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A HIGH YIELD CYCLIZATION REACTION FOR THE FRAMEWORK OF ASPIDOSPERMA ALKALOIDS SYNTHESIS OF (±)-KOPSININE AND ITS RELATED ALKALOIDS

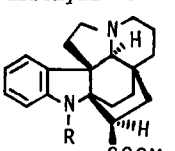
Masashi Ogawa, Yoshinori Kitagawa, and Mitsutaka Natsume*
Research Foundation Itsuu Laboratory
2-28-10 Tamagawa, Setagaya-ku, Tokyo 158, Japan

Summary: Formal synthesis of (±)-kopsinine (1) and its related alkaloids 2 – 4 was accomplished using a high-yield reaction (11 → 12) effected with a base.

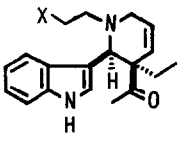
Previously we reported a formal synthesis of (±)-vindorosine (7) utilizing our novel reaction (5 → 6) to produce the framework of aspidospermidine.[1,2] In order to make this reaction more general, we have extensively studied an analogous cyclization reaction of methoxycarbonyl homologue 11, and here established a reaction condition for construction of the methyl aspidospermidine-3-carboxylate system 12 in a high yield. Using this result, synthesis of (±)-kopsinine (1) and its related alkaloids 2, 3, and 4 was achieved in the formal sense.

Formation of the β-ketoester functionality as in 9 was performed by treatment of the methyl ketone derivatives 8a[2] and 8b[3] with lithium bis(trimethylsilyl)amide [$(TMS)_2NLi$] (4 equiv) in THF-HMPA at -70°C for 30 min, followed by reaction with NC-COOMe[4] (4.8 equiv) at -70°C for 10 min. The expected substances 9a and 9b were obtained in 92% and 89% yields, respectively. The protecting group at the N(b) function of 9a and 9b was cleaved (H_2, 10% Pd-C, MeOH) and the resulting secondary amines were reacted with ethylene oxide in MeOH at about 8-10°C for two days to afford 10a and 10b in 79% and 84% yields.[5] Activation of the hydroxyl group of 10a or 10b was only possible by treatment with $MeSO_2Cl$ (2 or 3 equiv) in the presence of K_2CO_3 (10 equiv) in CH_2Cl_2 for one day for 10a or three days for 10b. Chlorides 11a and 11b were obtained in respective yield of 81% and 83%.

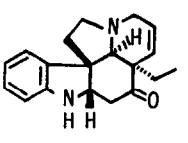
We found previously that the COOMe group at the indole nitrogen is readily hydrolyzed with diluted alkali.[6] This meant that 1-indolyl anion could be directly generated from 1-methoxycarbonylindole by treatment with a base in an aprotic solvent. So, purified t-BuOK (2.5 equiv)



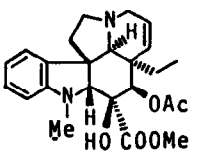
1 R=H kopsinine
2 R=Me pleiocarpinine
3 R=CHO aspidofractine
4 R=COOMe pleiocarpine



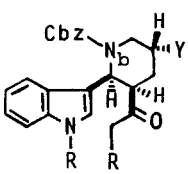
5 X=leaving group



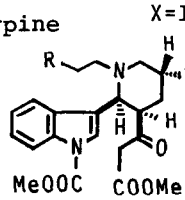
6



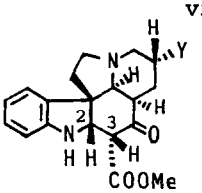
7 vindorosine



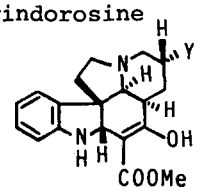
8a, 8b R=H
9a, 9b R=COOMe



10a, 10b R=OH
11a, 11b R=Cl

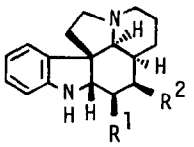


12a, 12b

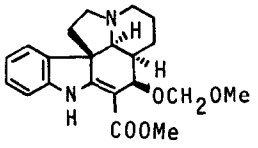


13a, 13b

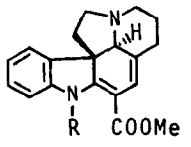
a series: Y=H b series: Y=OCH_2OMe



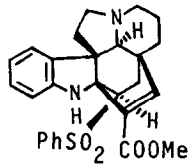
14 R^1=COOMe R^2=OH
15 R^1=CH_2OH R^2=OH
16 R^1=COOMe R^2=OCH_2OMe



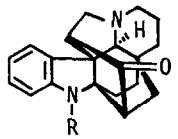
17



18a R=H
18b R=Me



19



20a R=H
20b R=Me

was added to a solution of the respective chlorides 11a and 11b in THF-HMPA (5:1) at -75 to -70°C. After 15 min, the reaction temperature was raised to 20°C and maintained for 15 min until completion of the cyclization reaction. The desired products 12a[7] and 12b were obtained in 91% and 87% yields, respectively, as equilibrium mixtures with enol forms 13a and 13b.

With an efficient and high yield key reaction in hand, we planned transformation of 12a to diene derivatives 18, which constitutes a formal synthesis of the kopsinine (1) type of alkaloids in the light of Kuehne and co-workers' recent synthesis.[8] The $NaBH_4$ reduction of 12a was carried out in a mixture of MeOH and dimethoxyethane (1:1) at room temperature for 7 min to give 14 in 81% yield, accompanied by a by-product 15 in 5% yield.[9] The hydroxyl function was protected by a methoxymethyl group[10] [(i) $MeOCH_2Cl$, i-Pr_2NEt, $ClCH_2CH_2Cl$, 40°C, 3 d; (ii) HOAc in MeOH, r.t., 3 h] and compound 16, obtained in 72% yield, was oxidized with phenylseleninic anhydride[11] in benzene in the presence of Et_3N at 65-70°C for 30 min. The product 17 (59% yield) was so sensitive to acid that a brief treatment with ca. 2% TsOH in MeOH at room temperature for 30 min was enough to convert it into 18a in 80% yield. The Diels-Alder adduct 19, obtained in 67% yield by heating 18a and phenyl vinyl sulfone in xylene at 120-125°C for three days, was shown to be identical with Kuehne's sample by comparison of their spectra.

An anion derived from 17 with $(TMS)_2NK$ in THF at -70°C was methylated with Me_2SO_4 (-70°C, 5 min and then 0°C, 30 min) and the crude N-Me derivative was treated with TsOH in MeOH as above. The N-Me diene substance 18b obtained in 80% yield from 17 was compared directly with the Kuehne's sample to establish the identity by admixture and comparison of the spectra. As 19 and 18b were transformed into 1, 2, 3, and 4 as well as kopsanone (20a) and N-methylkopsanone (20b),[8] our investigation implied a formal synthesis of these hexa- and heptacyclic alkaloids.

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9. This condition minimized the over-reduction to 15.
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