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A New Concise Stereoselective Total Synthesis of (+)-Azimic Acid

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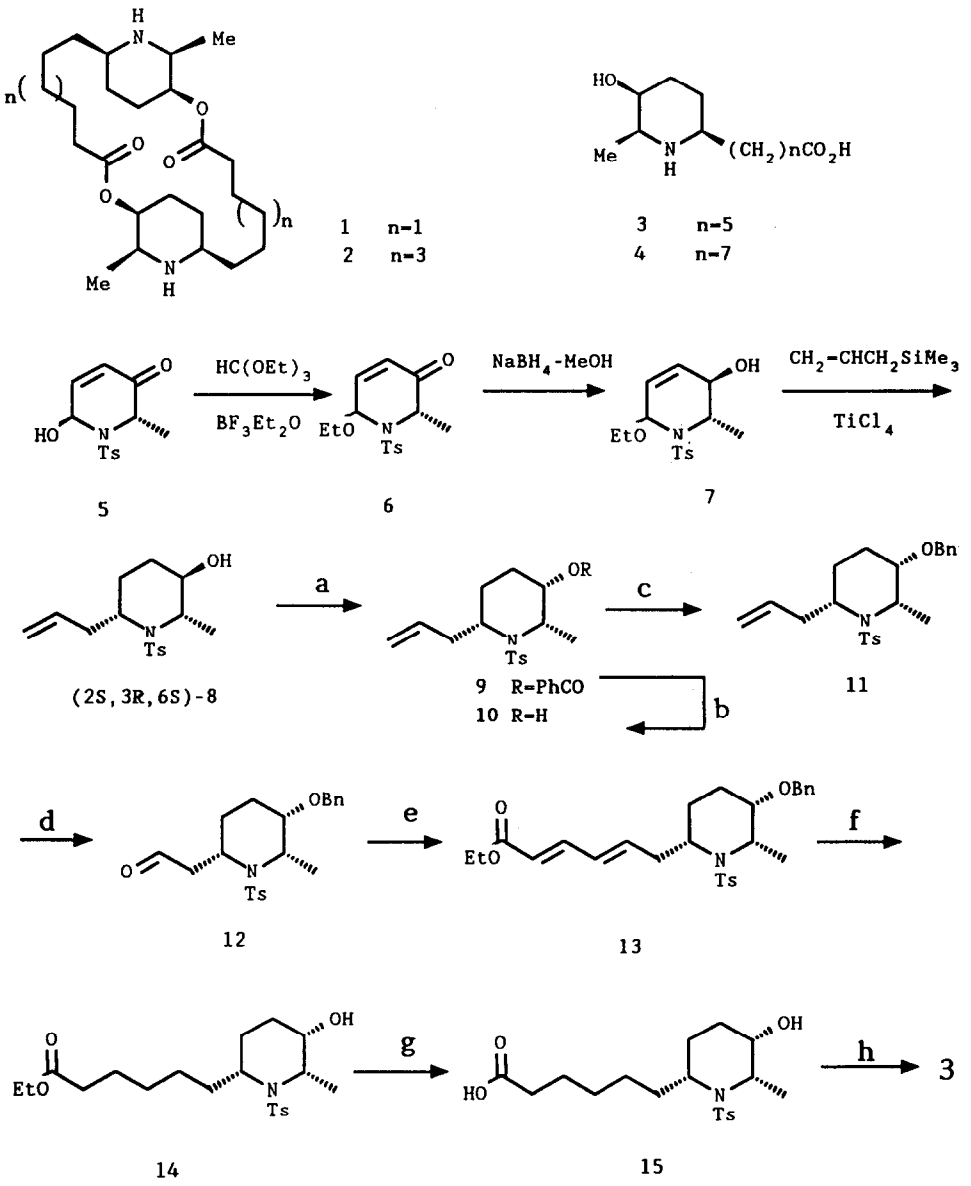
Abstract: A new concise stereoselective total synthesis of (+)-azimic acid, which is the immediate precursor of macrocyclic dilactone azimine, has been achieved in eleven steps from (2S,6S)-6-hydroxy-2-methyl-N-tosyl-Δ^4-piperidone-3 (**5**) with a high overall yield (36%).

