Synthesis of Pyrrolidine Based Natural or Unnatural Product Derivatives (1): Application of Efficient Asymmetric Induction of C-2 Position in Polysubstituted Pyrrolidines

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A novel method for synthesis of polysubstituted pyrrolidines, which possess a C-2 stereocenter, was developed. The strategy involves Grignard addition to the succinimide, derived from L-tartaric acid, followed by stereocontrolled triethylsilane promoted reduction of the resulting cyclic amidols.

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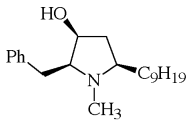
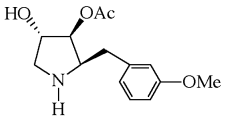
Much recent interest has focussed on the chemistry and biological activity of polysubstituted natural and unnatural pyrrolidines. Members of this *N*-heterocycle family are known to have powerful biological activities. Examples of this are found in the pyrrolidines (-)-anisomycin, which has been used clinically for the treatment of amebic dysentery and trichomonas vaginitis [1], and (+)-preussin, which possesses significant broad-spectrum antibiotic activity against both filamentous fungi and yeasts [2].

Our recent interest in the chemistry and biological activity of polysubstituted natural and unnatural pyrrolidines has led to the development of new methods to prepare polysubstituted-pyrrolidines and -piperidines [3,4]. Our continuing studies in this area required us to devise procedures to prepare a variety of highly functionalized, C-2 substituted pyrrolidines for the purpose of biological evaluation. Specific targets of this effort were *trans*-3,4-dihydroxylated pyrrolidine derivatives, which possess various C-2 substituents. Below, we describe the novel and versatile method we have developed to synthesize these targets.



(+)-Preussin

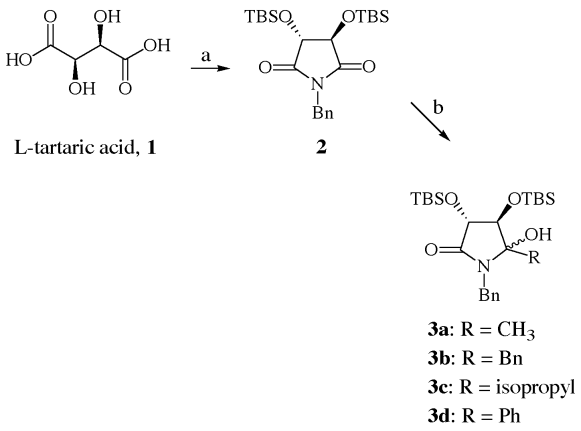


(-)-Anisomycin

The strategy involves Grignard addition [5-9] to the succinimide, derived from L-tartaric acid, coupled with stereocontrolled triethylsilane promoted reductive removal of the C-5 hydroxyl group in the cyclic amidol products.

The methodology we have devised for preparation of these targets begins with the conversion of L-tartaric acid (**1**) to the bis-OTBS blocked *N*-benzyl-succinimide **2**. This is accomplished by treatment of acid **1** with benzylamine followed by diol protection with *t*-butyldimethylsilyl chloride [10] (Scheme 1). Reactions of tartarimide **2** with Grignard reagents afford the corresponding alcohols **3** in moderate to high yields (76 - 91%). The alcohols **3a**, **3b** and **3d** are obtained as *ca.* 1:1 mixtures of separable C-5 epimers (tlc R_f-value differences of *ca.* 0.1), while **3c** is isolated as a single diastereomer. The low stereoselectivity observed in these Grignard addition reactions might be a result of competition between two different modes of chelation control (α and β) and steric effects [11]. In the case of isopropylmagnesium chloride addition, steric effects are more pronounced and, consequently, one diastereomer of **3c** is produced (presumably 5*R*).

Scheme 1



L-tartaric acid, **1**

2

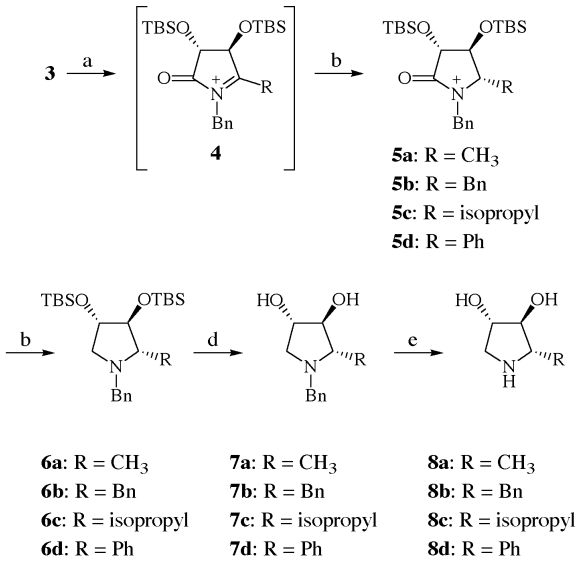
3a: R = CH_3
3b: R = Bn
3c: R = isopropyl
3d: R = Ph

Reagents and conditions: a) $BnNH_2$, TBSCl, imidazole, 70%; b) RMgX, THF, -78 °C to 0 °C. TBS = *tert*-Butyldimethylsilyl.

