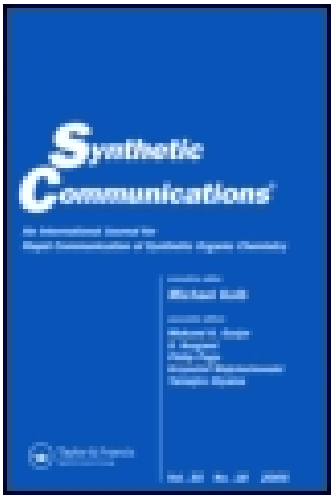

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A New Enantioselective Synthesis of (2S)-Pipecolic Acid

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A NEW ENANTIOSELECTIVE SYNTHESIS OF (2*S*)-PIPECOLIC ACID

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ABSTRACT: A synthesis of enantiomerically pure (2*S*)-pipecolic acid, involving a highly diastereoselective reaction between iminium ion and vinylsilane moieties, is described.

The non-proteinogenic amino acid (2*S*)-pipecolic acid **1** is widely distributed in plants,[1] and is the most simple representative of a highly studied class of cyclic α-amino acids with a piperidine ring; pipecolic acid itself has attracted much attention as a component and as a starting material for various synthetic or natural peptides[2] and drugs,[3] potential enzyme inhibitors,[4] the immunosuppressant natural product FK506[5] and the antifungal antibiotic dimethoxyrapamycin.[6] These numerous applications have resulted in many elegant stereoselective syntheses of pipecolic acid.[7] We describe, in this communication, a new route to access enantiomerically pure (2*S*)-pipecolic acid which makes use of a totally stereoselective iminium ion/vinylsilane cyclization.

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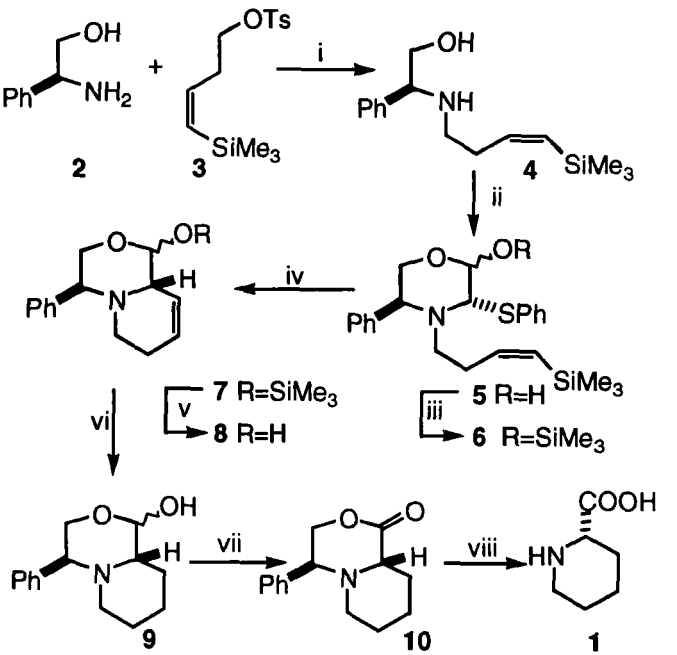
The synthesis of pipecolic acid (Scheme 1) commences with the reaction of (*S*)-phenylglycinol **2** with the tosylate **3** of the known (*Z*)-4-trimethylsilylbuten-3-ol-1.[8] The resulting amino alcohol was treated with a solution of glyoxal in the presence of thiophenol in order to afford substituted morpholine **5** whose hemiacetal function was then protected as a trimethylsilyloxy group. Cyclization of compound **6** was induced by the action of $ZnCl_2$. Easy desilylation of compound **7** on silica gel was followed by hydrogenation of the double bond. Swern oxidation gave the diastereomerically pure lactone **10** which, treated with hydrogen in the presence of Pearlman's catalyst, afforded (2*S*)-pipecolic acid **1** in optically pure form.



