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A FACILE SYNTHESIS OF (±)-SESBANINE VIA γ-ADDITION OF KETENE SILYL ACETAL WITH QUATERNIZED METHYL NICOTINATE

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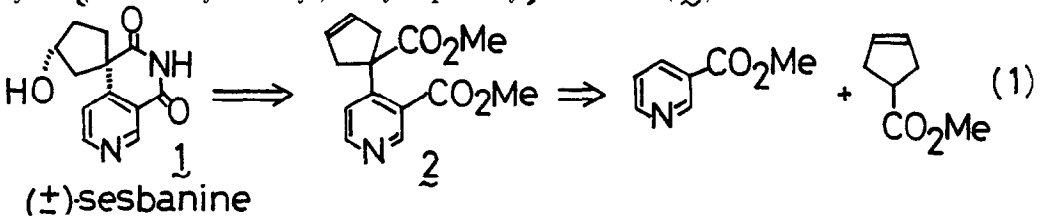
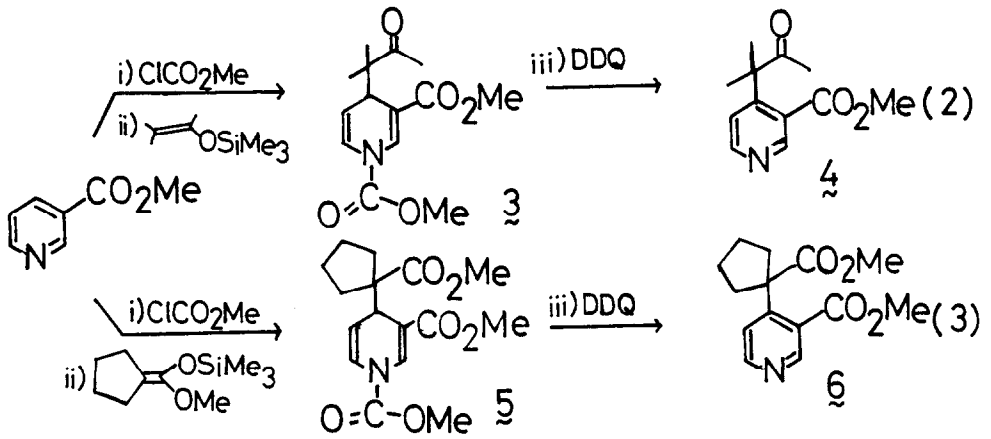
Abstract : Total synthesis of (±)-sesbanine (1) was carried out using γ-addition of ketene silyl acetal of methyl 3-cyclopentenecarboxylate to quaternized methyl nicotinate. The resulting 1, 4-dihydropyridine (7) was oxidized with DDQ to give 4-substituted nicotinate (2) and 2 was converted to alcohol (8) by stereoselective oxymercuration followed by treatment with ammonia to give 1.

Highly regioselective introduction of substituents into 4-position of pyridine has been achieved recently by quaternization of the nucleus followed by reaction with organometallic reagents[1] or phosphite.[2] In connection with the subject, we developed a convenient and practical method for the synthesis of 4-(2-oxoalkyl)pyridines via regioselective γ-addition of silyl enol ethers to pyridinium salts.[3] Now we report a facile synthesis of (±)-sesbanine (1), which has antileukemic activity,[4] using the above mentioned method as a key reaction. According to the retrosynthesis of 1 as shown in eq 1, the key intermediate should be methyl 4-[(1-methoxycarbonyl)-3-cyclopentenyl]nicotinate (2).



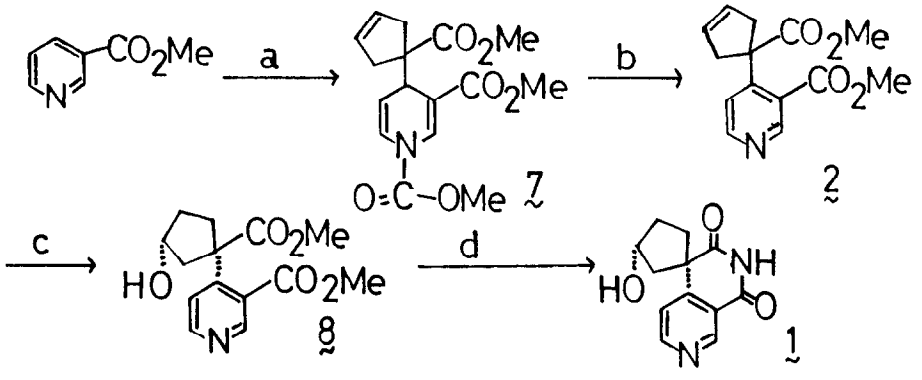
(1)

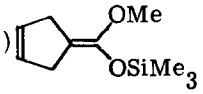
Hence, we first tried to prepare 4-substituted nicotinates (4 and 6) as shown below. The 1, 4-dihydropyridines (3 and 5) were obtained in dichloromethane in high yields (3, 93%; 5, 94%) without the formation of any regioisomer. Oxidation of 3 and 5 with oxygen or silver nitrate did not proceed contrary to those without the methoxycarbonyl group at 3-position.[3] The oxidation took place by refluxing 3 and 5 with an equimolar amount of DDQ in benzene for ca.6 h (4, 63%; 6, 60%).