Removal of the C-5 hydroxyl group was first attempted by using zinc and acetic acidic or the Barton's stannylhydride procedure [12]. However, under these conditions mixtures of diastereomeric products are produced. To overcome this problem, we resorted to the use of the silane reduction procedure [13], since we reasoned that complexation of an oxophilic silane reagent to the C-4 ether oxygen might guide diastereo-controlled hydride delivery to the intermediate *N*-acyliminium ion. Accordingly, addition of triethylsilane to a CH_2Cl_2 solution of **3a** (mixture of diastereomers) at -78 °C and borontrifluoride etherate (BF_3•OEt_2), leads to formation of the reduction product **5a**

as a single diastereomer. In addition, reductive dehydroxylation of the cyclic amidols **3b-c**, by using this same procedure, occurs stereoselectively to yield **5b-d** in 85 - 90% yields (Scheme 2). As anticipated [13], the high -*trans*-selectivity associated with these reactions most likely results from chelation of the silane to the C-4 oxygen (Figure 1). Consequently, hydride delivery occurs selectively from the top-face at C-5 in the iminium ion to give only *trans* **5**.

Scheme 2



Reagents and conditions: a) BF_3•OEt_2, CH_2Cl_2, -78 °C to 0 °C; b) Et_3SiH, CH_2Cl_2, -78 °C to 0 °C, 88%; c) (i) $(CH_3)_2S$•BH_3, THF, rt. TBS = *tert*-Butyldimethylsilyl.

The existence of oxygen linked, pentavalent organo-silicon species, like that shown in Figure 1, is well documented [14].

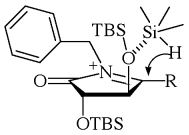


Figure 1. The reaction pathway to the enantioselective hydride attack in iminium ion **4**.

The 5-substituted 2-pyrrolidinones **5**, prepared by the methodology described above**,** are converted to 2-substituted 3,4-dihydroxypyrrolidines **8** by the sequence shown in Scheme 2. Removal of the C-2 carbonyl functional group is performed by treatment of **5** with the borane-methyl sulfide complex at room temperature in THF for 6 hours. Excess reducing agent is quenched prior to work-up by the careful addition of EtOH (5 mL) at -5 °C. With this process pyrrolidines **6** are obtained in moderate yields. The *t*-butyldimethylsilyl blocking group in **6** is removed by treatment with tetrabutylammonium fluoride in THF at room temperature, giving the *N*-benzyl-pyrrolidines **7**. Finally, hydrogenolytic *N*-benzyl removal, by using $Pd(OH)_2$ and H_2 (1 atm) in methanol at room temperature, affords the target 2-substituted 3,4-dihydroxypyrrolidines **8** in good yields.

Further studies probing the mechanism of the reductive dehydroxylation reaction and the biological properties of the target pyrrolidines are in progress.

EXPERIMENTAL

All non-aqueous reactions were carried out under nitrogen. THF was distilled from Na/benzophenone; methanol was distilled from Mg; methylene chloride was distilled from CaH_2. NMR spectra were measured on a Bruker ARX-300 (500 MHz) spectrometer in $CDCl_3$ solution used as an internal standard unless otherwise noted (value in ppm); coupling constants are reported in Hz. Ir spectra were taken on a Hitachi 270-50 FT/IR spctrophotometer (λ_{max}, cm^{-1}). Optical rotations were measured on a JASCO DIP -1000 digital polarimeter in a 1-dm cell. The elemental analyses were performed with LECO Micro Carbon Hydrogen Determinator (CHN-800). Mass spectra were obtained by using JEOL JMS-700 spectrophotometer. TLC was run on Merck precoated silica gel plates. Merck silica gel 60 (230-400 mesh) was used for column chromatography. All organic extracts were dried over $MgSO_4$.

(3*R*,4*R*)-3,4-*bis*[(*tert*-Butyldimethylsiloxy]-1-benzylsuccinimide (**2**).

A solution of *L*-tartaric acid (9.0 g, 60.0 mmol) and benzylamine (8.05 mL, 78.0 mmol) in xylene (150 mL) was stirred at reflux for 15 hours, cooled to 0 °C and the precipitated solid was collected by filtration. The precipitate was dried *in vacuo* and then used in the next reaction. A solution of the solid (3.0 g, 13.5 mmol) in DMF (15.0 mL) containing imidazole (4.8 g, 68.0 mmol) and *t*-butyldimethylsilyl chloride (6.3 g, 40.0 mmol) was stirred for 12 hours at 25 °C, diluted with water and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed with water, dried over $MgSO_4$ and concentrated *in vacuo* giving a residue that was subjected to flash column chromatography (silica gel, hexane/EtOAc, 30/1, v/v) to afford **2** (5.01 g, 83%) as colorless oil. The spectral data and mp of this substance are identical to those previously reported [8].

Grignard Addition to Succinimide **2**: Synthesis of 5-Substituted 3,4-bis[(*tert*-butyldimethylsiloxy]-5-hydroxy -2-pyrrolidinones (**3**).

A solution of the appropriate Grignard reagent (3.0 *M* , THF, 11.1 mmol, 5 equivalents) in THF was added dropwise to a THF (40 mL) solution of pyrrolidinedione **2** (2.2 mmol) at -78 °C. After stirring at 0 °C for 6 hours, saturated aqueous ammonium chloride was added and the mixture was extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* giving a residue which was subjected to flash column chromatography (Hexane/EtOAc = 10/1, v/v) to

give the corresponding adducts **3** as oils. Yields, **3a**: 81.7% (0.89 g), **3b**: 76.1% (0.91 g), **3c**: 75.1% (0.82 g), **3d**: 91% (1.00 g). R_f values, **3a**-1: 0.22 (Hexane/EtOAc = 10/1, v/v), **3a**-2: 0.16 (Hexane/EtOAc = 10/1, v/v), **3b**-1: 0.42 (Hexane/EtOAc = 10/1, v/v), **3b**-2: 0.26 (Hexane/EtOAc = 10/1, v/v), **3c**: 0.42 (Hexane/EtOAc = 10/1, v/v), **3d**-1: 0.26 (Hexane/EtOAc = 10/1, v/v), **3d**-2: 0.13 (Hexane/EtOAc = 10/1, v/v).

