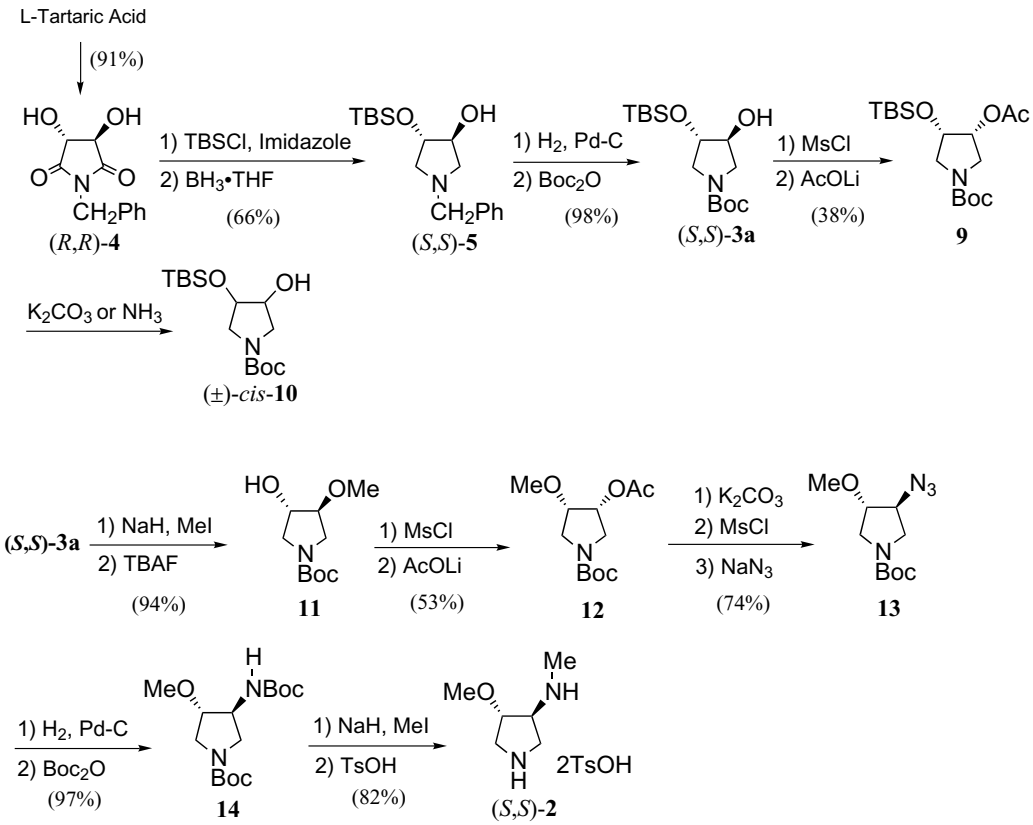
Our synthesis started with the monoprotection of the known tartarimide (*S*,*S*)-**4**[5] which was readily prepared from commercially available D-tartaric acid (Scheme 2). Any attempt to monoprotect the tartarimide (*S*,*S*)-**4** with methyl, acetyl or benzyl group resulted in failure. On the other hand, the protection of (*S*,*S*)-**4** with a bulky silyl group successfully afforded a monoprotected compound. Thus, (*S*,*S*)-**4** was treated with 1.0 equiv. of *tert*-butyldimethylsilyl chloride (TBSCl) and 2.1 equiv. of imidazole in DMF at 0°C to give the monosilyl ether in quantitative yield. The imide moiety of the monosilyl ether was reduced by borane-tetrahydrofuran complex (BH_3·THF) to give the pyrrolidine derivative (*R*,*R*)-**5** in 68% yield. After removal of benzyl group of compound (*R*,*R*)-**5**, the resulting secondary amine was immediately reprotected with di-*tert*-butyl dicarbonate (Boc_2O) to give compound (*R*,*R*)-**3a** in good yield. The alcohol (*R*,*R*)-**3a** was converted into the corresponding mesylate, and S_N2 displacement of the mesylate by azide anion (NaN_3) in DMF introduced the nitrogen function, thus the *cis*-azide **6** was obtained in 71% yield with complete inversion of configuration. The stereochemistry of azide-bearing carbon in **6** was confirmed by NOESY experiments in ^1H NMR. After catalytic hydrogenation of the azide group over Pd–C, followed by treatment with Boc_2O, the silyl group was removed by treatment with tetrabutylammonium fluoride (TBAF) to give the *cis*-alcohol **7** in 71% yield. The alcohol **7** was converted into mesylate, followed by treatment with AcOK and successive basic treatment with K_2CO_3, giving the *trans*-alcohol **8** in 76% yield with another complete inversion of configuration. Thus, compound **8**, possessing the required stereochemistry, was obtained by one inversion of each hydroxyl group on the pyrrolidine ring of (*S*,*S*)-**4**. Compound **8** was smoothly methylated with NaH and MeI in DMF to give the *N*,*O*-dimethyl analog in quantitative yield. Removal of both Boc groups from the *N*,*O*-dimethyl compound with *p*-toluenesulfonic acid (TsOH) in *i*-PrOH completed the synthesis of one enantiomer (*S*,*S*)-**2**·2TsOH in 81% yield. Spectroscopic data and the