Thus, (±)-sesbanine was synthesized in 40% total yield via only four steps starting from methyl nicotinate as outlined in the Scheme.

Scheme



(a) (i) $ClCO_2Me$, CH_2Cl_2, 0 °C, 10 min (ii)  , rt, 30 min

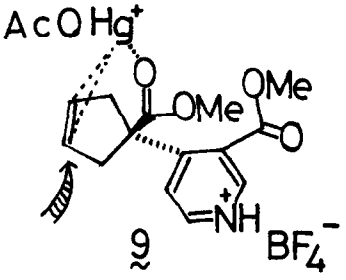
(b) DDQ, C_6H_6, reflux 6 h

(c) (i) aq. HBF_4, THF, rt (ii) $Hg(OAc)_2$, THF-H_2O, rt, 1 h
(iii) 5% aq. Na_2CO_3 (pH 8~9), $NaBH_4$

(d) NH_3, MeOH, 100 °C, 3 h in a sealed tube

Condensation of the pyridinium salt generated in situ with ketene silyl acetal of methyl 3-cyclopentenecarboxylate[5] gave the corresponding 1, 4-dihydropyridine derivative (7),[6] which was converted into methyl 4-[(1-methoxycarbonyl)-3-cyclopentenyl]nicotinate (2)[7] by using DDQ as an oxidizing reagent in 77% yield (from methyl nicotinate). Standard oxymercuration of 2 did not afford the desired alcohol at all, presumably due to the formation of the nitrogen-mercuric acetate complex.[8] Therefore, 2 was treated with HBF_4 first and with $Hg(OAc)_2$ in aqueous THF, then the mixture was reduced carefully

with $NaBH_4$. Fourtunately, the desired alcohol (8)[9] was obtained stereoselectively in 64% yield together with the epimeric alcohol (7%). The stereoselective formation of 8 can be explained by the preferable formation of mercuric acetate complex (9) in which the mercury (II) is held on the same side as the ester group by coordination. The complex (9) is attacked by a water molecule from the opposite side of the mercury (II) to give 8. This rationalization is supported by the literature that Lewis base groups (OMe, OAc, CO_2Me, CH_2OH, CN) can exert a directing effect on the stereochemistry of addition of HgX and OR at a double bond by coordination.[10]



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The final stage for the synthesis of (±)-sesbanine (1) was achieved in 86% yield by heating 8 in methanolic NH_3 at 100 °C in a sealed tube.[4f] The spectral data and melting point of the synthetic alkaloid (1) thus obtained were in agreement with those of the literature.[11]

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References and Notes

1. a) E. Piers and M. Soucy, Can. J. Chem., 52, 3563 (1974). b) D. L. Comins and A. H. Abdullah, J. Org. Chem., 47, 4315 (1982). c) D. L. Comins, Tetrahedron Lett., 24, 2807 (1983). d) K. Akiba, Y. Iseki, and M. Wada, ibid., 23, 429 (1982). e) K. Akiba, Y. Iseki, and M. Wada, ibid., 23, 3935 (1982). f) K. Akiba, Y. Iseki, and M. Wada, Bull. Chem. Soc. Jpn., 57, 1994 (1984).
2. K. Akiba, H. Matsuoka, and M. Wada, Tetrahedron Lett., 22, 4093 (1981).
3. K. Akiba, Y. Nishihara, and M. Wada, ibid., 24, 5269 (1983).
4. a) R. G. Powell, C. R. Smith. Jr, D. Weisleder, D. A. Muthard, and J. Clardy, J. Am. Chem. Soc., 101, 2784 (1979). For synthesis of sesbanine, see : b) A. S. Kende and T. P. Demuth, Tetrahedron Lett., 21, 715 (1980). c) J. C. Bottaro and G. A. Berchtold, J. Org. Chem., 45, 1176 (1980). d) M. J. Wanner, G-J, Koomen, and U. K. Pandit, Heterocycles., 15, 377 (1981). e) H. Iida, Y. Murayama, and T. Kikuchi, IUPAC Fourth International Conference on Organic Synthesis, Tokyo, Japan, Aug, 1982, Abstr, p 55. f) M. Iwao and K. Kuraishi, Tetrahedron Lett., 24, 2649 (1983). g) K. Tomioka and K. Koga, ibid., 21, 2321 (1980).