Compound **3a**-1 has IR (KRS-5): 3520, 3130, 2930, 2860, 1720; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.03 - 7.12 (m, 5H), 4.38 (d, 1H, J = 15.5 Hz), 4.28 (d, 1H, J = 15.5 Hz), 3.95 (d, 1H, J = 2.80 Hz), 3.62 (d, 1H, J = 2.80 Hz), 3.29 (s, OH), 1.18 (s, 3H), 0.75 (s, 9H), 0.73 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H), -0.01 (s, 3H), -0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.9, 138.5, 128.4, 127.5, 127.0, 88.0, 79.1, 76.3, 42.2, 25.7, 25.6, 24.8, 18.1, 18.0, -4.2, -4.3, -4.8, -4.9.

Anal. Calcd for $C_{24}H_{43}NO_4Si_2$: C, 61.89; H, 9.31; N, 3.01. Found: C, 61.49; H, 9.51; N, 3.21.

Compound **3a**-2 has IR (KRS-5): 3510, 3130, 2950, 2850, 1710; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.05 - 7.07 (m, 5H), 4.46 (d, 1H, J = 15.7 Hz), 4.16 (d, 1H, J = 15.7 Hz), 3.78 (d, 1H, J = 2.80 Hz), 3.60 (d, 1H, J = 2.80 Hz), 2.81 (s, OH), 1.03 (s, 3H), 0.72 (s, 9H), 0.68 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H), -0.08 (s, 3H), -0.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.9, 138.2, 128.4, 127.3, 127.0, 92.1, 79.7, 76.3, 42.0, 25.7, 25.6, 20.1, 18.1, 17.9, -4.51, -4.53, -4.8, -5.0.

Anal. Calcd for $C_{24}H_{43}NO_4Si_2$: C, 61.89; H, 9.31; N, 3.01. Found: C, 61.45; H, 9.50; N, 3.19.

Compound **3b**-1 has IR (KRS-5): 3490, 3030, 2930, 2860, 1710; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.27 -7.41 (m, 10H), 4.57 (d, 1H, J = 2.3 Hz), 4.11 (s, 1H), 4.01 (s, 1H), 3.59 (d, 1H, J = 1.68 Hz), 3.27 (d, 1H, J = 13.7 Hz), 2.85 (d, 1H, J = 13.7 Hz), 1.08 (s, 9H), 0.83 (s, 9H), 0.35 (s, 3H), -0.33 (s, 3H), 0.00 (s, 3H), -0.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.6, 138.7, 135.9, 131.1, 128.4, 128.0, 127.4, 127.0, 126.7, 90.9, 74.7, 43.7, 42.2, 25.8, 25.5, 18.2, 17.9, -4.4, -5.0, -5.1, -5.8; EIMS (*m/e*): (M^+) Calcd for $C_{30}H_{47}NO_4Si_2$, 541.8; found, 541.0; MS *m/e*. 523.8(M-H_2O, 6), 484(60), 466(100), 450(27), 219(68), 91(90).

Anal. Calcd for $C_{30}H_{47}NO_4Si_2$: C, 66.50; H, 8.74; N, 2.58. Found: C, 66.48; H, 8.76; N, 2.60.

Compound **3b**-2 has IR (KRS-5): 3390, 3030, 2930, 2860, 1690; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.22 -7.33 (m, 10H), 4.69 (d, 1H, J = 15.1 Hz), 4.17 (d, 1H, J = 15.1 Hz), 3.90 (d, 1H, J = 6.5 Hz), 3.49 (d, 1H, J = 6.5 Hz), 3.13 (d, 1H, J = 14.0 Hz), 3.02 (d, 1H, J = 14.0 Hz), 2.51(s, OH), 0.98 (s, 9H), 0.84 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H), 0.03 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.6, 138.6, 134.7, 131.1, 128.6, 128.1, 128.0, 127.2, 127.1, 92.0, 83.4, 775.0, 43.1, 39.4, 26.0, 25.8, 18.2, 18.1, -4.2, -4.4, -4.5, -4.8.

Anal. Calcd for $C_{30}H_{47}NO_4Si_2$: C, 66.50; H, 8.74; N, 2.58. Found: C, 66.49; H, 8.79; N, 2.58.

Compound **3c** has IR (KRS-5): 3480, 3020, 2950, 2860, 1700; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.20 - 7.02 (m, 10H), 4.28 (s, 1H), 3.85 (d, 1H, J = 0.8 Hz), 3.78 (d, 1H, J = 0.8 Hz), 3.73 (s, OH), 1.98 (m, 1H). 0.79 (d, 3H, J = 6.85 Hz), 0.71 (s, 9H), 0.72 (s, 9H), 0.49 (d, 3H, J = 7.05 Hz), 0.02 (s, 3H), 0.01 (s, 3H), 0.00 (s, 3H), -0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.9, 138.3, 128.6, 127.0, 92.7, 77.7, 74.4, 43.2, 34.0, 25.8, 25.6, 18.1, 17.9, 17.3, 16.6, -4.0, -4.1, -5.1, -5.3; EIMS (*m/e*): (M^+) Calcd for $C_{26}H_{47}NO_4Si_2$, 493.83; found, 493.0; MS *m/e*: 478(M-H_2O, 5), 436(100), 418(71), 304(30), 171(82), 91(76).

