A NEW ENANTIOSELECTIVE ROUTE TO (+)-QUEBRACHAMINE

Morio Asaoka* and Hisashi Takei
Department of Life Chemistry, Tokyo Institute of Technology,
Nagatsuta, Midori-ku, Yokohama 227, Japan

Abstract - Formal synthesis of (+)-quebrachamine was achieved using a new chiral building block 3-ethyl-5-trimethylsilyl-2-cyclohexenone.

Pictet-Spengler condensation has widely been used in the syntheses of isoquinoline and indole alkaloids, because of its general applicability. For the chiral synthesis of (+)-quebrachamine, the parent base of Aspidosperma indole alkaloid, based on Pictet-Spengler condensation, an efficient preparation of suitably functionalized C9 unit with chiral quaternary carbon center is necessary.1 Concerning with our recent effort for the construction of optically active quaternary carbon center starting from newly developed building block, 5-trimethylsilyl-2-cyclohexenone,2 a formal synthesis of (+)-quebrachamine via an efficient preparation of a new C9 unit was carried out. The optically pure enone (S)-1 ([α]D 22+52.95° (c 1.08, CHCl3), bp 102-103°C/5 mmHg, mp 25-28°C) was easily prepared from (R)-(−)-5-trimethylsilyl-2-cyclohexenone via reaction with ethyllithium followed by oxidation with PCC in 90% overall yield.2 Hydrocyanation of 1 with Et2AlCN3 in THF at -40°C-rt gave (3R,5S)-2 as an exclusive diastereoisomer [75%, [α]D 27-80.00° (c 1.00, CHCl3), mp 66-66.5°C].4 Hydrolysis (conc. HCl, reflux 30 h) and esterification [(MeO)3CH, MeOH, cat. TSOH, reflux 30 h, and then acetone-water, cat. TSOH, rt, 0.5 h) of 2 gave slightly impure 3 in almost quantitative yield. Baeyer-Villiger oxidation of the crude 3 with m-CPBA (CH2Cl2-H2O, Na2HPO4, at 0°C-rt) proceeded regiospecifically directed by TMS group5 to give 7-membered lactone 4 [80% from 2, [α]D 25+56.36° (c 1.54, CHCl3), mp 41-42°C]. Reduction of 4 with DIBAH in THF at -100°C gave hemiacetal derivative 5 in 87% yield which reacted with tryptamine in 90% acetic acid at reflux for 5 h to give 6a6 and 6b6 in 84% combined yield [(5S)-6a: 41%, [α]D 22+189.5° (c 0.433, CHCl3), mp 183.5-185°C, lit.1b (5R)-6a: [α]D -161.7° (c 1.066, CHCl3), mp 182-184°C; (5S)-6b: 43%, [α]D 22-133.3° (c 0.527, CHCl3), mp 116-118.5°C, lit.1b (5R)-6b: [α]D +126.6° (c 1.160, CHCl3), mp 113-116°C]. Both (5S)-6a
and (5S)-6b are reported to give (+)-quebrachamine via amino alcohol 7a,b.\textsuperscript{1a,b}

Thus the present synthesis provides a new efficient enantioselective route to (+)-quebrachamine.

\( \text{[Equation]} \)

\[ \text{(5S)-6b} \]

\[ \text{(3R,SS)-2} \]

\[ \text{3} \]

\[ \text{m-CPBA} \]

\[ \text{4} \]

\[ \text{DIBAH} \]

\[ \text{TMSO} \]

\[ \text{(RR)-Tryptamine} \]

\[ \text{5} \]

\[ \text{(5S)-6a,b} \]

\[ \text{7a,b} \]

\( \text{(+)-quebrachamine} \)

\( \text{REFERENCES AND NOTES} \)


4) The absolute stereochemistry of 2 was tentatively assigned at this stage and it was confirmed by the transformation to lactam derivative 6.


6) (5S)-6a: \( ^1\text{H-nmr (CDCl}_3\): \( \delta = 0.72(3\text{H, t, } J=7\text{Hz}), 1.20-3.40(10\text{H, m}), 4.33-5.25(3\text{H, m, vinylic CH}_2\text{ and C-3 proton}), 5.43-6.12(1\text{H, m, vinylic CH}), 6.84-7.47(4\text{H, m, aromatic}), 8.63(1\text{H, br s, NH}); \text{ir (KBr): 3270 (NH), 1660 cm}^{-1} (\text{C=O}); \text{ms: 294(M}^+)\).

(5S)-6b: \( ^1\text{H-nmr (CDCl}_3\): \( \delta = 0.97(3\text{H, t, } J=7\text{Hz}), 1.45-3.40(10\text{H, m}), 4.32-5.06(3\text{H, m, vinylic CH}_2\text{ and C-3 proton}), 5.20-5.93(1\text{H, m, vinylic CH}), 6.86-7.50(4\text{H, m, aromatic}), 8.86(1\text{H, br s, NH}); \text{ir (KBr): 3260 (NH), 1660 cm}^{-1} (\text{C=O}); \text{ms: 294(M}^+)\).