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TOTAL SYNTHESIS OF N_a-METHYL-Δ^{18}-ISOKOUMIDINE, A POSSIBLE PRECURSOR OF THE KOUMINE TYPE INDOLE ALKALOIDS[1]

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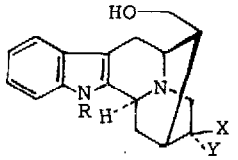
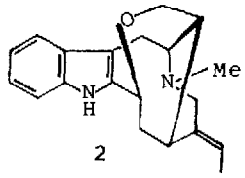
Abstract A novel total synthesis of title compound **3** is described.

The recent appearance of a communication from Magnus et al. on the total synthesis of (+)koumidine **1** and (+)taberpsychine **2**[2] prompts us to report our recent result on the total synthesis of the title compound **3**. Based on the transformation of (-)taberpsychine to natural (-)koumine **4**[3] and ready access of the former from koumidine[2,4], **3** might be considered as a key intermediate for the total synthesis of N_a-methyl koumine or, after demethylation, of koumine itself, inspite of the presence of a vinyl side chain in **3** instead of an ethylidene side chain in **1**.



1 X,Y:=$CHCH_3$(Z), R:H
3 X:H, Y:$CH=CH_2$, R:Me



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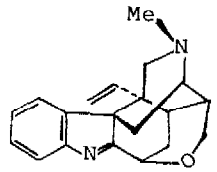

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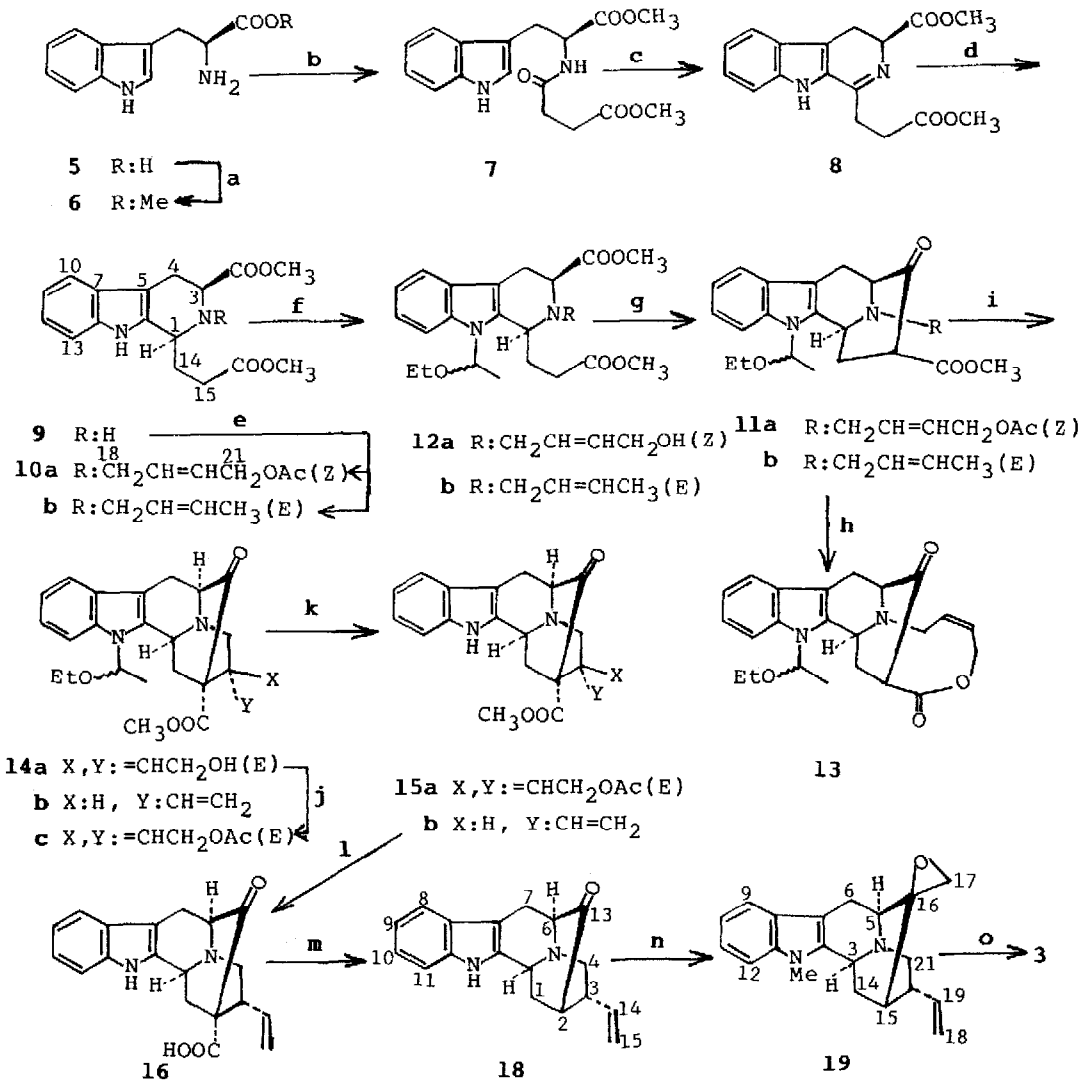
With our recently developed methodology of the asymmetric synthesis of 1,2,3,4-tetrahydro-β-carbolines in hand[5], L-tryptophan **5** was used as the starting materical for our approach. Treatment of the methyl ester of L-tryptophan **6**, which was obtained by exposure of L-tryptophan **5** to $SOCl_2$/MeOH/r.t./2d[6], with succinic half methyl ester acid chloride(Py/r.t./2d) afforded amide **7** in 81% yield, $[\alpha]_D$+80°(c1.1 in $CHCl_3$). The labile β-carboline **9** was obtained through a Bischler-Napieralski reaction($POCl_3$/60°C/10h), followed by hydrogenolysis of the resulting **8** (PtO_2/EtOH) in 99% yield[7]. N_b-alkylation of **9** to give **10** was achieved by treatment with 1-bromo-4-acetoxy-Z-butene-2 or 1-bromo-E-butene-2/$NaHCO_3$/CH_3CN. Exposure of **10** to CH_2=CHOEt/PTS(cat.)/30°C afforded the N_a-protected tetrahydro-β-carboline **11**. Then the Dieckmann cyclizations gave the expected β-keto esters **12**.

