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An intramolecular Michael reaction strategy for the synthesis of 2,6-disubstituted-3-piperidinols

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Dedicated in memory of Dr Darshan Ranganathan

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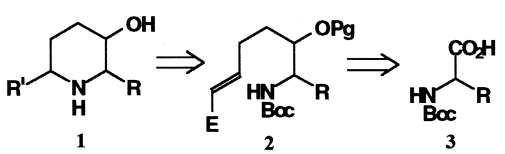
Abstract—A new synthetic strategy for 2,6-disubstituted-3-hydroxypiperidines via intramolecular Michael reaction of an α-amino-β-hydroxy-δ-acrylate is described. The latter was derived from L-alanine in a few steps via the key intermediacy of an enantiopure γ-amino-β-keto sulfone. © 2002 Published by Elsevier Science Ltd.

The *Cassia* and *Prosopis* species produce a number of 2,6-disubstituted-3-piperidinol alkaloids **1** (e.g. cassine, azimic acid, spectaline, julifloridine, prosopinine, etc.) which show a broad spectrum of biological properties including anaesthetic, analgesic, antitumor and antibiotic activities.[1–3] The 2-substituents (R) in **1** can be a methyl or a hydroxymethyl group whereas the 6-substituents (R′) are usually long-chain saturated or unsaturated appendages. All four pairs of diastereomeric racemates that are possible for a 2,3,6-trisubstituted piperidine ring have been found in these alkaloids. In view of such structural diversity and their significant biological properties, in recent years, much attention has been paid towards stereo- and enantioselective syntheses of these alkaloids.[4] We now present a new strategy by which 2,6-disubstituted-3-piperidinol rings can be readily constructed via intramolecular Michael reaction of a chiral-pool derived α-amino-β-hydroxy-δ-acrylates viz. **2** (Scheme 1). Recently, intramolecular Michael additions in δ-unsaturated amines and amides[5] have been shown to provide an attractive synthetic route to piperidine rings,[6] albeit for simpler targets, which formed the basis of our present strategy.

With a goal of the synthesis of spectaline, azimic acid and julifloridine,[1] all having a C_2-methyl substituent (R=Me in **1**), L-alanine was chosen as the chiral-pool precursor (Scheme 2). Thus, Boc-L-alanine (**4**) was first converted to the corresponding α-diazoketone **5** (65%) via the mixed carbonate method ($ClCO_2Et$, Et_3N, THF, 0°C then excess CH_2N_2). The latter upon treatment with 47% aqueous HBr in ether at 0°C produced the corresponding α-bromo ketone which, without purification, was reacted with $NaSO_2Tol$ (DMF, rt) to give the enantiopure γ-amino-β-keto sulfone **6** (70%) in a good overall yield.[7,8] α-Alkylation of **6** with ethyl γ-bromocrotonate using K_2CO_3 in DMF at room temperature[7,8] produced the α-alkylated β-keto sulfone **7a** as a 50:50 diastereomeric mixture. In this reaction, care must be taken not to use more than one equivalent of the bromocrotonate electrophile as formation of the α,α-dialkylated product can easily occur. Subsequent desulfonation of **7a** with Al(Hg) in 10% aqueous THF gave the *trans*-γ-unsaturated α-amino ketone **7b** in 86% overall yield. The keto-group in **7b** was reduced under chelation controlled conditions ($NaBH_4$, MeOH, −50°C)[9] to produce the *anti*-amino alcohol (78% de) and its hydroxy group protected as the acetate (Ac_2O, Et_3N, CH_2Cl_2, rt) to give the key α-amino-β-acetoxy-δ-acrylate **8** in 83% yield from **7**. Intramolecular Michael addition in **8** was first attempted using KOBu-*t* in THF according to the Hirama-protocol.[5b] However, repeated attempts at this reaction under a variety of conditions failed to induce any cyclization, returning the starting material on each occasion. In order to increase the nucleophilicity of the amine group, the Boc-protecting group in **8** was removed (TFA, CH_2Cl_2, rt) and the liberated amine salt **9**, without isolation, was treated with excess Et_3N to induce the intramolecular Michael reaction. This indeed led to a smooth cyclization reaction producing the diastereomeric piperidines **10a** and **b** in an 82% combined yield. Although the diastereoselectivity of this cyclization step is poor, perhaps due to lack of any stereochemical bias



Scheme 1.