Piperidine alkaloids are abundant in nature and many of them exhibit important biological activity.[1] The macrocyclic dilactones azimine(**1**)[2] and carpaine (**2**)[3] belong to a small subgroup containing a 2,3,6-trisubstituted piperidine alkaloid, azimic (**3**) and carpanic (**4**) acids, whose total stereospecific synthesis from D-glucose based on the concept of "chiral templates" [4] have been achieved by Hanessian and coworkers.[5] The transformation of carpanic acid (**4**) into carpaine (**2**) has been reported by Corey and coworkers.[6] We described herein a concise total stereoselective synthesis of azimic acid (**3**) (Scheme 1).

The synthesis of (+)-azimic acid (**3**) starts with (2S,6S)-6-hydroxy-2-methyl-N-tosyl-Δ^4-piperidone-3 (**5**)[7] which was transformed stereoselectively into (2S,3R,6S)-**8** in three steps with a high overall yield (66%).[8] Inversion of the configuration of hydroxy group at C3 in (2S,3R,6S)-**8** to (2S,3S,6S)-**9** with Mitsunobu reaction[9] in 88% yield, followed by hydrolysis of the resulting benzoate with 3N NaOH in ethanol led to (2S,3S,6S)-**10** in 98% yield. Benzylation of the resulting alcohol with benzyl bromide provided (2S,3S,6S)-**11** as an oil in quantitative yield. Ozonolysis of (2S,3S,6S)-**11** in CH_2Cl_2-MeOH (9:1) furnished the aldehyde (2S,3S,6S)-**12** as a colourless oil in 90% yield, which on reaction with 3-carboethoxy allylidene triphenylarsorane[10] gave (2S,3S,6S)-**13** as an oil in 83% yield. Catalytic hydrogenation of (2S,3S,6S)-**13** with 10% palladium on carbon afforded (2S,3S,6S)-**14** as an oil in quantitative yield and hydrolysis of the resulting compound **14** with 1N NaOH in ethanol gave carboxyl compound (2S,3S,6S)-**15** as an oil in 98% yield. Finally, cleavage of the tosyl protecting group in **15** with naphthalene/sodium in DME gave (+)-azimic acid (**3**) in 85% yield, mp. 210-214°C, $[\alpha]_D^{25}$ +7.9°(c 1.0, MeOH), {Lit.[5] mp. 214-215°C, $[\alpha]_D^{25}$ +8° (MeOH)}.



Scheme 1 ***Reagents.*** a. DEAD, Ph_3P, benzoic acid, THF. b. 3N NaOH in EtOH. c. $C_6H_5CH_2Br$, NaH, Bu_4NI, THF. d. O_3, CH_2Cl_2:CH_3OH (9:1). e. Ph_3As=CHCH=$CHCO_2Et$, THF:Et_2O:H_2O (4:5:1). f. 10% Pd/C, EtOH, H_2(1 atm). g. 1N NaOH, EtOH. h. Na/naphthalene, DME.

DEAD = EtO_2C-N=N-CO_2Et

The described stereoselective total synthesis of (+)-azimic acid (**3**) may prove useful in studies directed toward the total synthesis of the substituted piperidine alkaloids.

Experimental:

Melting points were determined with a Buchi 535 melting point apparatus and are uncorrected. All reactions were carried out under dried nitrogen. Addition of reagents was made by syringes. Reactions were monitored by using thin layer chromatography (TLC). IR spectra were measured on Shimadzu IR 400 spectrometer, ^{1}H-NMR spectra were recorded on JEOL FX-90Q (90 MHz), Varian-200 (200 MHz), AM-400 (400 MHz) and AMX-600 (600 MHz) spectrometers with $CDCl_3$ as solvent and values were reported in ppm, using TMS or residual $CHCl_3$ as internal standard; MS spectra were conducted on a Finnigan 4021 GC-MS instrument and JMS-01U spectrometer. The optical rotations were measured on Autopol spectrometer III automatic polarimeter. Elemental analyses were performed by the Analytical Department of this Institute.

