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FORMAL SYNTHESIS OF (-)-VALLESAMIDINE A 2,2,3-TRIALKYLINDOLINE ALKALOID

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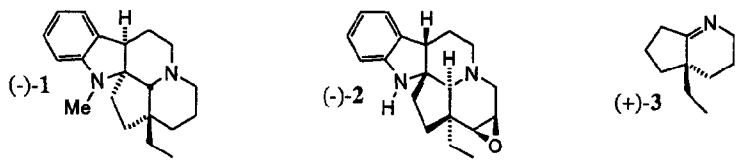
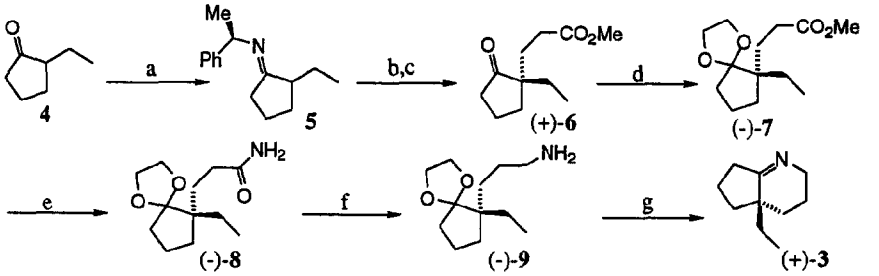
Abstract: (S)-(+)-2-ethyl-2[2'-carboxymethyl]cyclopentanone **6** was prepared regio- and enantioselectively (ee = 90%) by "deracemizing alkylation" of the chiral imine **5** with methylacrylate. Compound **6** was transformed into the bicyclic imine (R)-(+)-**3**. This intermediate was used by Heathcock, in the racemic form, to the total synthesis of (±)-Vallesamidine **1**, a 2,2,3-trialkylindoline alkaloid.

The interest in Aspidosperma, Hunteria and Strychnos alkaloids is reflected in the numerous syntheses of these compounds either in their racemic or optically active forms.[1-4] However, much less attention has been given to 2,2,3-trialkylindoline alkaloids, such as (-)-vallesamidine **1** and (-)andragine **2**[5]



Recently, Heathcock and coworkers[5,6] described a new approach for the synthesis of (±)-**1** by using, in the key step, the reaction between (±)-**3** and *ortho*-nitrocinnamic acid. In this work we describe the first enantioselective synthesis of (+)-**3**; via the "deracemizing alkylation"[7] of the chiral imine **5** (Scheme).



Scheme: a) R-(+)-1-phenylethylamine, toluene, TsOH cat., reflux; b) methyl acrylate, R.T.; c) 10% aq. AcOH, R.T., 70%; d) $(CH_2OH)_2$, toluene, TsOH cat., reflux, 75%; e) Aq. NH_4OH, R.T., 90%; f) $LiAlH_4$, THF, reflux, 100%; g) 10% aq. R.T., 96%.

Compound 5, easily obtained from (±)-2-ethyl-cyclopentanone (4) and R-(+)-1-phenylethylamine, was alkylated with methyl acrylate leading, after hydrolysis, to S-(+)-**6** in 70% yield, as the only regioisomer detected in the ^1H and ^{13}C NMR spectra. The same regioselectivity was observed when (±)-**6** was synthesized by the same reaction sequence, but using benzylamine instead of R-(+)-1-phenylethylamine. Comparison of ^1H NMR spectra of (±)-**6** and S-(+)-**6**, recorded in the presence of $Eu(tfc)_3$, showed that this last compound was present in 90% of enantiomeric excess.[8] The absolute configuration S for (+)-**6** was assigned based on the previously proposed reaction mechanism[7,9,10] for the "deracemizing alkylation" of chiral imines, as well as on our published results.[11]

The ketalamine (-)-**8** was easily obtained by ketalization of (+)-**6** to give (+)-**7**, followed by reaction of this compound with aq. ammonium hydroxide. Reduction of (-)-**8** with LAH led to the amine (-)-**9**. A one pot hydrolysis of the ketal group, followed by cyclic Schiff base formation took place when (-)-**9** was allowed to react with 10% aq. hydrochloric acid, leading to (+)-**3**. Since no epimerization of the quaternary stereogenic center can occur under the conditions used, one can assume that **3** was obtained in the S configuration, in 90% e.e. It is noteworthy that in the described synthetic sequence only compounds S-(+)-**6** and S-(-)-**7** must be purified. From S-(-)-**7** to R-(+)-**3**, the crude products obtained were shown to be pure by high resolution gas chromatography, giving satisfactory ^{1}H and ^{13}C NMR spectra and high resolution mass spectra. Since both R-(+)- and S-(-)-1-phenyl-ethylamine are commercially available, the bicyclic imine **3** can be obtained in both absolute stereochemistries.

Experimental Section:

(S)-(+)-2-ethyl-2-2'-carboxymethyl-ethylcyclopentanone 6: This compound was synthesized from rac-2-ethyl-cyclopentanone by using the "deracemizing alkylation" protocol described in ref. 7. $[\alpha]_D^{20}$ + 27.5 (c = 14.52 mg/mg, CCl_4), 90% ee (established by ^{1}H NMR spectroscopy using $Eu(tfc)_3$ as chiral shift reagent - $CDCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 0.76 (t,3), 1.35 - 1.45 (m,2); 1.60 - 1.90 (m,6), 2.15 - 2.37 (m, 4), 3.63 (s,3). ^{19}C NMR ($CDCl_3$): 8.31, 18.51, 26.82, 29.91, 33.23, 38.11, 50.95, 51.56, 173.89, 222.27. HRMS for $C_{11}H_{18}O_3$ calcd. 198.125595, found 198.125504.

(S)-(+)-4a-ethyl-3,4,4a,5,6,7-hyexahydro-2H-1-pyridine 3. A solution of (-)-ketalamine 9 (0.213 g, 1 mmol) in 2.7 ml of aq. 10% HCl and some drops of THF was stirred at room temperature for 3 h. The mixture was then diluted with 5 ml of diethyl ether and the organic phase was separated. After the aqueous phase was made alkaline by addition of concentrated NaOH (pH 9) it was extracted with CH_2Cl_2 (5 x 10 ml). The combined organic layers were dried over Na_2SO_4, filtered, and the excess solvent was removed by rotatory evaporator under reduced pressure to give 0.136 g (95%) of 3 as a pale yellow oil. $[\alpha]_D^{20}$ + 5.1 (c = 1.03 CH_2Cl_2). IR (film): 1678 cm^{-1}. MS (70eV): m/z 122(100), 151(39), 95(35), 136(21), 108(20), 41(12), 55(10). ^{1}H NMR ($CDCl_3$): 0.83 (t, 3, J = 7.0 Hz), 1.00 - 1.51 (m,1), 1.16 - 1.25 (m,1), 1.26 - 1.40 (m,2), 1.41 - 1.75 (m,4), 1.85 - 1.95 (m,2), 2.10 - 2.25 (m,1), 2.40 - 2.55 (m,1), 3.40 - 3.61 (m,2). ^{13}C NMR ($CDCl_3$): 7.84, 17.65, 17.96, 24.75, 27.83, 32.29, 35.28, 42.19, 48.50, 182.66. HRMS for $C_{10}H_{17}N$ calcd. 151.123524, found 251.102146.

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8. The ee in (+)-**6** was determined by the integration of the triplets corresponding to the methyl groups. The relationship was corrected taking into consideration the fact that (R)-(+)-1-phenylethylamine used was 90% optically pure.
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