Keywords: intramolecular Michael reaction; diastereomeric piperidines; unsaturated amines.

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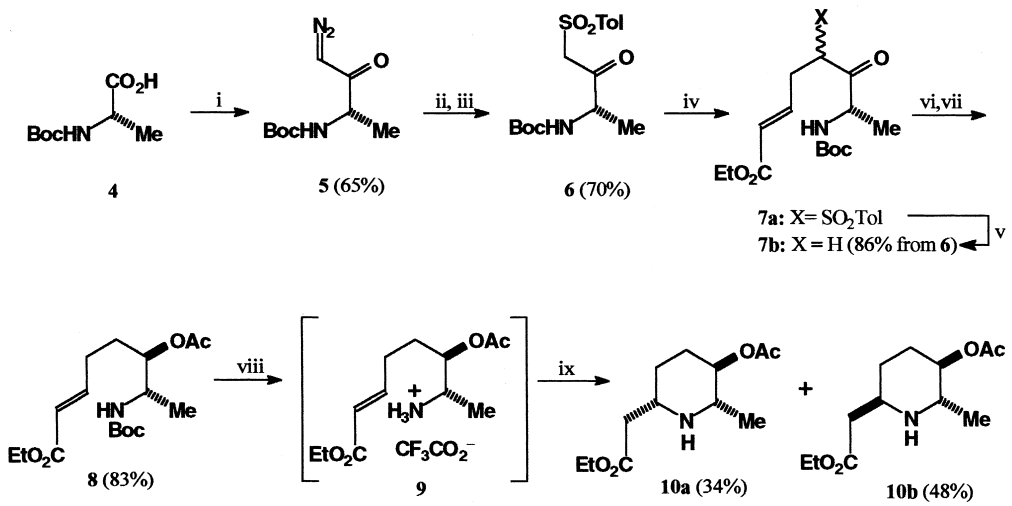
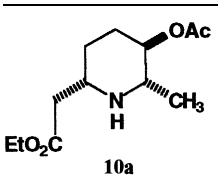


Scheme 2. (i) EtO_2CCl, Et_3N, THF, 0°C then excess CH_2N_2, ether; (ii) 47% HBr, ether, 0°C; (iii) $NaSO_2Tol$, DMF, rt; (iv) ethyl γ-bromocrotonate, K_2CO_3, DMF, rt; (v) Al(Hg), THF–H_2O, reflux; (vi) $NaBH_4$, MeOH, −50°C; (vii) Ac_2O, Et_3N, CH_2Cl_2, rt; (viii) TFA, CH_2Cl_2, rt; (ix) Et_3N (excess), CH_2Cl_2, rt.

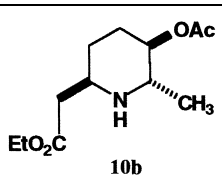
between the two transition states (e.g. absence of any allylic chiral center which could have provided π-face differentiation during the cyclization reaction[5b–d]) and/or the reversible nature of the reaction, the two diastereomers could be easily separated by column chromatography over silica gel (**10a** (38%): R_f 0.5; **10b** (44%): R_f 0.3 in 40% EtOAc in light petroleum).