Scheme 2.

specific rotation of this enantiomer (*S*,*S*)-**2**·2TsOH {$[\alpha]_D^{29}=+10.4$ (*c* 1.00, MeOH)} were in good agreement with the values of our originally synthesized (+)-enantiomer **2**·2TsOH {$[\alpha]_D^{29}=+10.5$ (*c* 1.00, MeOH)}. Since the desired (*S*,*S*)-**2** was obtained from D-(*S*,*S*)-tartaric acid of known configuration in 19% overall yield by the stereospecific and efficient way, the absolute configuration of AG-7352 was deduced as (3′*S*,4′*S*). Also, utilizing this methodology, the opposite enantiomer (*R*,*R*)-**2**) could be obtained conveniently from L-tartaric acid.

Furthermore, starting from L-tartaric acid, a stereospecific synthesis of (*S*,*S*)-**2** was also achieved via two S_N2 displacement reactions (Scheme 3). By the similar method for the synthesis of (*R*,*R*)-**3a**, benzyl group of the monoprotected intermediate (*S*,*S*)-**5** obtained from (*R*,*R*)-**4** was removed by catalytic hydrogenation, followed by treatment with Boc_2O to give the corresponding alcohol (*S*,*S*)-**3a**. The alcohol (*S*,*S*)-**3a** was converted into mesylate, followed by treatment with AcOLi to afford the *cis*-acetate **9**. The stereochemistry of **9** was confirmed by NOEs in the ^1H NMR spectrum. Compound **9**, however, gave racemate (±)-*cis*-**10** when it was treated with alkaline such as K_2CO_3 and NH_3.[6] The deacetylated compound given under basic conditions was presumably racemized since an oxygen ion attacked the neighboring silicon. The formation of **10** inspired us to design a replacement of *O*-silyl group of **9** by *O*-methyl group. Thus, compound (*S*,*S*)-**3a** was easily converted to the monomethyl ether **11** in good yield by methylation and successive removal of silyl group. The alcohol **11** was converted to the desired *cis*-acetate **12** in 53% yield by mesylation and S_N2 displacement of the mesylate. The stereochemistry of acetoxy group in **12** was also confirmed by NOE in the nuclear of ^1H NMR spectra. Compound **12** was treated with K_2CO_3, and the given alcohol was converted to the *trans*-azide **13** in 74% yield by mesylation and displacement with NaN_3. Thus, compound **13**, possessing the required stereochemistry, was successfully obtained by two inversions of either hydroxyl group on pyrrolidine ring of (*R*,*R*)-**4**. After catalytic hydrogenation of the azide group over Pd–C, the resulting amine was protected with Boc_2O to give the compound **14** in 97% yield. Compound **14** was methylated with NaH and MeI in DMF, followed by removal of both Boc groups with TsOH to give the desired (*S*,*S*)-**2**·2TsOH in 82% yield. The chiral pyrrolidine (*S*,*S*)-**2** was obtained from L-tartaric acid in 17% overall yield by the stereoselective way, while this method included additional one step to the above method from D-tartaric acid. Spectroscopic data and the specific rotation of (*S*,*S*)-**2**·2TsOH {$[\alpha]_D^{26}=+10.3$ (*c* 1.01, MeOH)} were in good agreement with the values of our originally synthesized (+)-enantiomer **2**·2TsOH. As a result, the stereospecific synthesis of the chiral pyrrolidine (*S*,*S*)-**2** was achieved from both enantiomers of tartaric acid.



Scheme 3.