After the failure to complete the desired sarpagine ring system via a



Reagents and Conditions: **a**: $SOCl_2$, MeOH, rt, 2d. **b**: $MeOOCCH_2CH_2COCl$, Py, rt. 2d. **c**: $POCl_3$, 60°C, 10h. **d**: H_2, PtO_2; EtOH. **e**: $BrCH_2CH=CHCH_2OAc(Z)$ or $BrCH_2CH=CHCH_3(E)$, $NaHCO_3$, CH_3CN, reflux, 10h. **f**: $CH_2=CHOEt$, PTS(cat.), CH_2Cl_2, 30°C, 10h. **g**: **11a→12a**: NaH, MeOH(cat.), C_6H_6, reflux, 6h. **11b→12b**: $(Me_3Si)_2NNa$, DME, 100°C, 5.5h. **h**: DCC, CF_3COOH, DMSO, C_6H_6, Py, rt, 8h. **i**: $Mn(OAc)_3 \cdot H_2O$, $Cu(OAc)_2 \cdot H_2O$, HOAc, rt, 8h. **j**: Ac_2O, Py, rt, 24h. **k**: HOAc-MeOH-H_2O(2:1:1), 90°C, 2h. **l**: 2N KOH, MeOH, 60°C, 2h. **m**: N-hydroxy-2-pyridinethinone **17**, DCC, DMAP, THF or CH_2Cl_2, rt, 2d; then t-BuSH, hv, 2-3h. **n**: NaH, DMSO; then $(CH3)_3SI$, THF, rt, 20h. **o**: $AlClH_2$, THF, reflux, 5h.

Pd^{0} mediated alkylization of **12a**($Pd(PPh_3)_4$, As_2O_3), we attempted to oxidize **12a** with DCC/DMSO/CF_3COOH into the corresponding $\alpha\beta$-unsaturated aldehyde in order to conduct a subsequent intromolecular Michael addition. Quite unexpectedly, **12a** preferred an intromolecular ester exchange to form the 10-membered macrolacton **13** instead of undergoing the desired oxidation into the corresponding aldehyde.

We then turned to apply the recently developed cyclization process of alkenes[9] which might be more efficient in strained molecules. It involved a manganes(III)-based oxidative free radical cyclization, which was initiated by oxidation of β-carbonyl compound with $Mn(OAc)_3 \cdot H_2O/Cu(OAc)_2 \cdot H_2O$ in situ. Fortunately, in our case, treatment of **12** with $Mn(OAc)_3 \cdot H_2O/Cu(OAc)_2 \cdot H_2O$ in HOAc readily effected the expected cyclization in almost quantitative yield.

After removal of the N_a-protecting group in **14b**, **14c** by heating in HOAc:MeOH:H_2O=2:1:1, **15a** and **15b** were, respectively, obtained in good yield.

Many attempts to remove the bridge-head carboxylic group by conventional methods[12], have all failed. However, we finally found that Barton's decarboxylation method[11] proved effective in our case. Treatment of **16** with DCC/DMAP/**17** in excess dry THF or CH_2Cl_2, followed by the addition of t-BuSH and photolysis with a 300W tungsten slide lamp for several hours afforded **18** in 55% yield, $[\alpha]_D$+11.7°(c0.6in $CHCl_3$)[10].

At this stage all what we needed to do was to homologate the carbonyl group of **18** into a hydroxymethyl function in a stereospecific manner. While this carbonyl appeared to resist conventional Wittig reagents, treatment of **18** with $(CH_3)_2S{=}CH_2$/DMSO/THF/r.t., followed by reduction of the resulting epoxide **19** with AlH_2Cl/THF regio- and stereoseletively gave rise to N_a-methyl-Δ^{18}-iso-koumidine **3**[13].