Stereochemical assignments to **10a** and **b** were made on the basis of their ^1H and ^{13}C NMR spectra. Unfortunately, neither **10a** or **10b** gave any nOe enhancement between their H-2 and H-6 protons, which could have identified the 2,6-*cis* diastereomer of this pair. Hence, the 2,6-relative stereochemistries in **10a** and **b** were assigned on the basis of the chemical shift differences of their ^1H and ^{13}C NMR spectra and comparing them with literature reports on similar systems.[4,10] Two-dimensional NMR techniques (^1H–^1H COSY) were used to determine the chemical shifts of the H-2, H-3 and H-6 protons in **10a** and **b**. Thus, for **10a**, cross-peaks were obtained between the three-proton doublet at δ 1.07 (C_2-*Me*) and a one-proton double quartet at δ 2.74. The latter was thus assigned as the H-2 ring proton. Similarly, cross-peaks between two one-proton signals at δ 2.74 (dq) and 4.35 (ddd) led us to assign the latter as the ring H-3 proton. Additional cross-peaks were found between the two-proton multiplet at δ 2.30–2.44 (due to the methylene hydrogens of the C_6–CH_2CO_2Et substituent) and the one-proton multiplet at δ 2.96–3.00. The latter resonance was thus assigned to the H-6 proton of the piperidine ring. Chemical shift values for the hydrogens in the other diastereomer **10b** were similarly determined and are listed together with those of **10a** in Table 1. Pertinent ^{13}C NMR resonances (C-2, C-3, C-6 and C_2-*Me* carbons) of the two diastereomers are also listed in Table 1. The chemical shift values for the C-2 and C-6 carbons could not be assigned with certainty and may be interchanged. As evident from Table 1, the proton chemical shifts of the H-2, H-3, H-6 and the C_2-Me hydrogens in **10a** are consistently upfield relative to the corresponding protons in **10b**. On the other hand, the carbon chemical shifts of the C-2, C-3, C-6 and the C_2-*Me* in **10a** are all deshielded relative to the corresponding carbons in **10b**. Literature reports on 2,3,6-trisubstituted piperidine ring systems revealed that the H-2, H-3 and H-6 protons of the 2,6-*cis* isomers appear at a more upfield region than the corresponding protons of the 2,6-*trans* isomers ($\Delta\delta \approx 0.4$ ppm),[10] based on which we assigned **10a** as the 2,6-*cis* and **10b** as the 2,6-*trans* isomer. The trend in the ^{13}C NMR chemical shift differences, as observed in our case, was also corroborated by the literature data on similar systems.[10c]

Table 1. Diagnostic ^1H and ^{13}C NMR data of **10a** and **10b**



10a



10b

^1H NMR (δ)		^{13}C NMR (δ)		^1H NMR (δ)		^{13}C NMR (δ)	
H-2	2.74	C-2	55.4/60.4[a]	H-2	3.08	C-2	50.1/60.4[a]
H-3	4.35	C-3	75.4	H-3	4.35–4.58	C-3	73.0
H-6	2.96–3.00	C-6	60.4/55.4[a]	H-6	3.30–3.40	C-6	60.4/50.1[a]
CH_3	1.07	CH_3	18.8	CH_3	1.15	CH_3	17.6

[a] These values are interchangeable.

In conclusion, we have described a new synthetic route to 2,6-disubstituted-3-piperidinols via an intramolecular Michael reaction strategy. The ester functionality in the C_6-side chain of **10** can be suitably exploited to construct the C_6-appendages of the target alkaloids.

1. Experimental

1.1. General

All melting points are uncorrected. IR spectra were recorded on a Perkin–Elmer-297 spectrophotometer. ^1H NMR spectra were recorded in $CDCl_3$ on a Brucker DPX-200 (200 MHz) or a Brucker AVANCE 300 (300 MHz) instrument and are reported in parts per million (ppm) downfield from tetramethylsilane as internal standard. ^{13}C