3. Conclusion

In summary, a concise synthesis of (*S*,*S*)-**2** was achieved through a simple and efficient reaction sequence with a stereospecific manner, starting from D- or L-tartaric acid. Based on the result, the absolute configuration of (+)-**2** was determined as (3*S*,4*S*) and AG-7352 was found to have (3′*S*,4′*S*) absolute configuration. In addition, this approach could be readily applicable to the general synthesis of optically active 3,4-disubstituted pyrrolidine derivatives. A large scale synthetic method for (*S*,*S*)-**2** will be reported in a future.

4. Experimental

4.1. General

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin–Elmer 1600 Series FT-IR spectrophotometer. ^{1}H NMR spectra were taken at 300 MHz on a JOEL JNM-LA 300 spectrometer. Chemical shifts are expressed in ppm (δ) with tetramethylsilane as an internal standard. Mass spectra (MS) were obtained on a Hitachi M-80B or Hitachi M-1000 spectrometer. Optical rotations were measured on a Jasco P-1020 digital polarimeter.

4.2. (3*R*,4*R*)-1-Benzyl-3-(*tert*-butyldimethylsilyl)oxy-4-hydroxypyrrolidine (*R*,*R*)-5

A solution of *tert*-butyldimethylsilyl chloride (20.7 g, 0.137 mol) in dry DMF (150 mL) was added to a mixture of (3*S*,4*S*)-1-benzyl-2,5-pyrrolidinedione (*S*,*S*)-**4**[5] (30.0 g, 0.136 mol) and imidazole (19.4 g, 0.285 mol) in dry DMF (400 mL) over a period of 30 min at 0°C. The reaction mixture was stirred at rt for 24 h, concentrated in vacuo, and AcOEt was added. The precipitate that formed was filtered off and the filtrate was successively washed with saturated NH_4Cl and saturated NaCl, dried over Na_2SO_4, and then concentrated in vacuo. The residue was triturated with *i*-Pr_2O, and the resultant precipitates were collected by filtration. The given monosilyl compound was dissolved in dry THF (400 mL), and then the solution was added into borane–tetrahydrofuran complex (1 M solution in THF, 500 mL, 0.50 mol) over a period of 1 h under ice cooling. The mixture was stirred at rt for 2 h, and then heated at 70°C for 2 h. The solvent was distilled off under reduced pressure and EtOH (900 mL) was added to the resulting residue. The mixture was heated under reflux for 15 h and concentrated in vacuo to leave a residue. The residue was dissolved in water, and the mixture was extracted with $CHCl_3$. The extract was washed with saturated NaCl, dried over Na_2SO_4 and concentrated in vacuo. The resulting residue was chromatographed on silica gel with $CHCl_3$–MeOH (50:1) to give (*R*,*R*)-**5** as white crystals (28.1 g, 68%): mp 55–56°C; $[\alpha]_D^{26}=-33.8$ (*c* 1.00, MeOH); ^{1}H NMR ($CDCl_3$): δ 0.05 (s, 3H), 0.07 (s, 3H), 0.88 (s, 9H), 1.80 (br s, 1H), 2.17 (dd, 1H, *J*=9.9, 4.6 Hz), 2.66 (dd, 1H, *J*=10.0, 4.8 Hz), 2.72 (dd, 1H, *J*=9.9, 1.8 Hz), 3.20 (dd, 1H, *J*=9.9, 6.4 Hz), 3.61 (d, 1H, *J*=13.0 Hz), 3.66 (d, 1H, *J*=13.0 Hz), 3.92–3.98 (m, 1H), 4.10–4.15 (m, 1H), 7.24–7.35 (m, 5H); MS *m*/*z* 308 (M^++1); IR (KBr): 3350 cm^{-1}. Anal. calcd for $C_{17}H_{29}NO_2Si$: C, 66.40; H, 9.51; N, 4.55. Found: C, 66.20; H, 9.46; N, 4.48%.

