A NEW ENANTIOSELECTIVE ROUTE TO (+)-QUEBRACHAMINE

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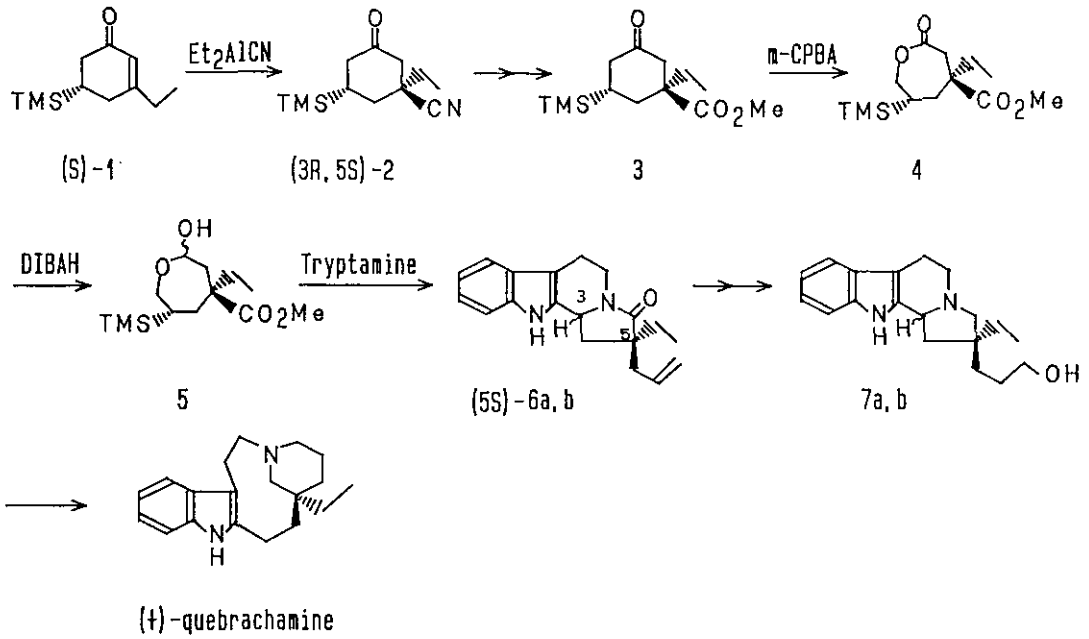
Abstract - Formal synthesis of (+)-quebrachamine was achieved using a new chiral building block 3-ethyl-5-trimethylsilyl-2-cyclohexenone.

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 C_9 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 C_9 unit was carried out.

The optically pure enone (S)-**1** [$[\alpha]_D^{22}$+52.95°(c 1.08, $CHCl_3$), 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 Et_2AlCN[3] in THF at -40°C-rt gave (3R,5S)-**2** as an exclusive diastereoisomer [75%, $[\alpha]_D^{27}$-80.00°(c 1.00, $CHCl_3$), 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 (CH_2Cl_2-H_2O, Na_2HPO_4, at 0°C-rt) proceeded regiospecifically directed by TMS group[5] to give 7-membered lactone **4** [80% from **2**, $[\alpha]_D^{25}$+56.36°(c 1.54, $CHCl_3$), 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 **6a**[6] and **6b**[6] in 84% combined yield [(5S)-**6a**: 41%, $[\alpha]_D^{22}$+189.5°(c 0.433, $CHCl_3$), mp 183.5-185°C, lit.[1b] (5R)-**6a**: $[\alpha]_D$-161.7°(c 1.066, $CHCl_3$), mp 182-184°C; (5S)-**6b**: 43%, $[\alpha]_D^{22}$-133.3°(c 0.527, $CHCl_3$), mp 116-118.5°C, lit.[1b] (5R)-**6b**: $[\alpha]_D$+126.6°(c 1.160, $CHCl_3$), mp 113-116°C]. Both (5S)-**6a**

and (5S)-**6b** are reported to give (+)-quebrachamine via amino alcohol **7a,b.**[1a,b] Thus the present synthesis provides a new efficient enantioselective route to (+)-quebrachamine.



REFERENCES AND NOTES

1)a)S. Takano, K. Chiba, M. Yonaga, and K. Ogasawara, J. Chem. Soc., Chem. Commun., 1980, 616; b)S. Takano, M. Yonaga, and K. Ogasawara, **ibid.**, 1981, 1153; c)M. Node, H. Nagasawa, and K. Fuji, J. Am. Chem. Soc., 1987, **109**, 7901.

2)M. Asaoka, K. Takenouchi, and H. Takei, Tetrahedron Lett., 1988, **29**, 325.

3)M. Samson and M. Vandewalle, Synth. Commun., 1987, **8**, 231.

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

5)P. F. Hudrlik, A. M. Hudrlik, G. Nagendrappa, T. Yimenu, E. T. Zellers, and E. Chin, J. Am. Chem. Soc., 1980, **102**, 6894.

6)(5S)-**6a**: ^{1}H-nmr ($CDCl_3$): δ =0.72(3H, t, J=7Hz), 1.20-3.40(10H, m), 4.33-5.25(3H, m, vinylic CH_2 and C-3 proton), 5.43-6.12(1H, m, vinylic CH), 6.84-7.47(4H, m, aromatic), 8.63(1H, br s, NH); ir (KBr): 3270 (NH), 1660 cm^{-1} (C=O); ms: 294(M^+).
(5S)-**6b**: ^{1}H-nmr ($CDCl_3$): δ =0.97(3H, t, J=7Hz), 1.45-3.40(10H, m), 4.32-5.06(3H, m, vinylic CH_2 and C-3 proton), 5.20-5.93(1H, m, vinylic CH), 6.86-7.50(4H, m, aromatic), 8.86(1H, br s, NH); ir (KBr): 3260 (NH), 1660 cm^{-1} (C=O); ms: 294(M^+).

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