NMR spectra were recorded in $CDCl_3$ on a BRUCKER AVANCE 300 (75 MHz) instrument. Optical rotations were measured on a JASCO DIP-360 polarimeter. Elemental analyses were performed at the Indian Association for the Cultivation of Science. All reactions were carried out under a nitrogen atmosphere. Reactions were monitored by thin layer chromatography (TLC) on glass plates precoated with silica gel G (Tara Chemicals). Compounds were visualized by staining with iodine or warming on a hot plate after spraying with aqueous H_2SO_4. Column chromatography was performed on silica gel (60–120 mesh, Tara Chemicals). Light petroleum refers to the fraction boiling at 60–80°C range. The α-amino diazoketone **5** was prepared from L-alanine (**4**) according to the method of Ye and McKervey.[11]

1.1.1. (*S*)-3-(*t*-Butyloxycarbonylamino)-1-(*p*-toluenesulfonyl)butan-2-one (6). 47% HBr (0.3 ml, 6.0 mmol) was added dropwise to a solution of the α-amino diazoketone **5**[11] (0.60 g, 2.8 mmol) in ether (15 ml) at 0°C. After 30 min, the reaction was neutralized with satd $NaHCO_3$ solution and the ether layer was separated. It was washed with water, dried (Na_2SO_4) and the solvent removed in vacuo to give the corresponding α-bromo ketone. The latter was dissolved in DMF (5 ml) and $NaSO_2Tol$ (0.55 g, 3.1 mmol) was added to it at room temperature. After 30 min, the reaction was diluted with CH_2Cl_2 (10 ml) and washed with water. The organic layer was dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by column chromatography over silica gel (30% EtOAc in light petroleum) to give **6** (0.67 g, 70%) as a white crystalline solid; mp 121–122°C (ether–light petroleum); [Found: C, 56.24; H, 6.80; N, 4.05%; $C_{16}H_{23}NO_5S$ requires: C, 56.28; H, 6.80 and N, 4.10%]; $[\alpha]_D^{20}=-1.8$ (*c* 1.8, $CHCl_3$); ν_{max} ($CHCl_3$) 3420, 2980, 1700, 1590, 1490, 1445, 1360, 1320, 1220, 1150 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.24 (d, 3H, *J*=8.0 Hz, *Me*), 1.44 (s, 9H, $C(CH_3)_3$), 2.45 (s, 3H, Ph-*Me*), 4.21 (d, 1H, *J*=13.8 Hz, NCH–C*H*–SO_2), 4.29–4.36 (m, 1H, NC*H*Me–), 4.42 (d, 1H, *J*=13.8 Hz, NCH–C*H*–SO_2), 5.18 (br s, 1H, N*H*), 7.36 (d, 2H, *J*=8.0 Hz, *Ph*), 7.77 (d, 2H, *J*=8.1 Hz, *Ph*); δ_C (75 MHz, $CDCl_3$) 16.3, 21.6, 28.2, 56.0, 63.3, 80.4, 128.4, 129.9, 135.9, 145.4, 155.2, 198.4.