4.3. (3*R*,4*R*)-1-*tert*-Butoxycarbonyl-3-(*tert*-butyldimethylsilyl)oxy-4-hydroxypyrrolidine (*R*,*R*)-3a

A solution of (*R*,*R*)-**5** (13.9 g, 45.3 mmol) in EtOH (85 mL) was hydrogenated over 5% Pd–C (1.39 g) at 40°C for 2 h. The mixture was filtered and EtOH (120 mL) was added to the filtrate. Then Boc_2O (10.4 g, 47.5 mmol) was added to the mixture under ice cooling. The reaction mixture was stirred at rt for 3 h, and then concentrated in vacuo. The residue was chromatographed on silica gel with $CHCl_3$–MeOH (100:1) to give (*R*,*R*)-**3a** as a colorless oil (13.8 g, 96%): $[\alpha]_D^{26}=+16.1$ (*c* 1.06, MeOH); ^{1}H NMR ($CDCl_3$): δ 0.08 (s, 6H), 0.87 (s, 9H), 1.46 (s, 9H), 1.84 (br s, 1H), 3.18–3.38 (m, 2H), 3.51–3.66 (m, 2H), 4.03–4.11 (m, 2H); MS *m*/*z* 318 (M^++1); IR (NaCl): 3410, 1675 cm^{-1}. Anal. calcd for $C_{15}H_{31}NO_4Si\cdot0.25H_2O$: C, 55.95; H, 9.86; N, 4.35. Found: C, 56.11; H, 9.82; N, 4.33%.

4.4. (3*S*,4*R*)-3-Azido-1-*tert*-butoxycarbonyl-4-(*tert*-butyldimethylsilyl)oxypyrrolidine 6

A solution of methanesulfonyl chloride (5.90 g, 51.5 mmol) in CH_2Cl_2 (60 mL) was added to a mixture of (*R*,*R*)-**3a** (13.6 g, 42.9 mmol) and triethylamine (6.07 g, 60.1 mmol) in CH_2Cl_2 (400 mL) over a period of 10 min under ice cooling. The reaction mixture was stirred at rt for 1.5 h, taken up with water, and extracted with CH_2Cl_2. The extract was washed with saturated NaCl, dried over Na_2SO_4, and then concentrated in vacuo. A mixture of the residual mesylate and sodium azide (5.58 g, 85.8 mmol) in DMF (100 mL) was heated at 120°C for 8 h. The reaction mixture was poured into water and the mixture was extracted with toluene. The extract was washed with saturated NaCl, dried over Na_2SO_4, and then concentrated in vacuo. The residue was chromatographed on silica gel with hexane–AcOEt (25:1) to give **6** as a colorless oil (10.4 g, 71%): $[\alpha]_D^{26}=-85.3$ (*c* 1.02, MeOH); ^{1}H NMR ($CDCl_3$): δ 0.10 (s, 3H), 0.12 (s, 3H), 0.88 (s, 9H), 1.46 (s, 9H), 3.21–3.52 (m, 3H), 3.55 (dd, 1H, *J*=11.0, 5.8 Hz), 3.74–3.79 (m, 1H), 4.38 (ddd, 1H, *J*=10.2, 6.0, 4.2 Hz); MS *m*/*z* 343 (M^++1); IR (NaCl): 2105, 1695 cm^{-1}. Anal. calcd for $C_{15}H_{30}N_4O_3Si$: C, 52.60; H, 8.83; N, 16.36. Found: C, 52.57; H, 8.89; N, 16.45%. The NOE observed from C(3)H to C(4)H enabled structural assignment of **6**.

4.5. (3*S*,4*R*)-1-*tert*-Butoxycarbonyl-3-*tert*-butoxycarbonylamino-4-hydroxypyrrolidine 7

A solution of **6** (9.05 g, 26.4 mmol) in EtOH (90 mL) was hydrogenated over 5% Pd–C (450 mg) at 20°C for 2 h. The mixture was filtered and EtOH (70 mL) was added to the filtrate. Then Boc_2O (6.05 g, 27.7 mmol) was added to the mixture under ice cooling. The reaction mixture was stirred at rt for 15 h, and then

concentrated in vacuo. The residue was chromatographed on silica gel with $CHCl_3$–MeOH (200:1). The given *tert*-butylcarbonylamino compound was dissolved in THF (90 mL), and then the solution was added into tetrabutylammonium fluoride (1 M solution in THF, 36.1 mL, 36.1 mmol) under ice cooling. The mixture was stirred at rt for 1 h, and then concentrated in vacuo. The residue was poured into water and the mixture was extracted with AcOEt. The extract was washed with saturated NaCl, dried over Na_2SO_4, and then concentrated in vacuo. The residue was chromatographed on silica gel with $CHCl_3$–MeOH (200:1) to give **7** as white crystals (5.66 g, 71%): mp 107–108°C; $[\alpha]_D^{26}=+3.5$ (*c* 1.01, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.45 (s, 18H), 3.08–3.19 (m, 1H), 3.35–3.57 (m, 2H), 3.73 (dd, 1H, $J=10.3$, 7.7 Hz), 4.08–4.20 (m, 1H), 4.27–4.34 (m, 1H), 5.02 (br s, 2H); MS *m*/*z* 303 (M^++1); IR (KBr): 3450, 3350, 1685 cm^{-1}. Anal. calcd for $C_{14}H_{26}N_2O_5\cdot0.25H_2O$: C, 54.8; H, 8.70; N, 9.13. Found: C, 55.04; H, 8.51; N, 9.00%.