Anal. Calcd for $C_{26}H_{47}NO_4Si_2$: C, 63.24; H, 9.59; N, 2.84. Found: C, 63.27; H, 9.57; N, 2.86.

Compound **3d**-1 has IR (KRS-5): 3530, 3130, 2950, 2860, 1710; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.99 - 7.15 (m, 10H), 4.51 (d, 1H, J = 15.0 Hz), 3.89 (d, 1H, J = 2.7 Hz), 3.71 (d, 1H, J = 15.0 Hz), 3.67 (d, 1H, J = 2.7 Hz), 3.01 (s, OH), 0.70 (s, 9H), 0.49 (s, 9H), -0.01 (s, 3H), -0.20 (s, 3H), -0.36 (s, 3H), -0.54 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.9, 138.0, 136.1, 128.6, 128.4, 128.3, 128.2, 127.9, 127.8, 127.1, 95.1, 81.2, 76.8, 44.2, 25.6, 18.0, -4.5, -5.0, -5.2, -5.4.

Anal. Calcd for $C_{30}H_{47}NO_4Si_2$: C, 61.89; H, 9.31; N, 3.01. Found: C, 61.49; H, 9.51; N, 3.21.

Compound **3d**-2 has IR (KRS-5): 3510, 3120, 2930, 2860, 1720; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.91 - 7.26 (m, 10H), 4.41 (d, 1H, J = 14.9 Hz), 4.18 (d, 1H, J = 5.5 Hz), 3.97 (d, 1H, J = 5.5 Hz), 3.82 (s, OH), 3.74 (d, 1H, J = 14.9 Hz), 0.77 (s, 9H), 0.64 (s, 9H), -0.11 (s, 3H), -0.00 (s, 3H), -0.12 (s, 3H), -0.61 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.9, 139.9, 137.8, 128.6, 128.4, 128.1, 127.2, 127.0, 89.4, 82.2, 76.1, 44.3, 25.8, 25.6, 18.3, 17.8, -4.0, -4.4, -4.8, -5.4.

Anal. Calcd for $C_{30}H_{47}NO_4Si_2$: C, 61.89; H, 9.31; N, 3.01. Found: C, 61.48; H, 9.49; N, 3.19.

Reaction of Alcohol **3** with Boron Trifluoride Diethyl Etherate and Triethylsilane Reagents: Synthesis of (3*R*,4*R*,5*S*)-3,4-Bis[(*tert*-butyldimethylsilyl)oxy]-5-(alkyl or -aryl)-1-benzyl-2-pyrrolidinone (**5**).

To a solution of the diasteremeric mixture alcohol (**3**, 2.14 mmol) in CH_2Cl_2 (30 ml), a solution of BF_3•OEt_2 (0.39 ml, 3.22 mmol, 1.5 equivalent) and Et_3SiH (3.53 ml. 21.4 mmol) was added under N_2, and the reaction mixture was kept at -78 °C for 6 hours then the temperature was slowly increased to 0 °C. After that, the reaction mixture was stirred for 12 hours at 0 °C and the excess BF_3•OEt_2 and Et_3SiH were quenched with saturated $NaHCO_3$ (4 ml) at 0 °C, extracted with CH_2Cl_2 (40 ml x 4), washed with water (30 ml x 3), dried over $MgSO_4$ and filtered through a glass filter. After the solvent was evaporated under reduced pressure, the residue was purified by flash column chromatography (*n*-hexane/EtOAc = 30/1) to give the corresponding **5** as oils. Yields, **5a**: 88.0% (0. 85 g), **5b**: 83% (0.93 g), **5c**: 88% (0.90 g), 5d: 87% (0.95 g).

Compound **5a** has the following physical and spectral properties: [α] $^{23}_D$ -1.09° (*c* 2.7, $CHCl_3$); IR (KRS-5): 3020, 2950, 2860, 1710; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.11 - 7.11 (m, 5H), 4.92 (d, 1H, J = 15.3 Hz), 4.01 (d, 1H, J = 4.2 Hz), 3.87 (d, 1H, J = 15.3 Hz), 3.63 (t, 1H, J = 4.2 Hz), 3.09 - 3.11 (m, 1H), 1.11 (d, 1H, J = 6.6 Hz), 0.85 (s, 9H), 0.75 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), -0.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.7, 136.5, 128.6, 127.8, 127.4, 79.8, 78.1, 58.4, 43.5, 25.9, 25.8, 25.7, 18.2, 17.8, 16.9, -4.1, -4.3, -4.5, -4.7.

Anal. Calcd for $C_{24}H_{43}NO_3Si_2$: C, 64.09; H, 9.64; N, 3.11. Found: C, 63.97; H, 9.61; N, 3.21.