1.1.2. (*S*)-Ethyl 7-(*t*-butyloxycarbonylamino)-6-oxooct-2-enoate (7b). Ethyl γ-bromocrotonate (0.17 g, 0.87 mmol) was added to a mixture of the γ-amino-β-keto sulfone **6** (0.30 g, 0.87 mmol) and K_2CO_3 (0.13 g, 0.96 mmol) in DMF (3 ml) at room temperature and the mixture stirred for 5 h. It was then acidified with dil. HCl and diluted with CH_2Cl_2 (15 ml). The aqueous layer was separated and the organic layer was washed with water and dried (Na_2SO_4). Removal of solvent under reduced pressure followed by column chromatography over silica gel (20% EtOAc in light petrioleum) gave the α-alkylated γ-amino-β-keto sulfone (**7a**) as a 50:50 diastereomeric mixture (by NMR). Freshly prepared Al(Hg) (from aluminum foil (0.3 g) and 2% aqueous $HgCl_2$ solution] was added to a solution of **7a** in THF–H_2O (9:1, 7 ml) and the mixture heated under reflux for 6 h. The reaction mixture was filtered, washed with THF and the filtrate diluted with CH_2Cl_2 (10 ml). It was washed with water, dried (Na_2SO_4) and the solvent removed under reduced pressure. The residue was purified by column chromatography over silica gel (20% EtOAc in light petroleum) to give **7b** (0.23 g, 86%) as a colorless oil; [Found: C, 60.12; H, 8.32; N, 4.75%; $C_{15}H_{25}NO_5$ requires: C, 60.18; H, 8.42 and N, 4.68%]; $[\alpha]_D^{20}=-2.0$ (*c* 1.0, $CHCl_3$); ν_{max} (neat) 3350, 2920, 1710, 1650, 1500, 1440, 1360, 1250, 1145 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.28 (t, 3H, *J*=7.5 Hz, CH_3CH_2O–), 1.32 (d, 3H, *J*=7.3 Hz, *Me*), 1.44 (s, 9H, $C(CH_3)_3$), 2.40–2.80 (m, 4H, CO–CH_2CH_2–CH═), 4.18 (q, 2H, *J*=7.1 Hz, CH_3CH_2O–), 4.21–4.33 (m, 1H, NC*H*Me), 5.10 (br s, 1H, NH), 5.84 (d, 1H, *J*=15.6 Hz, CH═C*H*–CO_2Et), 6.91 (dt, 1H, *J*=6.6, 15.6 Hz, CH_2–C*H*═CH); δ_C (75 MHz, $CDCl_3$) 14.2, 17.6, 25.7, 28.3, 37.1, 55.0, 60.2, 79.8, 122.3, 146.6, 155.4, 166.3, 208.0.

1.1.3. (6*R*,7*S*)-Ethyl 6-acetoxy-7-(*t*-butyloxycarbonylamino)oct-2-enoate (8). $NaBH_4$ (0.02 g, 0.6 mmol) was added to a solution of **7b** (0.15 g, 0.5 mmol) in MeOH (5 ml) at −50°C. After 15 min, the reaction was quenched with brine and the whole extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and the solvent removed under reduced pressure to give the hydroxy ester. The latter was dissolved in CH_2Cl_2 (3 ml) and was treated with Ac_2O (0.06 g, 0.06 ml, 0.06 mmol), Et_3N (0.06 g, 0.6 mmol) and a catalytic amount of DMAP at room temperature. After completion of the reaction (ca. 3 h), more CH_2Cl_2 (10 ml) was added and the whole washed with water. The organic layer was dried (Na_2SO_4) and the solvent removed under reduced pressure. The residue was purified by column chromatography over silica gel (30% EtOAc in light petroleum) to give **8** (0.15 g, 83%) as a colorless oil; [Found: C, 59.42; H, 8.55; N, 4.14%; $C_{17}H_{29}NO_6$ requires: C, 59.46; H, 8.51 and N, 4.08%]; $[\alpha]_D^{20}=-4.2$ (*c* 1.0, $CHCl_3$); ν_{max} (neat) 3340, 2970, 1700 (br), 1500, 1450, 1360, 1240 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.10 (d, 3H, *J*=6.9 Hz, *Me*), 1.28 (t, 3H, *J*=7.2 Hz, CH_3CH_2O–), 1.44 (s, 9H, $C(CH_3)_3$), 1.65–1.77 (m, 2H, CH_2–CH_2–CH═), 2.07 (s, 3H, $COCH_3$), 2.17–2.31 (m, 2H, CH_2–CH_2–CH═), 3.86 (m, 1H, NC*H*Me), 4.18 (q, 2H, *J*=7.2 Hz, CH_3CH_2O–), 4.58 (br s, 1H, NH), 4.84–4.89 (m, 1H, C*H*–OCO), 5.82 (d, 1H, *J*=15.6 Hz, CH═C*H*–CO_2Et), 6.92 (dt, 1H, *J*=6.9, 15.6 Hz, CH_2–C*H*═CH); δ_C (75 MHz, $CDCl_3$) 14.2, 15.6, 18.5, 21.0, 28.3, 48.3, 60.2, 75.7, 80.2, 121.9, 147.5, 155.1, 166.4, 170.3.