4.6. (3*S*,4*S*)-1-*tert*-Butoxycarbonyl-3-*tert*-butoxycarbonylamino-4-hydroxypyrrolidine 8

A solution of methanesulfonyl chloride (2.46 g, 21.5 mmol) in CH_2Cl_2 (20 mL) was added into a mixture of **7** (5.40 g, 17.9 mmol) and triethylamine (2.54 g, 25.1 mmol) in CH_2Cl_2 (90 mL) over a period of 10 min under ice cooling. The reaction mixture was stirred at rt for 2 h, taken up with water, and extracted with CH_2Cl_2. The extract was washed with saturated NaCl, dried over Na_2SO_4, and then concentrated in vacuo. A mixture of the residual mesylate and potassium acetate (4.73 g, 48.2 mmol) in DMF (120 mL) was heated at 110°C for 2 h. The reaction mixture was poured into water and extracted with toluene. The extract was washed with saturated NaCl, dried over Na_2SO_4, and then concentrated in vacuo. The residue was chromatographed on silica gel with $CHCl_3$–MeOH (200:1). The given acetoxy compound was dissolved in MeOH (90 mL), and then K_2CO_3 (4.01 g, 29.0 mmol) was added under ice cooling. The mixture was stirred at rt for 4 h, poured into water and extracted with AcOEt. The extract was washed with saturated NaCl, dried over Na_2SO_4, and then concentrated in vacuo to give **8** as white crystals (4.10 g, 76%): mp 147–148°C; $[\alpha]_D^{24}=+1.50$ (*c* 1.00, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.45 (s, 9H), 1.46 (s, 9H), 3.11–3.38 (m, 2H), 3.61–3.81 (m, 2H), 3.82–3.99 (m, 1H), 4.16–4.26 (m, 1H), 4.72 (br s, 2H); MS *m*/*z* 303 (M^++1); IR (KBr): 3470, 3300, 1670 cm^{-1}. Anal. calcd for $C_{14}H_{26}N_2O_5$: C, 55.61; H, 8.67; N, 9.26. Found: C, 55.69; H, 8.62; N, 9.24%.

4.7. (3*S*,4*S*)-3-Methoxy-4-methylaminopyrrolidine di-*p*-toluenesulfonic acid (*S*,*S*)-2·2TsOH

A solution of **8** (3.79 g, 12.5 mmol) in dry DMF (30 mL) was added to a suspension of NaH (1.25 g of 60% oil suspension, 31.3 mmol, washed with dry hexane before use) in a mixture of dry DMF (40 mL) and MeI (7.10 g, 50.0 mmol) over a period of 10 min at 0°C. The reaction mixture was stirred at rt for 2 h. After neutralization with 2% AcOH under ice cooling, toluene was added. The organic layer was separated, and the aqueous layer was extracted with toluene. The combined organic layer was washed with saturated NaCl, dried over Na_2SO_4, and then concentrated in vacuo. The residue was dissolved in *i*-PrOH (60 mL), and *p*-toluenesulfonic acid (5.21 g, 27.4 mmol) was added. The reaction mixture was heated at 65°C for 2 h, and then cooled to 0°C. The resultant precipitates were collected by filtration, washed with *i*-PrOH, and dried to give (*S*,*S*)-**2**·2TsOH as white crystals (4.79 g, 81%): mp 163–164°C; $[\alpha]_D^{29}=+10.4$ (*c* 1.00, MeOH); ^{1}H NMR (DMSO-d_6): δ 2.30 (s, 6H), 2.69 (s, 3H), 3.24–3.49 (m, 3H), 3.33 (s, 3H), 3.66 (dd, 1H, $J=13.2$, 7.5 Hz), 3.80–3.89 (m, 1H), 4.19–4.25 (m, 1H), 7.13 (d, 4H, $J=8.0$ Hz), 7.49 (d, 4H, $J=8.0$ Hz), 9.02 (br s, 4H); MS *m*/*z* 131 (M^++1); IR (KBr): 3060, 1615, 1570 cm^{-1}. Anal. calcd for $C_6H_{14}N_2O\cdot2C_7H_8O_3S$: C, 50.62; H, 6.37; N, 5.90; S, 13.51. Found: C, 50.48; H, 6.44; N, 5.90; S, 13.51%.