5. The ketene silyl acetal was prepared as follows. A mixture of methyl malonate and cis dichloro-2-butene was treated with 2 equiv. of NaH in DMF at 0 °C to afford the condensation product (60% yield), which was heated at 180 °C in HMPA-H_2O (20 : 1) in the presence of NaI (1 equiv.) for 30 min to give methyl 3-cyclopentenecarboxylate in 60% yield. The preparation of the ketene silyl acetal was easily accomplished with methyl 3-cyclopentenecarboxylate in 71% yield following the procedure of Tamura, et al. Y. Kita, J. Haruta, J. Segawa, and Y. Tamura, Tetrahedron Lett., 4311 (1979).

6. Data for 7: mp 109~111 °C ; ^{1}H NMR ($CDCl_3$) δ2.20~3.10 (m, 4H), 3.65 (s, 3H), 3.73 (s, 3H), 3.88 (s, 3H), 3.89 (d, 1H, J=5.0 Hz), 5.05 (dd, 1H, J=8.0, 5.0 Hz), 5.52 (s, 2H), 6.92 (dd, 1H, J=8.0, 1.0 Hz), and 7.97 (d, 1H, J=1.0 Hz) ; IR (KBr) 2950, 1710, 1705, 1235, and 980 cm^{-1} ; MS (m/e) 321 (M^+) ; Anal. Calcd for $C_{16}H_{19}NO_6$: C, 59.81 ; H, 5.96 ; N, 4.36. Found : C, 59.87 ; H, 6.08 ; N, 4.21.

7. The spectral data and melting point of 2 were in agreement with those of the literature.[4f] Data for 2: mp 40~41 °C (lit. 40.5~41 °C) ; ^{1}H NMR ($CDCl_3$) δ2.83 (d, 2H, J=15.0 Hz), 3.36 (d, 2H, J=15.0 Hz), 3.65 (s, 3H), 3.87 (s, 3H), 5.71 (s, 2H), 7.25 (d, 1H, J=5.0 Hz), 8.65 (d, 1H, J=5.0 Hz), and 9.03 (s, 1H) ; IR (KBr) 2950, 1710, 1585, 1435, 1285, and 670 cm^{-1} ; MS (m/e) 261 (M^+) ; Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36 ; H, 5.79 ; N, 5.36. Found : C, 64.60 ; H, 5.81 ; N, 5.10.

8. H. O. House, " Modern Synthetic Reactions ", 2nd ed, W. A. Benjamine, Menlo Park, Calif., 1972, pp 401~405.

9. The spectral data and melting point of 8 were in agreement with those of the literature.[4f] Data for 8: mp 129~130 °C (lit. 130.5~131 °C) ; ^{1}H NMR ($CDCl_3$) δ1.60~2.70 (m, 6H), 2.91 (dd, 1H, J=14.0, 6.0 Hz), 3.60 (s, 3H), 3.86 (s, 3H), 4.60 (bs, 1H), 7.54 (d, 1H, J=5.0 Hz), 8.65 (d, 1H, J=5.0 Hz), and 8.93 (s, 1H) ; IR (KBr) 3320, 2950, 1710, 1290, and 1040 cm^{-1} ; MS (m/e) 279 (M^+) ; Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.20 ; H, 6.14 ; N, 5.02. Found : C, 59.97 ; H, 6.23 ; N, 4.73.

10. a) H. O. House, " Modern Synthetic Reactions ", 2nd ed, W. A. Benjamine, Menlo Park, Calif., 1972, pp 391. b) H. B. Henbest and B. Nicholls, J. Chem. Soc., 227 (1959).

11. Data for 1: mp 238~240 °C (lit. 240~243 °C,[4a] 239~241.5 °C[4f]) ; ^{1}H NMR (DMSO-d_6) δ1.70~2.50 (m, 5H), 2.68 (dd, 1H, J=14.0, 5.0 Hz), 4.50 (bs, 1H), 4.99 (bs, 1H), 7.89 (d, 1H, J=5.0 Hz), 8.40~9.40 (b, 2H), and 9.90~11.2 (b, 1H) ; IR (KBr) 3500, 2800, 1710, 1690, and 1600 cm^{-1} ; MS (m/e) 232 (M^+) ; Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06 ; H, 5.21 ; N, 12.06. Found : C, 61.99 ; H, 5.23 ; N, 11.80.

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