Compound **5b** has the following physical and spectral properties: [α] $^{23}_D$ 6.30° (*c* 1.3, $CHCl_3$); IR (KRS-5): 3020, 2950, 2860, 1710; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32 - 7.57 (m, 10H), 5.36 (d, 1H, J = 15.3 Hz), 4.23 (s, 1H), 4.19 (d, 1H, J = 14.9 Hz), 4.07 (s, 1H), 3.59 (dd, 1H, J = 4.9 Hz, J = 4.9 Hz), 3.29 (dd, 1H, J = 4.9 Hz, J = 4.9 Hz), 3.00 (1H, dd, J = 13.4 Hz, J = 13.4 Hz), 1.25 (s, 9H), 0.96 (s, 9H), 0.49 (d, 6H, J = 5.1 Hz), -0.01 (s, 3H), -0.20 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.5, 137.6, 136.2, 129.3, 128.7, 128.5, 128.1, 127.4, 126.7,

78.4, 77.2, 74.0, 67.4, 44.2, 37.7, 28.5, 18.1, 17.6, -4.4, -5.1, -5.4, -5.5. EIMS (*m/e*): (M^+) Calcd for $C_{30}H_{47}NO_3Si_2$, 525.87; found, 525.0; MS *m/e*: 510(6), 468(100), 406(15), 91(29).

Anal. Calcd for $C_{30}H_{47}NO_3Si_2$: C, 68.52; H, 9.01; N, 2.66. Found: C, 68.53; H, 9.03; N, 2.68.

Compound **5c** has the following physical and spectral properties: $[\alpha]^{23}_D$ 7.37° (*c* 0.8, $CHCl_3$); IR (KRS-5); 3020, 2920, 2850, 1700; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.02 - 6.99 (m, 5H), 4.92 (d, 1H, J = 15.3 Hz), 3.83 (d, 1H, J = 0.9Hz), 3.73 (d, 1H, J = 15.3Hz), 3.65 (s, 1H), 2.91 (d, 1H, J = 4.7 Hz), 0.82 (s, 1H), 0.73 (d, 3H, J = 7.1 Hz), 0.62 (d, 3H, J = 7.0 Hz), 0.62 (d, 3H, J = 6.95 Hz), 0.71 (s, 9H), 0.63 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H), -0.01 (s, 3H), -0.20 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 140.8, 128.2, 128.0, 126.5, 80.6, 78.9, 78.3, 60.2, 59.9, 29.2, 25.8, 25.7, 20.2, 18.8, 17.9, 17.8, -4.1, -4.5, -4.7, -4.8; EIMS (*m/e*): (M^+) Calcd for $C_{26}H_{47}NO_3Si_2$, 477.83; found, 477.0; MS *m/e*: 462(6), 420(100), 288(8), 199(39), 91(31), 73(21).

Anal. Calcd for $C_{26}H_{47}NO_3Si_2$: C, 65.35; H, 9.91; N, 2.93. Found: C, 65.37; H, 9.93; N, 2.96.

Compound **5d** has the following physical and spectral properties: $[\alpha]^{23}_D$ 2.13° (*c* 1.67, $CHCl_3$); IR (KRS-5) 3050, 2930, 2860, 1710; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.81 - 7.17 (m, 10H), 4.89 (d, 1H, J = 14.8 Hz), 4.05 (d, 1H, J = 5.4 Hz), 3.87 (t, 1H, J = 5.1 Hz), 3.83 (d, 1H, J = 5.1 Hz), 3.27 (d, 1H, J = 14.8 Hz), 0.76 (s, 9H0, 0.59 (s, 9H), 0.11 (s, 3H), 0.01 (s, 3H), -0.24 (s, 3H), -0.61 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.1, 137.3, 136.4, 129.2, 129.0, 128.9, 128.8, 127.9, 82.3, 777.2, 66.6, 44.4, 26.3, 26.2, 26.0, 25.9, 18.7, 18.1, -3.6, -4.0, -4.2, -4.9.

Anal. Calcd for $C_{29}H_{45}NO_3Si_2$: C, 68.05; H, 8.86; N, 2.74. Found: C, 68.37; H, 8.61; N, 2.51.

Reduction of Lactam **5** with Borane-methyl Sulfide Complex: Synthesis of (2*S*,3*R*,4*R*)-3,4-Bis[(*tert*-butyldimethylsilyl)oxy]-2-(alkyl or -aryl)1-benzylpyrrolidine (**6**).

A solution of Me_2S•BH_3 (2 *M* in THF, 3.3 ml, 3.22 mmol) was added under N_2 to a solution of the lactam **5** (1.9 mmol) in THF (30 ml). The reaction mixture was kept at room temperature for 2 hours and refluxed for 1 hour. The excess $Me_2S{\cdot}BH_3$ was quenched with EtOH (2 ml) at -5 °C. After the solvent was evaporated under reduced pressure, the residue was dissolved in EtOH (20 ml) and heated at reflux for 2 hours. The reaction mixture was cooled to room temperature and treated with saturated $NaHCO_3$, extracted with CH_2Cl_2 (30 ml x 3). The collected CH_2Cl_2 was washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (*n*-hexane/EtOAc = 30/1) to give corresponding compounds **6** as oils. Yields, **6a**: 88.0% (0. 58 g), **6b**: 73% (0.71 g), **6c**: 82.8% (0.48 g), **6d**: 80% (0.76 g).