4.8. (3*S*,4*S*)-1-Benzyl-3-(*tert*-butyldimethylsilyl)oxy-4-hydroxypyrrolidine (*S*,*S*)-5

Following the procedure described for (*R*,*R*)-**5**, compound (*R*,*R*)-**4** was converted to (*S*,*S*)-**5** (95.0 g, 68%) as white crystals: mp 55–56°C; $[\alpha]_D^{26}=+33.9$ (*c* 1.02, MeOH). Anal. calcd for $C_{17}H_{29}NO_2Si$: C, 66.40; H, 9.51; N, 4.55. Found: C, 66.11; H, 9.41; N, 4.54%.

4.9. (3*S*,4*S*)-1-*tert*-Butoxycarbonyl-3-(*tert*-butyldimethylsilyl)oxy-4-hydroxypyrrolidine (*S*,*S*)-3a

Following the procedure described for (*R*,*R*)-**3a**, compound (*S*,*S*)-**5** was converted to (*S*,*S*)-**3a** (95.0 g, 68%) as a colorless oil: $[\alpha]_D^{26}=-16.2$ (*c* 1.04, MeOH). Anal. calcd for $C_{15}H_{31}NO_4Si\cdot0.25H_2O$: C, 55.95; H, 9.86; N, 4.35. Found: C, 56.19; H, 9.78; N, 4.37%.

4.10. (3*R*,4*S*)-3-Acetoxy-1-*tert*-butoxycarbonyl-4-(*tert*-butyldimethylsilyl)oxypyrrolidine 9

A solution of methanesulfonyl chloride (2.18 g, 19.0 mmol) in CH_2Cl_2 (40 mL) was added to a mixture of (*S*,*S*)-**3a** (5.00 g, 15.8 mmol) and triethylamine (2.23 g, 22.1 mmol) in CH_2Cl_2 (75 mL) over a period of 10 min under ice cooling. The reaction mixture was stirred at rt for 1.5 h, taken up with water, and extracted with CH_2Cl_2. The extract was washed with saturated NaCl, dried over Na_2SO_4, and then concentrated in vacuo. A mixture of the residual mesylate and lithium acetate (3.13 g, 47.4 mmol) in DMF (80 mL) was heated at 150°C for 15 h. The reaction mixture was poured into water and the mixture was extracted with toluene. The extract was washed with saturated NaCl, dried over Na_2SO_4, and then concentrated in vacuo. The residue was chromatographed on silica gel with hexane–AcOEt (15:1) to give **9** as a colorless oil (2.15 g, 38%): $[\alpha]_D^{26}=+18.2$ (*c* 1.02, MeOH); ^{1}H NMR ($CDCl_3$): δ 0.05 (s, 3H), 0.06 (s, 3H), 0.87 (s, 9H), 1.45 (s, 9H), 2.08 (s, 3H), 3.15–3.27 (m, 1H), 3.32–3.63 (m, 3H), 4.26–4.35 (m, 1H), 5.11–5.19 (m, 1H); MS *m*/*z* 360 (M^++1); IR (NaCl): 1747, 1700 cm^{-1}. Anal. calcd for $C_{17}H_{33}NO_5Si$: C, 56.79; H, 9.25; N, 3.90. Found: C, 56.89; H, 9.20; N,

3.93%. The NOE observed from C(4)H to C(3)H enabled structural assignment of **9**.