1. (2S,3S,6S)-6-Allyl-3-benzoyloxy-2-methyl-N-tosyl-piperidine (9)

A solution of DEAD (2.5 ml, 15.95 mmol) in anhydrous THF (15 ml) was added dropwise to a solution of the alcohol **8**[8] (2.22 g, 7.2 mmol), Ph_3P(4.08 g, 15.6 mmol) and benzoic acid (1.95 g, 15.98 mmol) in anhydrous THF (50 ml) at 0°C. The reaction mixture was stirred at rt for 3.5 h and the solvent was removed under reduced pressure to give a residue. Ether was added and white precipitate was filtered off. The filtrate was evaporated to give a crude product, which was purified by column chromatography on silica gel [petroleum ether-ethyl acetate (90:10) as eluent] to give crystalline **9** (2.6 g, 88%). mp. 95.3-95.7°C. $[\alpha]_D^{25}$ +0.34°(c 1.3, EtOAc); IR (film) ν_{max}: 1700 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): 7.0-7.7 (br, 9H), 5.90 (m, 1H), 5.16 (m, 2H), 4.44 (m, 1H), 4.28 (m, 1H), 4.17 (m, 1H), 2.20 (s, 3H), 1.80 (m, 2H), 1.30-1.50 (br, 4H), 1.26 (d, 3H, J=8Hz); MS m/z: 384 (M^+-29), 223 (M^++1-C_3H_5-$C_7H_6O_2$), 155 (Ts^+), 105 ($C_7H_5O^+$, 100%), 91 ($C_7H_7^+$); Anal.: Calcd. for $C_{23}H_{27}NO_4S$, C 66.8%, H 6.53%, N 3.39%, Found: C 66.75%, H 6.30%, N 3.48%.

2. (2S,3S,6S)-6-Allyl-3-hydroxy-2-methyl-N-tosyl-piperidine (10)

To a solution of **9** (2.5 g, 6.05 mmol) in ethanol (15 ml) was added 3 ml of 3N NaOH. After stirring for 8 h, the reaction mixture was extracted with ether, washed with brine and dried over $MgSO_4$. The solution was evaporated under reduced pressure to give crystalline **10** (1.83 g, 98%). mp. 134-135°C. IR (film) ν_{max}: 3250, 3050, 1700, 1560, 1480 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 7.80 (d, 2H, J=8), 7.32 (d, 2H, J=8), 5.90 (m, 1H), 5.10 (m, 2H), 3.7-4.4 (m, 4H), 2.40 (s, 3H), 1.84 (m, 2H), 1.18-1.58 (br, 7H); MS m/z: 310 (M^++1), 309 (M^+), 292 (M^+-OH), 268 (M^+-C_3H_5), 235 (M^+-C_3H_5-CH_3-H_2O), 155 (Ts^+), 154 (M^+-Ts), 91 ($C_7H_7^+$, 100%); Anal.: Calcd. for $C_{16}H_{23}NO_3S$, C 62.13%, H 7.66%, N 4.50%, Found: C 61.71%, H 7.54%, N 4.46%.

3. (2S,3S,6S)-6-Allyl-3-benzyloxy-2-methyl-N-tosyl-piperidine (11)

To a solution of compound **10** (500 mg, 1.62 mmol) in dry THF (10 ml), was added sodium hydride (75 mg, 80% purity, 2.5 mmol). After the reaction mixture was stirred at rt for 30 min, a catalytic amount of Bu_4NI (59 mg, 1% equiv.) and benzyl bromide (0.2 ml, 1.62 mmol) was added. The reaction mixture was stirred at rt for 3 h and aq. NH_4Cl solution was added. The mixture was extracted with ethyl acetate, washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure to afford a residue which was purified by silica gel column chromatography [petroleum ether-ethyl acetate (92:8) as eluent] to give a light yellow oil **11** (0.64 g, 99.4%). $[\alpha]_D^{25}$+0.52 (c 1.7, EtOAc). IR (film) ν_{max}: 1600 (C_6H_6) 1500 (C_6H_6) cm^{-1}; ^{1}H-NMR ($CDCl_3$): 7.8 (2H, d, J=7.2), 7.3 (5H, m), 7.10 (2H, d, J=7.2), 5.80 (1H, m), 5.0 (2H, m), 4.25 (s, 2H), 3.5-4.0 (m, 3H), 2.20 (s, 3H), 1.85 (m, 2H), 1.1-1.60 (7H, br); MS m/z: 400 (M^++1), 384 (M^+-CH_3), 358 (M^+-C_3H_5, 100%), 308 (M^+-C_7H_7), 292 (M^+-C_7H_7-CH_3), 268 (M^++1-C_7H_7-C_3H_5, 11%), 203 (M^+-Ts-C_3H_5), 155 (Ts^+).