Compound **6a** has the following physical and spectral properties: $[\alpha]^{23}_D$ 13.55° (*c* 2.67, $CHCl_3$); IR (KRS-5): 3020, 2950, 2850, 1460; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.13 - 7.23 (m, 5H), 3.88 (d, 1H, J = 13.8 Hz), 3.85 (dd, 1H, J = 3.1 Hz, J = 6.9 Hz), 3.61 (dd, 1H, J = 3.4 Hz, J = 6.4 Hz), 3.12 (d, 1H, J = 13.48 Hz), 2.64 (dd, 1H, J = 2.5 Hz, J = 10.4 Hz), 2.43 (dd, 1H, J = 6.8 Hz, J = 10.35 Hz), 2.64 - 2.66 (m, 1H), 1.10 (d, 1H, J = 6.3 Hz), 0.81 (s, 9H), 0.77 (s, 9H), 0.00 (s, 6H), -0.08 (s, 3H), -0.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.1, 128.7, 128.0, 126.7, 86.3, 77.8, 76.8, 65.3, 59.9, 57.7, 25.9, 17.9, 16.8, -4.1, -4.3, -4.4, -4.6; EIMS (*m/e*): (M^+) Calcd for $C_{30}H_{47}NO_3Si_2$, 435.79; found, 435.0; MS *m/e*: 420(50), 401(5), 378(15), 147(100), 91(53), 73(35).

Anal. Calcd for $C_{24}H_{45}NO_2Si_2$: C, 66.15; H, 10.41; N, 3.21. Found: C, 66.16; H, 10.43; N, 3.24.

Compound **6b** has the following physical and spectral properties: $[\alpha]^{23}_D$ 3.67° (*c* 2.60, $CHCl_3$); IR (KRS-5): 3020, 2950, 2850, 1460; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.07 - 7.29 (m, 10H), 3.86 (d, 1H, J = 4.2 Hz), 3.80 (d, 1H, J = 13.4Hz), 3.76 (s, 1H), 3.47 (d, 1H, J = 13.4Hz), 2.73 - 2.82 (m, 4H), 2.66 (dd, 1H, J = 4.3Hz, J = 10.0 Hz), 0.87 (s, 9H), 0.73 (s, 9H), 0.00 (s, 3H), -0.04 (s, 3H), -0.22 (s, 3H), -0.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 140.4, 140.2, 129.6, 129.4, 128.7, 128.3, 128.1, 128.0, 126.6, 125.8, 125.7, 81.7, 78.6, 73.9, 39.6, 26.0, 25.9, 25.7, 18.0, 17.7, 0.0, -4.6, -4.7, -4.9, -5.1.

Anal. Calcd for $C_{30}H_{49}NO_2Si_2$: C, 70.39; H, 9.65; N, 2.74. Found: C, 70.37; H, 9.61; N, 2.71.

Compound **6c** has the following physical and spectral properties: $[\alpha]^{23}_D$ 5.73° (*c* 0.30, $CHCl_3$); IR (KRS-5): 3020, 2940, 2860, 1450; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.18 - 7.37 (m, 5H), 4.05 (d, 1H, J = 13.8 Hz), 3.88 (s, 1H), 3.83 (d, 1H, J = 3.9 Hz), 3.33 (d, 1H, J = 13.8 Hz), 2.75 (d, 1H, J = 10.2 Hz), 2.45 (dd, 1H, J = 4.1 Hz, J = 9.9 Hz), 2.31 (dd, 1H, J = 2.4 Hz, J = 5.9 Hz), 1.94 - 1.95 (m, 1H), 1.01 (d, 3H, J = 6.8 Hz), 0.97 (d, 3H, J = 6.8 Hz), 0.88 (s, 9H), 0.85 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.00 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 140.8, 128.2, 128.0, 126.5, 80.6, 78.9, 78.3, 60.2, 59.9, 29.2, 25.8, 25.7, 20.2, 18.8, 17.9, 17.8, -4.1, -4.5, -4.7, -4.8.

Anal. Calcd for $C_{26}H_{49}NO_2Si_2$: C, 67.32; H, 10.65; N, 3.02. Found: C, 67.37; H, 10.35; N, 3.05.

Compound **6d** has the following physical and spectral properties: $[\alpha]^{23}_D$ 12.19° (*c* 2.87, $CHCl_3$); IR (KRS-5): 3060, 3020, 2930, 2850, 1460; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.17 - 7.49 (m, 10H), 3.93 - 4.05 (m, 1H), 3.93 (dd, 1H, J = 3.7 Hz, J = 6.7 Hz), 3.76 (d, 1H, J = 13.7 Hz), 3.28 (d, 1H, J = 6.7 Hz), 3.06 (d, 1H, J = 13.7 Hz), 2.91 (dd, 1H, J = 2.5 Hz, J = 10.3 Hz), 2.60 (dd, 1H, J = 6.9 Hz, J = 10.2 Hz), 0.86 (s, 9H), 0.86 (s, 9H), 0.01 (s, 3H), -0.04 (s, 3H), -0.15 (s, 3H), -0.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 141.0, 139.2, 128.6, 128.3, 128.2, 128.0, 127.4, 126.6, 87.6, 77.8, 75.6, 59.3, 57.6, 25.9, 25.8, 17.9, 17.8, -4.4, -4.5, -4.5, -5.3.

Anal. Calcd for $C_{29}H_{47}NO_2Si_2$: C, 69.96; H, 9.52; N, 2.81. Found: C, 69.97; H, 9.53; N, 2.84.

Deprotection of the TBDMS Group of **6** with Tetrabutylammonium Fluoride: Synthesis of (2*S*,3*R*,4*R*)-3,4-Dihydroxy-2-(alkyl or aryl)-1-benzylpyrrolidine (**7**).