1.1.4. 3-Acetoxy-6-ethoxycarbonylmethyl-2-methylpiperidine (10a,b). Trifluoroacetic acid (0.40 g, 0.25 ml, 3.48 mmol) was added to a solution of **8** (0.10 g, 0.29 mmol) in CH_2Cl_2 (2 ml) at 0°C and the solution stirred at room temperature for 1 h. All volatiles were then removed under reduced pressure and the residue was redissolved in CH_2Cl_2 (3 ml). Excess Et_3N (0.15 g, 0.2 ml, 1.45 mmol) was added to it and the mixture stirred overnight at room temperature. The reaction was then diluted with CH_2Cl_2 (10 ml) and washed with water. The organic layer was dried (Na_2SO_4) and the solvent removed under reduced pressure. The residue was purified by column chromatography over silica gel (30–50% EtOAc in light petroleum) to give the cyclized products **10a** and **b**.

10a (0.024 g, 34%); mp 52–53°C (EtOAc–light petroleum); [Found: C, 59.40, H, 8.59, N, 5.82%; $C_{12}H_{21}NO_4$ requires: C, 59.24, H, 8.70 and N, 5.76%]; $[\alpha]_D^{20}=-6.9$ (*c* 0.5, $CHCl_3$); ν_{max} ($CHCl_3$) 3320, 2940,

1725, 1575, 1430, 1365, 1280 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.07 (d, 3H, J=6.1 Hz, *Me*), 1.25 (t, 3H, J=7.1 Hz, CH_3CH_2O-), 1.25–1.39 (m, 3H), 1.67–1.71 (m, 1H), 2.04 (s, 3H, $OCOCH_3$), 2.04–2.11 (m, 1H), 2.30–2.44 (m, 2H, EtO_2CCH_2-CH), 2.74 (dq, 1H, J=6.0, 9.0 Hz, Me–C*H*–N), 2.96–3.00 (m, 1H, EtO_2CCH_2-CH-N), 4.14 (q, 2H, J=7.1 Hz, CH_3CH_2O-), 4.35 (ddd, 1H, J=4.6, 5.5, 9.8 Hz, AcOC*H*–CHN); δ_C (75 MHz, $CDCl_3$) 14.1, 18.8, 21.1, 30.1, 31.2, 40.6, 52.5, 55.4, 60.4, 75.4, 170.4, 172.2.

10b (0.034 g, 48%); colorless oil; [Found: C, 59.33, H, 8.51, N, 5.89%; $C_{12}H_{21}NO_4$ requires: C, 59.24, H, 8.70 and N, 5.76%]; $[\alpha]_D^{20}$=+4.2 (*c* 0.3, $CHCl_3$); ν_{max} ($CHCl_3$) 3320, 2940, 1725, 1580, 1430, 1365, 1230 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.15 (d, 3H, J=6.6 Hz, *Me*), 1.26 (t, 3H, J=7.1 Hz, CH_3CH_2O-), 1.40–1.60 (m, 1H), 1.62–1.70 (m, 2H), 1.80–1.94 (m, 2H), 2.07 (s, 3H, $OCOCH_3$), 2.39 (dd, 1H, J=5.4, 15.6 Hz, EtO_2CCH_2-CH), 2.57 (dd, 1H, J=8.2, 15.5 Hz, EtO_2CCH_2-CH), 3.08 (dq, 1H, J=6.0, 6.8 Hz, Me–C*H*–N), 3.30–3.40 (m, 1H, EtO_2CCH_2-CH-N), 4.15 (q, 2H, J=7.0 Hz, CH_3CH_2O-), 4.35–4.58 (m, 1H, AcOC*H*–CHN); δ_C (75 MHz, $CDCl_3$) 14.2, 17.6, 21.3, 24.5, 27.6, 38.9, 46.8, 50.1, 60.4, 73.0, 170.4, 172.1.

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