4. (2S,3S,6S-3-benzyloxy-2-methyl-N-tosyl-6-piperidinyl)-acetaldehyde (12)

To the solution of **11**(555 mg,, 1.39 mmol) in 10 ml of CH_2Cl_2-MeOH (9:1) was bubbled with ozone at -78°C for 5 min until a light blue colour appeared. The excess of ozone was removed by passing through N_2 and 2 ml of Me_2S was added. The reaction mixture was stirred at rt for 1 h and evaporated under reduced pressure to give a residue which on purfication with flash column chromatography on silica gel [ethyl acetate-petroleum ether (25:75) as eluent], gave colourless oil **12** (502 mg, 90%). $[\alpha]_D^{25}$ +0.63 (c 7.9, EtOAc). IR (film) ν_{max}: 1730 (C=O), 1600, 1500 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 9.70 (s, 1H), 7.0-7.7 (m, 9H), 4.0-4.7 (br, 3H), 3.37 (s, 2H), 2.5 (s, 3H), 2.3 (d, 2H, J=6), 1.75 (br, 4H), 1.35 (d, 3H, J=7); MS (FAB) m/z: 402(M^++1), 400 (M^+-1), 386 (M^+-CH_3), 372 (M^+-CHO), 358 (M^+-C_2H_3O, 100%), 324 (M^+-C_6H_5), 310 (M^+-C_7H_7), 268 (M^++1-C_7H_7-C_2H_3O), 250 (M^+-1-C_7H_7-H_2O-C_2H_3O), 246 (M^+-Ts), 203 (M^+-C_2H_3O-Ts), 155(Ts^+), 140 (M^+-C_7H_7-CH_3-Ts), 91 ($C_7H_7^+$); HREIMS Calcd. for $C_{20}H_{24}NO_3S$ (M^+-C_2H_3O), 358.1477, Found: 358.1477

5. Ethyl [6-(2'S,3'S,6'S-3'-benzyloxy-2'-methyl-N-tosyl-piperdine-6'-yl)-2,4-hexadienoate (13)

To a solution of carboethoxy allylidene triphenylarsorane (0.4 g, 0.975 mmol) in 10 ml of Et_2O:THF:H_2O (5:4:1) was added the solution of the aldehyde **12** (290 mg, 0.723 mmol) in Et_2O (5 ml). After the reaction mixture was vigorously stirred at rt for 48 h, water was added. The mixture was extracted with ethyl acetate, washed with brine and dried over $MgSO_4$. The solution was evaporated under reduced pressure to give a crude product which was purified by flash chromatography on silica gel [petroleum ether-ethyl acetate (90:10) as eluent] to afford a light yellow oil **13** (298.5 mg, 83%) . $[\alpha]_D^{25}$ -0.60° (c 3.7, EtOAc). IR (film) ν_{max}: 3060, 3040, 1700, 1600, 1650,1610 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 7.74 (d, 2H, J=8), 7.10-7.40 (m, 5H), 7.02 (d, 2H, J=8), 6.33 (dd, 1H, J=18, 2.8), 6.20 (d, 1H, J=11.2), 5.82 (d, 1H, J=18), 5.73 (dd, 1H, J=11.2, 2.8), 4.10-4.43 (m, 3H), 3.82 (br, 2H), 3.40 (s, 2H), 2.30 (s, 3H), 1.66-1.82 (m, 6H), 1.28 (d, 3H, J=8), 1.34 (t, 3H); MS m/z: 498 (M^++1), 391 (M^+-1-C_7H_7-CH_3), 358 (M^+-$C_8H_{11}O_2$, 100%), 268 (M^+-C_7H_7-$C_8H_{11}O_2$), 203 (M^+-Ts-$C_8H_{11}O_2$), 155 (Ts^+), 91 ($C_7H_7^+$); HREIMS Calcd. for $C_{20}H_{24}NO_3S$ (M^+-$C_8H_{11}O_2$), 358.1477, Found: 358.1477.