Scheme 1

Reagents and conditions: i, DIPEA, CH_3CN, reflux, 85%; ii, CHOCHO, THF/H_2O, then PhSH, 100%; iii, Me_3SiCl, NEt_3, 0°C, 100%; iv, $ZnCl_2$, THF, rt, 3h, 82%; v, SiO_2, 100%; vi, H_2, Raney Ni, 81%; vii, $(COCl)_2$, DMSO, CH_2Cl_2, then NEt_3, -50°C to rt, 78%; viii, H_2, $Pd(OH)_2$, EtOH, 96%.

As regards asymmetric synthesis, the key-step of these reactions is the intramolecular cyclization which occurred between the vinylsilane moiety and the iminium ion generated from aminothioether **6**. As a result, the formation of the allylic amino group was entirely stereoselective, with the new C-C bond being created on the less hindered iminium ion diastereofacially, i.e. in an *anti* disposition with respect to the phenyl substituent. This assignment was inferred from the final obtention of (2*S*)-pipecolic acid. This outcome corresponds to what was already observed in similar condensations involving the attack of an allylsilane moiety onto iminium ions (cf. Fig.1).[9]

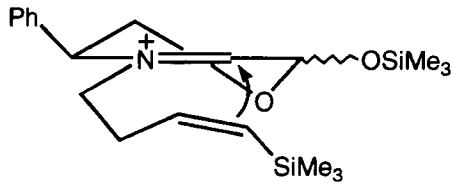


FIG.1

Diastereoselective attack of the vinylsilane moiety on the iminium ion leading to bicyclic compound **7**

In conclusion, we have synthesized optically pure (2*S*)-pipecolic acid in 42% overall yield and this synthesis emphasized the great reactivity between a chiral iminium ion and a vinylsilane moieties in intramolecular cyclization.

EXPERIMENTAL

General

Mention of usual work-up means that the reaction mixture was poured into water and then extracted with diethyl ether, the organic layers were separated, dried over $MgSO_4$ and evaporated under reduced pressure. ^1H NMR and ^{13}C NMR were recorded on a Brucker 250 and 62.5 MHz respectively in $CDCl_3$ solution (unless otherwise noted); positions of characteristic signals are reported in ppm. Optical rotations were determined with a Perkin Elmer 141 polarimeter.

(*Z*)-2-Phenyl-2-(4-trimethylsilylbut-3-enylamino)-ethanol 4

(2*S*)-Phenylglycinol (3 g, 21.8 mmol) and diisopropylethylamine (7.4 ml) were

successively added to a solution of tosylate **3** (5.8 g, 19.5 mmol) in acetonitrile (130 ml). The mixture was refluxed for 48 h and, after cooling, the solution was poured into water (30 ml). Usual work-up was followed by chromatography on silica gel (ether/petroleum ether: 30/70) to afford the aminovinyl silane **4** (4.35 g, 16.6 mmol, 85%) as an oil. ^{1}H NMR: 0.03 (s, 9H, $Si(CH_3)_3$), 2.20-2.28 (m, 2H, NCH_2CH_2), 2.56 (m, 2H, NCH_2), 3.43 (dd, J=10.2 and 8.5Hz, 1H, NCHPh), 3.60-3.75 (m, 2H, CH_2O), 5.51 (dd, J=14 and 1Hz, 1H, CHSi), 6.11-6.22 (m, 1H, CH_2CH=), 7.17-7.32 (m, 5H, Ph).^{13}C NMR: 0.0 ($Si(CH_3)_3$), 33.9 (NCH_2CH_2), 46.8 (NCH_2), 64.4 (NCHPh), 66.4 (CH_2O), 126.9, 127.4, 128.4 (Ph), 131.1 (=CHSi), 140.4 (Ph), 145.6 (CH_2CH=). $[\alpha]_D^{20}$ +32 (*c* 0.9, $CHCl_3$). Anal. calcd for $C_{15}H_{25}NOSi$: C, 68.38; H, 9.56; N, 5.31. Found: C, 68.34; H, 9.85; N, 5.17.