4.11. (±)-*cis*-*tert*-Butoxycarbonyl-3-(*tert*-butyldimethylsilyl)oxy-4-hydroxypyrrolidine (±)-*cis*-10

A solution of compound **9** (1.60 g, 4.32 mmol) in MeOH (30 mL), was treated with K_2CO_3 (678 mg, 4.91 mmol) with ice cooling. The mixture was stirred at rt for 30 min, poured into water and extracted with AcOEt. The extract was washed with saturated NaCl, dried over Na_2SO_4, and then concentrated in vacuo. The residue was chromatographed on silica gel with hexane–AcOEt (5:1) to give (±)-*cis*-**10** as a colorless oil (1.37 g, 97%): $[\alpha]_D^{25}=0$ (*c* 0.52, MeOH); ^{1}H NMR ($CDCl_3$): δ 0.19 (s, 6H), 0.91 (s, 9H), 1.45 (s, 9H), 2.61 (br s, 1H), 3.15–3.24 (m, 1H), 3.29–3.54 (m, 2H), 3.56–3.64 (m, 1H), 4.04–4.11 (m, 1H), 4.18–4.25 (m, 1H); MS *m*/*z* 318 (M^++1); IR (NaCl): 3445, 1700 cm^{-1}. (±)-*cis*-**10** was converted to (±)-**2** (43% yield for seven steps) as the racemate {$[\alpha]_D^{25}=0$ (*c* 0.20, MeOH)}.

4.12. (3*S*,4*S*)-1-*tert*-Butoxycarbonyl-3-methoxy-4-hydroxypyrrolidine 11

A solution of (*S*,*S*)-**3a** (3.00 g, 9.46 mmol) in dry THF (25 mL) was added to a suspension of NaH (456 mg of 60% suspension in oil, 11.4 mmol, washed with dry hexane before use) in a mixture of dry THF (25 mL) and MeI (2.02 g, 14.2 mmol) over a period of 5 min under ice cooling. The reaction mixture was stirred at rt for 5 h. After neutralization with saturated NH_4Cl under ice cooling, toluene was added. The organic layer was separated, and the aqueous layer was extracted with toluene. The combined organic extract was washed with saturated NaCl, dried over Na_2SO_4, and then concentrated in vacuo. The given methoxy compound was dissolved in THF (25 mL), and then the solution was added into tetrabutylammonium fluoride (1 M THF solution, 11.4 mL, 11.4 mmol) under ice cooling. The mixture was stirred at rt for 2 h, and then concentrated in vacuo. The residue was poured into water and the mixture was extracted with AcOEt. The extract was washed with saturated NaCl, dried over Na_2SO_4, and then concentrated in vacuo. The residue was chromatographed on silica gel with $CHCl_3$–MeOH (100:1) to give **11** as white crystals (1.93 g, 94%): mp 82–84°C; $[\alpha]_D^{25}=-13.7$ (*c* 1.05, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.46 (s, 9H), 2.25 (br s, 1H), 3.28–3.64 (m, 4H), 3.37 (s, 3H), 3.67–3.76 (m, 1H), 4.22–4.29 (m, 1H); MS *m*/*z* 218 (M^++1); IR (KBr): 3412, 1670 cm^{-1}. Anal. calcd for $C_{10}H_{19}NO_4$: C, 55.28; H, 8.81; N, 6.45. Found: C, 55.08; H, 8.61; N, 6.31%.

4.13. (3*R*,4*S*)-3-Acetoxy-1-*tert*-butoxycarbonyl-4-methoxypyrrolidine 12

Following the procedure described for **9**, compound **11** was converted to **12** (2.17 g, 53%) as a colorless oil: $[\alpha]_D^{24}=+8.1$ (*c* 1.00, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.46 (s, 9H), 2.13 (s, 3H), 3.25–3.70 (m, 4H), 3.39 (s, 3H), 3.91 (ddd, 1H, *J*=10.6, 6.6, 4.1 Hz), 5.24–5.36 (m, 1H); MS *m*/*z* 260 (M^++1); IR (NaCl): 1745, 1700 cm^{-1}. Anal. calcd for $C_{12}H_{21}NO_5$: C, 55.58; H, 8.16; N, 5.40. Found: C, 55.22; H, 7.94; N, 5.31%. The NOE observed from C(3)H to C(4)H enabled structural assignment of **12**.