6. Ethyl [6-(2'S,3'S,6'S-3'-hydroxy-2'-methyl-N-tosyl-piperidine-6'-yl)]-hexanoate(14)

To a solution of **13** (92 mg, 1.85 mmol) in absolute ethanol (5 ml) was added a catalytic amount of 10% palladium on carbon (5 mg). After mixture was stirred under H_2 atmosphere (1 atm) at rt for 24 h, filtration and removal of the solvent gave **14** as a colourless oil (76 mg, 99.6%). $[\alpha]_D^{25}$ -0.86 (c 5.25, EtOAc). IR (film) ν_{max}: 3510 (free OH), 3360 (OH), 1730 (C=O), 1600, 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 7.74 (d, 2H, J=8). 7.30 (d, 2H, J=8), 4.16 (q, 1H, J=7), 3.98 (m, 1H), 3.70 (m, 2H), 2.40 (s, 3H), 2.30 (t, 2H, J=7.2), 1.90-0.90 (br, 15H), MS m/z: 412 (M^++1), 394 (M^+-OH), 366 (M^+-C_2H_5O), 268 (M^+-$C_8H_{15}O_2$, 100%), 250 (M^+-$C_8H_{15}O_2$-H_2O), 211 (M^+-Ts-C_2H_5O), 155 (Ts^+), 91 ($C_7H_7^+$); HREIMS Calcd. for $C_{13}H_{18}NO_3S$(M^+-$C_8H_{15}O_2$), 268.1008, Found. 268. 1032.

7. Ethyl [6-(2'S,3'S,6'S-3'-hydroxy-2'-methyl-N-tosyl-piperidine-6'-yl)]-hexanoate(15)

To a solution of **14** (105 mg, 0.255 mmol) in ethanol (3 ml) was added 1N NaOH (1 ml) at rt with stirring for 1 h. Usual workup gave a light yellow oil **15** (96.6 mg, 98.7%). $[\alpha]_D^{25}$-4.8 (c 5, EtOAc); IR (film) ν_{max}: 3300 (CO_2H), 1710 (C=O), 1600, 1500 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 7.78 (d, 2H, J=8), 7.30 (d, 2H, J=8), 4.30 (d, 1H, J=4), 4.00 (m, 1H), 3.68 (m, 1H), 2.40 (s, 3H), 2.34 (t, 2H, J=6), 1.30-1.90 br, 12H), 1.27 (d, 3H, J=7); MS m/z: 384 (M^++1), 366 (M^+-OH), 268 (M^+-$C_6H_{11}O_2$, 100%, 228 (M^+-Ts), 210 (M^+-Ts-H_2O), 194 (M^++1-Ts-H_2O-OH), 155 (Ts^+), 91 ($C_7H_7^+$); HREIMS Calcd. for $C_{19}H_{28}NO_4S$(M^+-OH), 366.1738, Found: 366. 1723.

8. (+)-Azimic acid (3)

To a solution of naphthalene (0.2 g, 1.56 mmol) in freshly distilled DME (4 ml) was added sodium (36 mg, 1.56 mmol) under N_2. The reaction mixture was stirred at rt until the formation of naphthalide was indicated by the formation of a dark-green colour(ca.30min). A solution of **15** (100 mg, 0.26 mmol) in freshly distilled DME (1 ml) was added to the above mixture at -78°C. The reaction mixture was stirred at the same temperature for 30 min and quenched with 2 ml of saturated aq. NH_4Cl. The organic layer was extracted with H_2O and the combined aqueous layers were evaporated under reduced pressure (0.1 mm/Hg) to afford a crude product, which was extracted with absolute methanol to separate the inorganic salts (NH_4Cl, NaCl) which existed in the aqueous layer. Removal of methanol gave a white solid, which was purified by preparative thin layer chromatography (n-BuOH:EtOH:AcOH:H_2O, 4:2:2:1 as eluent) to give **3** as a powder (51 mg, 85.3%), mp. 210-214°C (d). $[\alpha]_D^{25}$ +7.9°(c 1.0, MeOH); [Lit.[5] mp. 214-215°C, $[\alpha]_D^{25}$ +8° (MeOH)]; IR (film) ν_{max}: 3200 (CO_2H), 1720 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6): 3.72 (m, 1H), 3.1-3.3 (br, 2H), 2.5 (t, 2H, J=6), 1.7-2.2 (br, 12H), 1.60 (d, CH_3, J=7); MS (FAB) m/z: 230(M^++1), 211(M^+-18), 196(M^+-18-CH_3), 193 (M^+-1-H_2O-OH), 166 (M^+-CO_2H-H_2O), 153 (M^++1-CO_2H-CH_3-OH), 152 (M^++1-CO_2-2×OH), 151 (M^+-CO_2H-H_2O-CH_3), 150 (M^+-1-CO_2H-H_2O-CH_3), 136 (M^+-CH_3-H_2O-CH_2CO_2H), 123 (M^+-CH_3-H_2O-C_2H_4-CO_2H), 115 ($C_6H_{11}O_2^+$), 109 (M^+-CH_3-H_2O-$C_3H_6CO_2H$).

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