To a solution of the *O*-TBDMS (*tert*-butyldimethylsilyl) protected **6** (2.0 mmol) in THF (20 ml) was added TBAF (tetrabutylammonium fluoride) (1.0 mol in THF, 4 ml) at room temperature and stirred for 1 hour. The reaction was quenched with water (10 ml) and extracted with EtOAc (30 ml x 3). The collected EtOAc was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (*n*-hexane/EtOAc = 3/1) to give corresponding compounds **7** as oils. Yields, **7a**: 93.0% (0. 39 g), **7b**: 70% (0.39 g), **7c**: 86% (0.21 g), **7d**: 77% (0.40 g).

Compound **7a** has the following physical and spectral properties: $[\alpha]^{23}_D$ 20.62° (*c* 0.20, $CHCl_3$); IR (KRS-5): 3370, 3230, 3020, 2960, 2860, 2800, 1630, 1450; ^{1}H NMR (500 MHz, acetone-d_6): δ = 7.13 - 7.49 (m, 5H), 3.98 (d, 1H, J = 13.2 Hz), 3.89 - 3.91 (m, 1H), 3.59 - 3.61 (m, 1H), 3.10 (d, 1H, J = 13.2 Hz), 2.71 (dd, 1H, J = 1.9 Hz, J = 10.3 Hz), 2.47 (dd, 1H, J = 6.9

Hz, J = 10.32 Hz), 2.27 - 2.30 (m, 1H), 2.04 - 2.08 (m, 1H), 1.23 (d, 3H, J = 6.0 Hz): ^{13}C NMR (125 MHz, acetone-d_6): δ = 140.4, 129.5, 128.9, 127.5, 86.4, 77.1, 66.8, 61.0, 58.5, 17.3.

Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.58; H, 8.29; N, 6.73.

Compound **7b** has the following physical and spectral properties: [α] $^{23}_{D}$ 7.64° (*c* 0.07, $CHCl_3$). IR (KRS-5): 3360, 3060, 3020, 2920, 2810, 1490; ^{1}H NMR (500 MHz, acetone-d_6): δ = 7.16 - 7.35 (m, 10H), 4.02 (d, 1H, J = 13.2 Hz), 3.90 - 3.91 (m, 2H), 3.83 - 3.84 (m, 1H), 3.45 - 3.73 (broad s, 1H), 3.28 (d, 1H, J = 13.2 Hz), 2.96 - 2.98 (m, 2H), 2.74 - 2.76 (m, 2H), 2.59 (dd, 1H, J = 6.0 Hz, J = 10.2 Hz); ^{13}C NMR (125 MHz, acetone-d_6): δ = 206.8, 206.6, 206.5, 141.2, 141.1, 131.0, 129.9, 129.3, 129.2, 127.9, 127.1, 82.9, 77.7, 73.5, 60.7, 60.1, 39.5.

Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.28; H, 7.49; N, 4.99.

Compound **7c** has the following physical and spectral properties: [α] $^{23}_{D}$ 14.60° (*c* 1.67, $CHCl_3$); IR (KRS-5): 3390, 3020, 2950, 2790, 1450; ^{1}H NMR (500MHz, $CDCl_3$): δ = 7.22 -7.32 (m, 10H), 4.01 (d, 1H, J = 13.2 Hz), 3.91 (d, 1H, J = 4.1 Hz), 3.76 (d, 1H, J = 3.9 Hz), 3.19 (d, 1H, J = 10.3 Hz), 2.47 (dd, 1H, J = 4.0 Hz, J = 10.3 Hz), 2.38 (broad s, 2OH), 2.22 (t, 1H, J = 4.2 Hz), 2.03 - 2.11 (m, 1H), 1.05 (d, 3H, J = 6.7 Hz), 0.09 (d, 3H, J = 6.8 Hz); ^{13}C NMR (125MHz, $CDCl_3$): δ = 138.8, 128.7, 128.3, 127.0, 78.6, 76.6, 76.5, 59.0, 57.6, 26.8, 19.8, 16.5; EIMS (*m/e*): (M^+) Calcd. for $C_{14}H_{21}NO_2$, 235.16; found, 235.0; MS *m/e*: 204(9), 192(75), 160(5), 91(100), 65(12).

Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.48; H, 8.97; N, 5.97.

Compound **7d** has the following physical and spectral properties: [α] $^{23}_{D}$ 11.70° (*c* 0.20, $CHCl_3$); IR (KRS-5): 3410, 3030, 2950, 2820, 1450; ^{1}H NMR (500 MHz, acetone-d_6): δ = 7.19 - 7.55 (m, 10H), 5.21 (broad s, 1 OH), 4.04 - 4.05 (m, 1H), 3.89 - 3.91 (m, 1H), 3.75 (d, 1H, J = 6.8 Hz), 3.29 (d, 1H, J = 13.4 Hz), 3.06 (d, 1H, J = 13.4 Hz), 2.93 (d, 1H, J = 10.3 Hz), 2.91 -2.99 (s, OH), 2.63 (dd, 1H, J = 6.8 Hz, J = 10.3 Hz); ^{13}C NMR (125 MHz, acetone-d_6): δ = 206.3, 206.2, 142.7, 140.1, 130.2, 129.3, 129.2, 129.1, 128.9, 128.8, 128.7, 128.1, 127.6, 87.9, 77.5, 77.3, 60.5, 58.5.

Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.77; H, 7.23; N, 5.31.

Deprotection of the Benzyl group of **7** with Palladium Hydroxide/Hydrogen: Synthesis of (2*S*,3*R*,4*R*)-3,4-Dihydroxy-2-(alkyl or aryl)-pyrrolidine (**8**).