Since N_a-methyl ajmaline has been recently converted into koumidine by Sakai[4], we believe that further elaboration of **3** would lead to Δ^{18}-iso-koumidine and eventully to the total synthesis of koumine.

The key intermediate **18** might also be an important precusor for synthesis of some other interesting indole alkaloids, such as the gelesmine type, the vobasine type, and the humantenine type. Those synthetic endeavors are now in progress in our laboratory. The crucial intromolecular radical cyclization (**12**→**14**) would offer a powerful way for constructing quinuclidine skeleton which might be valuable in other areas of alkaloid synthesis[14].

References and Notes

1. A part of our results was reported on the "2nd Sino-French Symposium on the Chemistry of Natural Products", Sept. 20-22, 1988, La Londe les Maures, France.

2. P.Magnus, B.Mugrage, M.DeLuca, G.A.Cain, J. Am. Chem. Soc., 1989, **111**, 786.
3. Z.J.Liu, Q.S.Yu, Youji Huaxue(Chin. J. Org. Chem.), 1986, **1**, 36; Acta Chim. Sinica, 1987, **2**, 181.
4. H.Takayama, M.Kitajima, S.Wongseripipatana, S.Sakai, J. Chem. Soc., Chem. Commun., in press(private communication with Prof. Sakai).
5. Z.J.Liu, F.Xu, to be published.
6. H.Peter, M.Brugger, J.Schreiber, A.Eschenmoser, Helv. Chim. Acta, 1963, **46**, 577.
7. The reduction **8**→**9** yielded within the limits of HPTLC and n.m.r. detection a single epimer, of which the C-3 configuration was determined as S (C-3H cis to C-5H) by applying the known ^{13}C NMR method[8] on its stable derivative **11a**. ^{13}C NMR specturm of **11a**:$\delta(CDCl_3)$:20.94(CH_3), 21.23(CH_2, 4-C), 28.94(CH_2, 15-C), 50.95(CH, 1-C), 51.64(OCH_3), 51.93(OCH_3), 55.64 (CH, 3-C), 59.40(CH_2, 18-C), 60.13(CH_2, 21-C), 106.70(C, 5-C), 110.89(CH, 13-C), 118.11(CH, 10-C), 119.33(CH, 11-C), 121.67(CH, 12-C), 126.85(C, 7-C), 131.39(CH, 19-C), 133.14(CH, 20-C), 136.17(2C, 6,8-C), 170.82(C=O), 173.65(C=O), 174.63(C=O)ppm.
8. (a) F.Ungemach, M.Dipierro, R.Veber, J.P.Cook, J. Org. Chem., 1981, **46**, 164.
   (b) P.D.Bailly, S.P.Hollinshead, Heterocycles, 1987, **26**, 389.
9. (a) B.B.Snider, M.A.Pombroski, J. Org. Chem., 1987, 52, 5487.
   (b) B.B.Snider, J.J.Patrica, S.A.Kates, ibid, 1988, 53, 2137.
   (c) J.R.Peterson, R.S.Egler, D.B.Horsley, T.J.Winter, Tetrahedron Lett., 1987, **28**, 6109.
10. **18**: IR(KCl): 1725cm^{-1}. ^1H NMR($CDCl_3$):1.79(1H, m, 1-Hax), 2.32(2H, m, 1-Heq), 2.46(1H, dXd, J_1=6Hz, J_2=13Hz, 4-Hax), 2.68(1H, dXd, J_1=8Hz, J_2=13Hz, 4-Heq), 2.78(2H, m, 2,3-H), 2.94(1H,dXd, J_1=6.2Hz, J_2=15.5Hz, 7-Hax), 3.31(1H, d(d), J_1=1Hz, J_2=15.5Hz, 7-Heq), 3.46(1H, m, 12b-H), 3.70 (1H, d(d), J_1=1Hz, J_2=6.2Hz, 6-H), 5.14(2H, m, 15-H), 5.62(1H, m, 14-H), 7.15(3H, m, 9,10,11-H), 7.49(1H, m, 8-H), 8.34(1H, s, 12-H)ppm.
11. (a) D.H.R.Barton, D. Chich, W.B. Motheruell, J. Chem. Soc.,Chem. Commun., 1983, 939.
   (b) D.H.R.Barton, S.Z.Zard, Pure and Appld. Chem., 1986, 675.
   (c) D.H.R.Barton, D.Bridon, I.F.Picot, S.Z.Zard, Tetrahedron, 1987, **43**, 2733.
   (d) D.H.R.Barton, B.Lacher, B.Misterkiewicz, S.Z.Zard, ibid, 1988, **44**, 1153.
12. (a) A.P.Krapcho, Synthesis, 1982, 805, 893.
   (b) N.Yoneda, Chem. Pharm. Bull., 1965, **13**, 1231.
13. **3**: IR($CHCl_3$): 3400cm^{-1}. MS:308(M^+), 290, 183(base peak).
14. All new compounds were characterized by ^1H NMR, ^{13}C NMR, IR, HRMS and/or microanalysis.

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