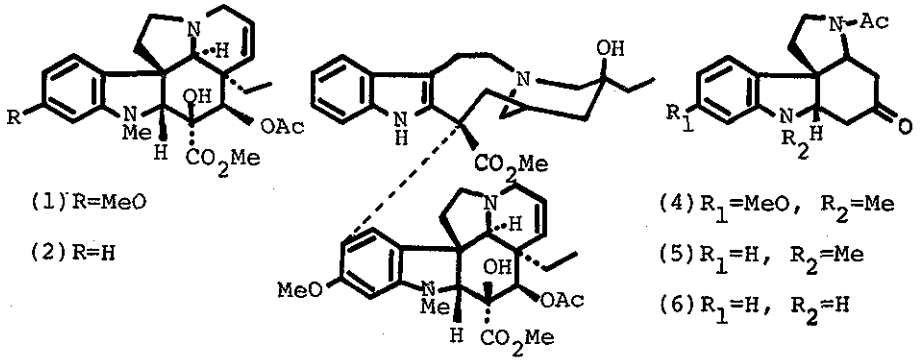
HETEROCYCLES, Vol. 6, Nos. 9, 10, 1977

TWO FACILE ROUTES TO THE INTERMEDIATES FOR THE SYNTHESES OF ASPIDOSPERMA INDOLE ALKALOIDS, VINDOLINE AND VINDOROSINE

Seiichi Takano*, Kozo Shishido, Masaaki Sato, and Kunio Ogasawara
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai, Japan 980.

Vindoline[1] (1), a highly functionalized Aspidosperma alkaloid and a structural component of the oncolytic dimeric alkaloid, vinblastine[2] (3) has been elegantly synthesized by Büchi and co-workers[3] along with its desmethoxy analog, vindorosine[4] (2). Although the synthesis was carried out in a highly sophisticated way, the preparation of the key intermediate, tetracyclic indoline (4), required extra steps in order to eliminate a formation of the undesired by-product.

Chart 1



(1) R=MeO

(2) R=H

(3)

(4) R_1=MeO, R_2=Me

(5) R_1=H, R_2=Me

(6) R_1=H, R_2=H

We have now developed two new schemes for the synthesis of the tetracyclic indoline(4) from readily available starting materials.

The first scheme, which involves an initial formation of α-keto-carbonium ion, was achieved by a four step sequence of reactions starting from tricyclic carboxylic acid(7;X=OH) to give the tetracyclic indoline(4).

The carboxylic acid(7;X=OH) prepared from 6-methoxy-1-methyl-tryptamine *via* a 3 step reaction(1)$EtOCOCH_2COCO_2H$-HCl 2)AcCl-Et_3N 3)ethanolic KOH) was treated with ethyl chlorocarbonate in the presence of triethylamine, followed by ethereal *diazo*-ketone(7;X=CHN_2) which upon exposure to trifluoroacetic acid in methylene chloride afforded tetracyclic *vinylogous amide*(11) in 35% yield as a 3:2 mixture of epimers. The reaction could be initiated by a formation of α-keto *carbonium* ion(9) which on an intramolecular nucleophilic reaction and subsequent rearrangement afforded the tetracyclic *vinylogous amide*(11) *via* the sequence shown in Chart 2.