4.14. (3*S*,4*S*)-3-Azido-1-*tert*-butoxycarbonyl-4-methoxypyrrolidine 13

Compound **12** (1.75 g, 6.76 mmol) was dissolved in MeOH (35 mL), and then K_2CO_3 (1.03 g, 7.44 mmol) was added under ice cooling. The mixture was stirred at rt for 30 min, poured into water and extracted with AcOEt. The extract was washed with saturated NaCl, dried over Na_2SO_4, and then concentrated in vacuo. The resulting residue and triethylamine (875 mg, 8.65 mmol) were dissolved in CH_2Cl_2 (30 mL), and then a solution of methanesulfonyl chloride (850 mg, 7.42 mmol) in CH_2Cl_2 (15 mL) was added into the mixture over a period of 10 min under ice cooling. The reaction mixture was stirred at rt for 1.5 h, taken up with water, and extracted with $CHCl_3$. The extract was washed with saturated NaCl, dried over Na_2SO_4, and then concentrated in vacuo. A mixture of the residual mesylate and sodium azide (806 mg, 12.4 mmol) in DMF (25 mL) was heated at 110°C for 2 h. The reaction mixture was poured into water and the mixture was extracted with AcOEt. The extract was washed with saturated NaCl, dried over Na_2SO_4, and then concentrated in vacuo. The residue was chromatographed on silica gel with hexane–AcOEt (10:1) to give **13** as a colorless oil (1.21 g, 74%): $[\alpha]_D^{25}=+14.5$ (*c* 1.01, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.47 (s, 9H), 3.33–3.64 (m, 4H), 3.39 (s, 3H), 3.73–3.78 (m, 1H), 3.95–4.00 (m, 1H); MS *m*/*z* 243 (M^++1); IR (NaCl): 2105, 1695 cm^{-1}. Anal. calcd for $C_{10}H_{18}N_4O_3$: C, 49.58; H, 7.49; N, 23.13. Found: C, 49.66; H, 7.54; N, 22.84%.

4.15. (3*S*,4*S*)-1-*tert*-Butoxycarbonyl-3-*tert*-butoxycarbonylamino-4-methoxypyrrolidine 14

A solution of **13** (1.04 g, 4.30 mmol) in EtOH (10 mL) was hydrogenated over 5% Pd–C (100 mg) at 20°C for 2 h. The mixture was filtered and EtOH (20 mL) was added to the filtrate. Then Boc_2O (987 mg, 4.52 mmol) was added to the mixture under ice cooling. The reaction mixture was stirred at rt for 15 h, and then concentrated in vacuo. The residue was chromatographed on silica gel with $CHCl_3$ to give **14** as a colorless oil (1.32 g, 97%): $[\alpha]_D^{25}=-18.1$ (*c* 1.08, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.45 (s, 18H), 3.20–3.55 (m, 3H), 3.41 (s, 3H), 3.59 (dd, 1H, *J*=11.7, 5.5 Hz), 3.71–3.80 (m, 1H), 4.05–4.13 (m, 1H), 4.56 (br s, 1H); MS *m*/*z* 317 (M^++1); IR (NaCl): 3330, 1695 cm^{-1}. Anal. calcd for $C_{15}H_{28}N_2O_5\cdot 0.35H_2O$: C, 55.83; H, 8.96; N, 8.68. Found: C, 56.08; H, 8.79; N, 8.28%.

4.16. (3*S*,4*S*)-3-Methoxy-4-methylaminopyrrolidine di-*p*-toluenesulfonic acid (*S*,*S*)-2·2TsOH

A solution of **14** (1.12 g, 3.54 mmol) in dry DMF (15 mL) was added into the suspension of NaH (177 mg of 60% suspension in oil, 4.43 mmol, washed with dry hexane before use) in a mixture of dry DMF (20 mL)

and MeI (1.01 g, 7.08 mmol) over a period of 10 min at 0°C. The reaction mixture was stirred at rt for 2 h. After neutralization with 2% AcOH under ice cooling, toluene was added. The organic layer was separated, and the aqueous layer was extracted with toluene. The combined organic layer was washed with saturated NaCl, dried over Na_2SO_4, and then concentrated in vacuo. The residue was dissolved in *i*-PrOH (20 mL), and *p*-toluenesulfonic acid (1.55 g, 8.14 mmol) was added. The reaction mixture was heated at 65°C for 2 h, and then cooled to 0°C. The resultant precipitates were collected by filtration, washed with *i*-PrOH, and dried to give 1.37 g (82%) of (*S*,*S*)-**2**·2TsOH as white crystals: mp 162–163°C; $[\alpha]_D^{26} = +10.3$ (*c* 1.01, MeOH). Anal. calcd for $C_6H_{14}N_2O \cdot 2C_7H_8O_3S$: C, 50.62; H, 6.37; N, 5.90; S, 13.51. Found: C, 50.49; H, 6.45; N, 5.81; S, 13.53%.

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