(*Z*)-5-Phenyl-3-phenylsulfanyl-4-(4-trimethylsilylbut-3-enyl)-morpholin-2-ol 5

Glyoxal (1.23 ml, 26.7 mmol) was added, at 0°C, to a mixture of the compound **4** (2 g, 7.6 mmol) in THF/H_2O (v/v:1/1, 18 ml). The resulting solution was stirred for 2 h at rt; thiophenol (0.8 ml, 7.6 mmol) was then added and stirring was continued for 2 h. The mixture was poured into water with the usual work-up to afford a residue which was obtained as a mixture of two diastereomers (80/20) at C-2 which was used in the next step without further purification. The characteristic peaks for the major diastereoisomer were as follows: ^{1}H NMR: 0.01 (s, 9H, $Si(CH_3)_3$), 1.65-1.85 (m, 2H, NCH_2CH_2), 2.15-2.40 (m, 1H, NCH*H*), 2.60-2.80 (m, 1H, NC*H*H), 3.54 (d, J=12Hz, 1H, CH*H*O), 3.60-3.75 (m, 2H, NC*H*Ph and C*H*HO), 4.45 (d, J=13.6Hz, 1H, OH), 4.74 (d, J=1.5Hz, 1H, NCHS), 4.98 (dd, J=13.6 and 1.6Hz, 1H, OCHO), 5.29 (d, J=14Hz, 1H, CHSi), 5.72 (dt, J=14 and 7Hz, 1H, CH_2CH=), 7.10-7.55 (m, 10H, Ph). ^{13}C NMR: 0.0 ($Si(CH_3)_3$), 34.5 (NCH_2CH_2), 49.9 (NCH_2), 62.4 (NCHPh), 72.7 (CH_2O), 81.5 (NCHS), 97.3 (OCHO), 126-139 (Ph), 132.5 (CHSi), 145.5 (CH_2C=).

Silylated compound 6

Trimethylsilyl chloride (0.65 ml, 5.1 mmol) and triethylamine (0.47 ml, 5.1 mmol) were successively added at 0°C to a solution of compound **5** (1.35 g, 3.27 mmol) in THF (20 ml). The mixture was stirred at rt for 12 h and usual work-up

gave quantitatively a residue which was used in the next step without further purification. ^{1}H NMR: 0.02 (s, 9H, $Si(CH_3)_3$), 0.32 (s, 9H, $Si(CH_3)_3$), 1.95-2.05 (m, 2H, NCH_2CH_2), 2.35-2.45 (m, 1H, NCH*H*), 2.95-3.05 (m, 1H, NC*H*H), 3.55-3.65 (m, 1H, CH*H*O) 3.80-3.92 (m, 2H, C*H*HO and NCHPh), 4.54 (d, J=1.3Hz, 1H, NCHS), 5.21 (d, J=1.5Hz, 1H, OCHO), 5.47 (d, J=14Hz, 1H, CHSi), 6.05 (dt, J=14 and 7Hz, 1H, CH_2CH=), 7.25-7.42 (m, 5H, Ph), 7.65-7.70 (m, 5H, Ph). ^{13}C NMR: -0.3 ($Si(CH_3)_3$), 0.0 ($Si(CH_3)_3$), 29.7 (NCH_2CH_2), 48.3 (NCH_2), 61.0 (NCHPh), 71.1 (CH_2O), 79.9 (NCHS), 95.8 (OCHO), 125.3-143.9 (Ph), 133.2 (CHSi), 145.6 (CH_2CH=).