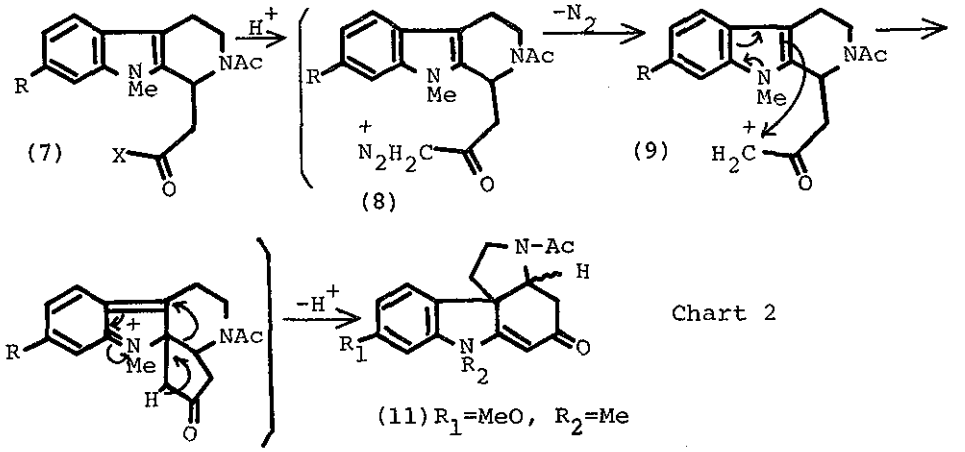


Chart 2

(11) R_1=MeO, R_2=Me

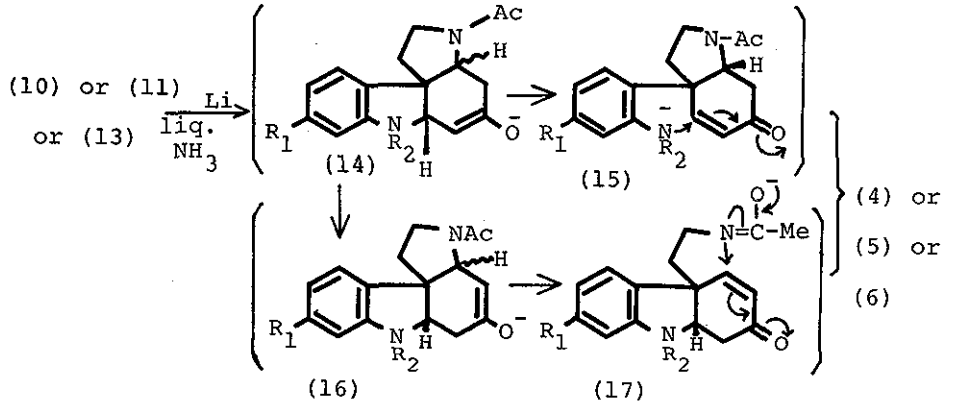
(12) R_1=H, R_2=Me

(13) R_1=H, R_2=Ac

An epimeric mixture of the vinylogous amide(11) which without separation was reduced with one molar equiv of lithium in liquid ammonia to give rise to tetracyclic indoline[3] (4) in 92% yield as a single isomer. Presumably, an intervention of enones, such as 15 and 17 formed from an enolate(14) made an exclusive formation of the most stable isomer possible.

Similarly, the tetracyclic indoline[4] (5), a key intermediate for the synthesis of vindorosine(2), was prepared starting with 1-methyltryptamine *via* the diazoketone intermediate(7;R=H, $X=CHN_2$).

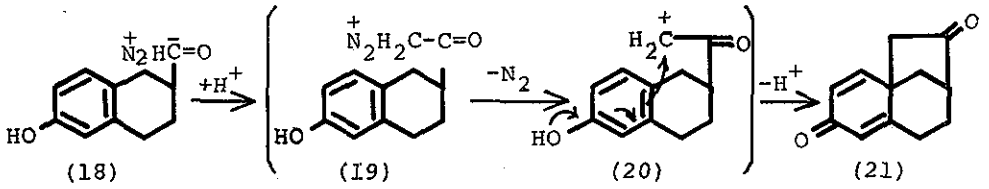
Chart 3



Formation of α-ketocarbonium ions from α-diazoketones and their highly electrophilic reactivity were originally examined and developed by Mander and co-workers[6,7] using phenolic or alkoxyphenyl diazoketons giving dienone derivatives(ex.Chart 4). However, no such attempts have been adopted on indolic compounds.

On the other hand, a prototype of the indole-indolenine

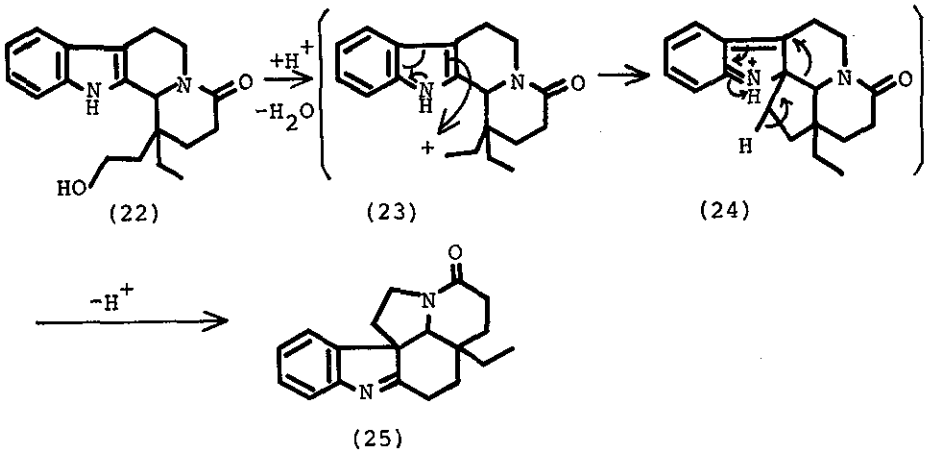
Chart 4



(18) (19) (20) (21)

rearrangement has been reported by Harley-Mason and co-worker[8] who showed an acid-catalyzed conversion of the indole(21) into the indolenine(24) possibly *via* a carbonium intermediate(22) (Chart 5). However, this could not be applied to the synthesis of a highly functionalized compounds, such as vindoline(1) and