To a solution of the *N*-benzyl protected **7** (1.1 mmol) in MeOH was added $Pd(OH)_2$ (0.1 g) under H_2 pressure (1 atm) at room temperature. After 12 hours, the inorganic salt was filtered through a Celite fitted glass filter and rinsed with MeOH. The MeOH solution was acidfied with HCl (2 *N*) at 0 °C. The solvents were evaporated under reduced pressure, and the residue was dissolved in MeOH. To the MeOH solution, to absorb the product, was added Dowex 50W-X8 (0.3 g) and was stirred for 30 minutes. The solvents were evaporated, and the mixture of Dowex 50W-X8 and product were subjected to column chromatography and purified by elution with ammonia water to give corresponding compounds **8** as solids. Yields, **8a**: 64% (82 mg), **8b**: 95.0% (200 mg), **8c**: 90% (140 mg), **8d**: 90% (240 mg).

Compound **8a** has the following physical and spectral properties: [α] $^{23}_{D}$ -7.13° (*c* 1.08, H_2O); ^{1}H NMR (500 MHz, D_2O): δ = 4.04 - 4.71 (m, 1H), 3.53 - 3.55 (m, 1H), 3.02 (dd, 1H, J = 6.3 Hz, J = 12.5 Hz), 2.81 (t, 1H, J = 6.5 Hz), 2.74 (dd, 1H, J = 3.5 Hz, J = 12.5 Hz), 1.15 (d, 3H, J = 6.6 Hz); ^{13}C NMR (125 MHz, D_2O): δ = 83.7, 77.7, 59.9, 50.8, 17.4; EIMS (*m/e*): (M^+) Calcd for $C_{14}H_{21}NO_2$, 117.15; found, 117.15; MS *m/e*: 99(16), 82(7), 71(8), 57(100), 56(33).

Anal. Calcd for $C_5H_{11}NO_2$: C, 51.26; H, 9.46; N, 11.96. Found: C, 51.28; H, 9.47; N, 11.97.

Compound **8b** has the following physical and spectral properties: [α] $^{23}_{D}$ 45.48° (*c* 0.35, H_2O); ^{1}H NMR (500 MHz, D_2O): δ = 7.12 - 7.24 (m, 5H), 4.01 - 4.03 (m, 1H), 3.72 (dd, 1H, J = 5.2 Hz, J = 5.2 Hz), 3.14 - 3.16 (m, 1H), 3.04 (dd, 1H, J = 5.7 Hz, J = 5.7 Hz), 2.94 (dd, 1H, J = 6.3 Hz, J = 6.3 Hz), 2.83 (dd, 1H, J = 3.1 Hz, J = 8.0 Hz), 2.71 (dd, 1H, J = 8.7 Hz, J = 8.7 Hz); ^{13}C NMR (125 MHz, D_2O): δ = 138.24, 129.8, 129.5, 129.3, 129.1, 127.4, 80.9, 76.9, 66.2, 50.8, 38.1; EIMS (*m/e*): (M^+) Calcd. for $C_{14}H_{15}NO_2$, 193.11; found, 191.0(M-2); MS *m/e*: 148(10), 132(13), 102(M-Bz, 100), 91(tropylium, 38), 77(14).

Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.47; H, 7.83; N, 7.19.

Compound **8c** has the following physical and spectral properties: [α] $^{23}_{D}$ 6.03° (*c* 0.20, H_2O); ^{1}H NMR (500 MHz, D_2O): δ = 4.08 - 4.10 (m, 1H), 3.82 - 3.83 (m, 1H), 2.98 (dd, 1H, J = 4.8 Hz, J = 12.5 Hz), 2.87 (dd, 1H, J = 2.4 Hz, J = 12.5 Hz), 2.53 (dd, 1H, J = 5.3 Hz, J = 8.1 Hz), 1.72 - 1.76 (m, 1H), 0.98 (d, 3H, J = 6.7 Hz), 0.95 (d, 3H, J = 6.7 Hz); ^{13}C NMR (125 MHz, D_2O): δ = 81.1, 78.5, 51.2, 31.2, 19.6, 19.3; EIMS (*m/e*): (M^+) Calcd for $C_7H_{15}NO_2$, 145.11; found, 145.0; MS *m/e*: 145(45) 128(52), 116(38), 102(80), 72(100), 56(64).

Anal. Calcd for $C_7H_{15}NO_2$: C, 57.90; H, 10.41; N, 9.65. Found: C, 57.92; H, 10.43; N, 9.67.

Compound **8d** has the following physical and spectral properties: [α] $^{23}_{D}$ -2.25° (*c* 0.10, H_2O); ^{1}H NMR (500 MHz, D_2O): δ = 7.27 - 7.39 (m, 5H), 3.82 - 3.86 (m, 1H), 3.53 - 3.56 (m, 1H), 2.90 (dd, 1H, J = 4.8 Hz, J = 4.8 Hz), 2.73 - 2.83 (m, 3H); ^{13}C NMR (125 MHz, D_2O): δ = 139.0, 129.8, 129.0, 126.9, 73.9, 73.7, 43.3, 39.1; EIMS (*m/e*): (M^+) Calcd. for $C_{14}H_{21}NO_2$,193.24; found, 193.0; MS *m/e*: 163(10), 134(17), 103(23), 91(100), 65(23).

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.04; H, 7.34; N, 7.83.

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