(1*R*,4S,9aS)-4-Phenyl-1,3,4,6,7,9a-hexahydropyrido[2,1-c][1,4]-1-trimethylsilyloxyoxazin 7

Zinc chloride (1 g, 7.6 mmol) was added to a solution of compound **6** (1.85 g, 3.8 mmol) in dichloromethane (20 ml) and the mixture was stirred for 3h at rt under nitrogen. The mixture was poured into water with the usual work-up to afford crude product **7**. Flash chromatography gave a sample of pure compound **7** as a single stereomer. ^{1}H NMR: 0.01 (s, 9H, $Si(CH_3)_3$), 1.50-1.61 (m, 1H, C*H*HC=), 2.01-2.16 (m, 1H, CH*H*C=), 2.52-2.74 (m, 2H, NCH_2), 3.40 (dd, J=12 and 10.5Hz, 1H, C*H*HO), 3.50 (bs, 1H, NCHC), 3.72-3.80 (m, 2H, CH*H*O and NCHPh), 4.94 (d, J=3.1Hz, 1H, OCHO), 5.83 (s, 2H, CH=CH), 7.10-7.21 (m, 3H, Ph), 7.28-7.31 (m, 2H, Ph). ^{13}C NMR: 0.0 ($Si(CH_3)_3$), 20.5 (NCH_2CH_2), 46.4 (NCH_2), 56.7 (NCHCH), 58.4 (NCHPh), 70.0 (CH_2O), 95.0 (OCHO), 123.4 (NCH*C*=), 127.0-138.5 (Ph and CH_2C=).

(4S, 9aS)-4-Phenyl-1,3,4,6,7,9a-hexahydropyrido[2,1-c][1,4] oxazin-1-ol 8

The silylated compound **7** (0.9 g, 3.11 mmol) was submitted to a slow chromatography on silica gel (ether/petroleum ether: 10/90) to afford the hemiketal **8** (0.72 g, 3.11 mmol) as a mixture of diastereomers at C-1. ^{1}H NMR (major diastereomer): 1.63-1.80 (m, 1H, NCH_2CHH), 2.10-2.30 (m, 1H, NCH_2CHH), 2.41 (dd, J=11.6 and 4.7Hz, 1H, NC*H*H), 2.73 (dd, J=12.9 and 6.1Hz, 1H, NCH*H*), 3.54 (bs, 1H, NCHC), 3.65-3.80 (m, 2H, C*H*HO and NCHPh), 4.01 (dd, J=10.6 and 5.9Hz, 1H, CH*H*O), 4.95 (d, J=2.3Hz, 1H, OCHO), 5.51-5.59 (m, 1H, NCHC*H*=), 5.70-5.80 (m, 1H, CH_2CH=), 7.13-7.25

(m, 3H, Ph), 7.37-7.41 (m, 2H, Ph). ^{13}C NMR (major diastereomer): 23.7 (NCH_2CH_2), 48.0 (NCH_2), 59.3 (NCHC), 60.3 (NCHPh), 67.5 (CH_2O), 96.5 (OCHO), 126.2 (NCHC=), 128.4-139.2 (Ph and CH_2CH=). HRMS: calcd for $C_{14}H_{18}NO_2$: ($M+H^+$) m/z 232.1338, obsd 232.1334.

(4S, 9aS)-4-Phenyloctahydropyrido [2,1-c][1,4] oxazin-1-ol 9

Raney nickel was added to a solution of compound **8** (0.2 g, 0.67 mmol) in absolute ethanol and the mixture was placed under hydrogen. After stirring for 4h, the suspension was filtered over celite and the resultant ethanolic solution was evaporated under reduced pressure. The residue was chromatogaphed on silica gel (ether/petroleum ether: 40/60) to afford compound **9** (0.13 g, 0.54 mmol, 81%) as a mixture of diastereomers at the hemiketalic carbon. ^1H NMR (major diastereomer): 1.10-1.31 (m, 2H, $NCH_2CH_2CH_2$), 1.43-1.64 (m, 4H, NCH_2CH_2 and $NCHCH_2$), 1.72-1.77 (m, 1H, NCH*H*), 2.62-2.72 (m, 2H, NC*H*H and NCHC), 3.81-3.88 (m, 2H, NCHPh and C*H*HO), 3.98 (dd, J=4.5Hz, 1H, CH*H*O), 4.68 (d, J=4.5 Hz, 1H, OCHO), 7.24-7.30 (m, 3H, Ph), 7.39-7.44 (m, 2H, Ph). ^{13}C NMR (major diastereomer): 22.4 (CH_2), 24.4 (CH_2), 25.0 (CH_2), 51.1 (NCH_2), 59.6 (NCHPh), 60.0 (NCHC), 67.1 (CH_2O), 96.6 (OCHO), 128.0-129.9 (Ph). HRMS: calcd for $C_{14}H_{20}NO_2$ ($M+H^+$) m/z 234.1494, obsd 234.1489.