Chart 5



(22) (23) (24) (25)

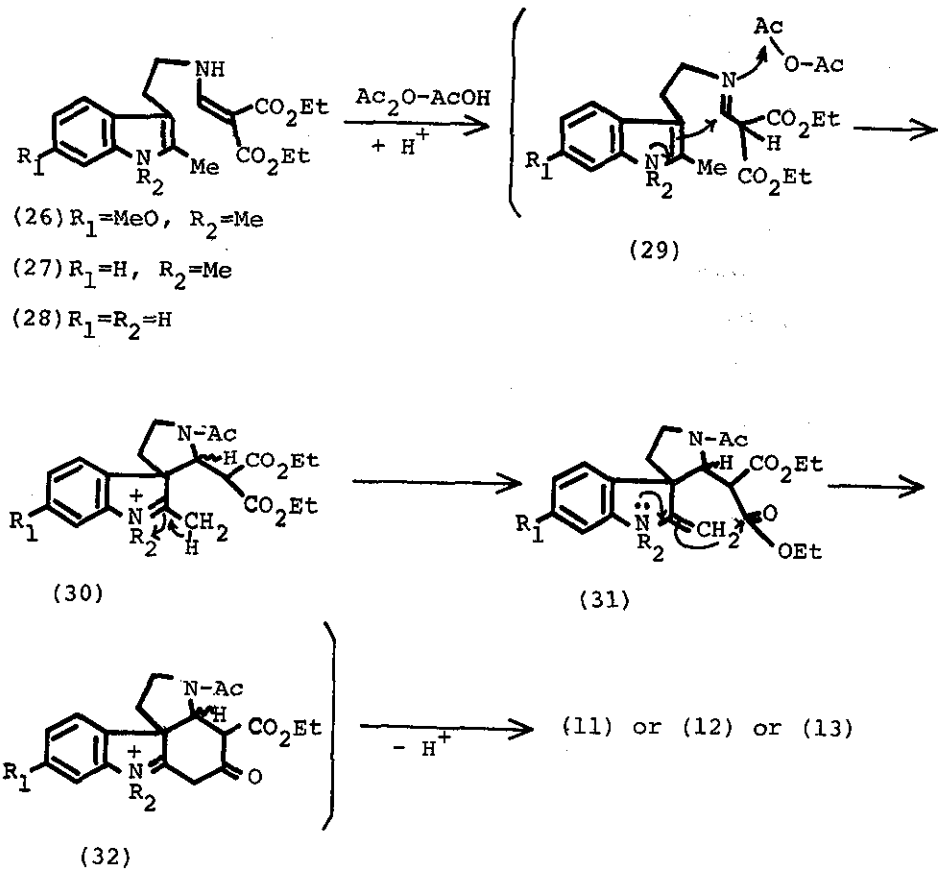
vindorosine(2), since no appropriate functional group could not be available at a proper position.

The second scheme, which involves initial formation of the

Fischer base[9] type intermediate, was achieved very efficiently by heating the iminomethylenemalonate(26) with a mixture of acetic anhydride and acetic acid to form the tetracyclic vinylogous amide(11).

Thus, the iminomethylenemalonate(26) prepared nearly quantitatively from 1,2-dimethyl-6-methoxytryptamine with diethyl ethoxymethylenemalonate was heated with a 3:2 mixture of acetic anhydride and acetic acid at a refluxing temperature for 72 hr

Chart 6



(26) R_1=MeO, R_2=Me

(27) R_1=H, R_2=Me

(28) R_1=R_2=H

(29)

(30)

(31)

(32)

to give the tetracyclic vinylogous amide(11) in 52% yield as a 3:2 mixture of epimers.

Similarly, the iminomethylenemalonates, (27) and (28), prepared from 1,2-dimethyltryptamine and 2-methyltryptamine afforded the corresponding tetracyclic vinylogous amides, (12) and (13) in 50% and 45% yields, respectively. When the latter(13) was reduced with 4 molar equiv of lithium in liquid ammonia, a concomitant regioselective deacetylation occurred to leave the secondary amine(6) in 65% yield.

At the present, the two schemes described consist merely an improvement of the key intermediates of Büchi's syntheses of vindoline(1) and vindorosine(2), however, these two approaches could generally be applicable to the synthesis of another Aspidosperma alkaloids and Strychnos alkaloids.

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