(4S, 9aS)-4-Phenylhexahydropyrido [2,1-c][1,4] oxazin-1-one 10

Dimethyl sulfoxide (0.078 ml, 1.1 mmol) was added dropwise to a solution of oxalyl chloride (0.052 ml, 0.6 mmol) in dichloromethane (1.5 ml) at –50°C. The mixture was stirred for 5 min and a solution of hemiketal **9** (0.12 g, 0.5 mmol) in dichloromethane (1.5 ml) was introduced. After 1h at –50°C, triethylamine (0.35 ml, 2.5 mmol) was added and the mixture was allowed to warm to 10°C in 1h. Usual work-up using dichloromethane as the solvant for extraction yielded a residue which was purified by flash chromatography (ether/petroleum ether: 30/70) to give the diastereoisomerically pure lactone **10** (0.09 g, 0.37 mmol, 75%). ^1H NMR: 1.10-1.31 (m, 2H, $NCHCH_2CH_2$), 1.35-1.50 (m,2H, NCH_2CH_2), 1.65-1.80 (m, 1H, NCHC*H*H), 1.95-2.04 (m, 1H, NCHCH*H*), 2.26 (ddd, J=9.5, 11.8 and 3.7Hz, 1H, NC*H*H), 2.72 (td, J=11.8 and 4.4Hz, 1H, NCH*H*), 3.25 (dd, J=9.2 and 3.6Hz, 1H, NCHCO), 3.91 (t, J=5Hz, 1H, NCHPh), 4.37 (dd, J=11.1

and 5.3Hz, 1H, C*H*HO), 4.61 (dd, J=11.1 and 4.7Hz, 1H, CH*H*O), 7.20-7.34 (m, 5H, Ph). ^{13}C NMR: 25.5 (CH_2), 26.0 (CH_2), 28.8 (CH_2), 53.8 (NCH_2), 59.9 N*C*HCO), 62.1 (NCHPh), 74.3 (CH_2O), 130.3, 130.4, 130.7, 137.6 (Ph), 172.8 (CO). $[\alpha]_D^{20}$ +18 (*c* 0.7, $HCCl_3$). HRMS: calcd for $C_{14}H_{17}NO_2$ ($M+H^+$): m/z 232.1338, obsd 232.1339.

(*S*)-Pipecolic acid 1

A solution of lactone **9** (0.081 g, 0.35 mmol) in absolute ethanol (2 ml) was injected into a hydrogenation flask containing a prehydrogenated suspension of 20% palladium hydroxide (Pearlman's catalyst) (0.065 g, 0.46 mmol) in absolute ethanol (1 ml). The hydrogenation was complete in 2h. The mixture was filtered through Celite 545 and the residue washed with absolute ethanol to afford (*S*)-pipecolic acid (0.044 g, 0.33 mmol, 91%) as a withe solid. $[\alpha]_D^{20}$ –25.5 (*c* 1.3, H_2O); litt[7]: $[\alpha]_D^{20}$ -26 (*c* 1.3, H_2O). ^{1}H NMR (D_2O): 1.32-1.38 (m, 6H, $(CH_2)_3$), 2.77 (t, J=11.1Hz, 1H, NC*H*H), 3.21-3.27 (m, 1H, NCH*H*), 3.45 (d, J=11.2Hz, 1H, NCH).

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