SYNTHETIC APPLICATIONS OF 2-(1,3-DITHIAN-2-YL)INDOLES. III[1]. A NEW ROUTE TO TETRACYCLIC [ABCD] INTERMEDIATES IN THE SYNTHESIS OF *ASPIDOSPERMA* INDOLE ALKALOIDS

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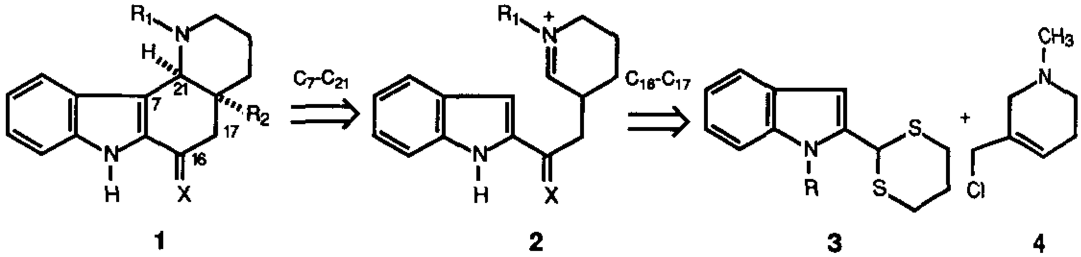
Abstract - The synthesis of tetracyclic [ABCD] framework of *Aspidosperma* alkaloids has been achieved *via* allylamine-enamine isomerization using $(Ph_3P)_3RhCl$ in hot aqueous acetonitrile of the 1,2,5,6- tetrahydro-3-(indolylethyl)-pyridine (**13**) which in turn was obtained by Raney nickel desulfurization of the corresponding 2-(1,3-dithian-2-yl)indole (**5a**).

The construction of a tetracyclic indole unit such as **1** (ABCD framework) and the subsequent elaboration of the remaining pyrrolidine or E ring is one of the major strategies employed in the synthesis of *Aspidosperma* indole alkaloids.[2-4] Within the context of our studies on the reactivity[5] and synthetic applications[1,6] of 2-(1,3-dithian-2-yl)indoles we report herein a new approach to the preparation of the key intermediate (**1**) (R_1=CH_3; R_2=H; X=H, H).



Scheme 1

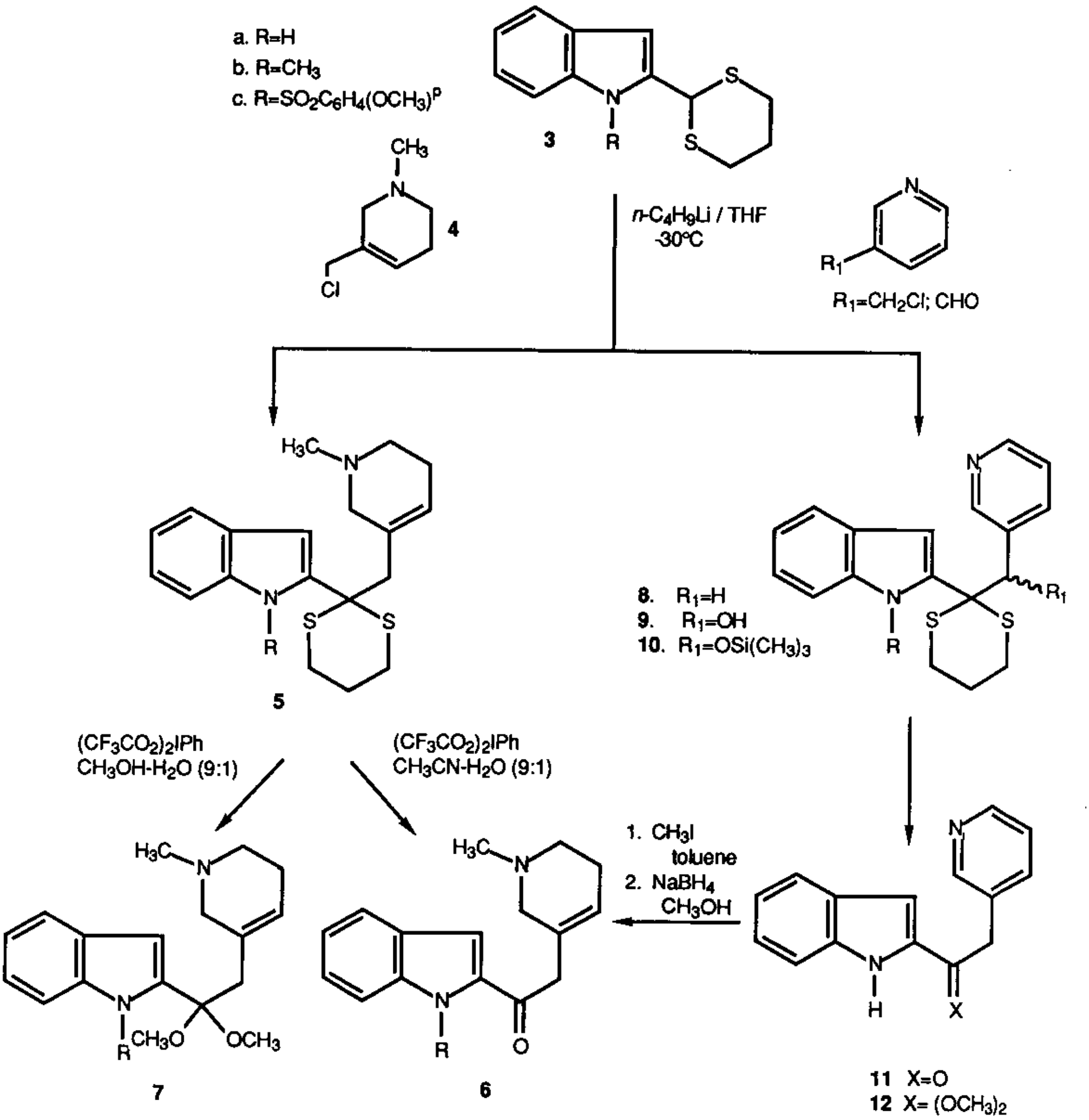
In the present work the C_7-C_{21} bond[7] is formed in the last step through cyclization of the iminium ion (**2**), generated by an allylamine-enamine isomerization[8] and further treatment with acid.

The starting indolyldithianes (**3a-c**) were prepared according to our previously described procedure.[5] Reaction of the dithiane anions formed by reaction of **3b** and **3c** with *n*-BuLi (THF, -20°C), and the corresponding dianion derived from **3a**, with 3-chloromethyl-1-methyl-1,2,5,6-tetrahydropyridine (**4**) gave the tetrahydropyridines (**5a-c**)[9] in *ca.* 95% yield. Transformation of dithianes (**5**) into the corresponding 2-acylindoles (**6**) was achieved in 87% yield by treatment with bis(trifluoroacetoxy)iodobenzene in aqueous acetonitrile.[10] When deprotection of dithianes (**5**) was effected in methanol-water (9:1), the dimethyl acetals (**7**) were obtained, in agreement with previous results.[5c]

Alternatively, ketone (**6a**)[11] was obtained from 3-pyridylmethyldithiane (**8**), itself being prepared in 75% yield by treatment of the dianion derived from **3a** with 3-chloromethylpyridine. Parallely, treatment of dianions derived from **3a** and **3b** with pyridine-3-carboxaldehyde gave, after addition at -20°C of NH_4Cl, alcohols (**9**) in good yield. When the reaction was quenched using trimethylsilyl chloride compound (**10**) was obtained in 35 % yield.

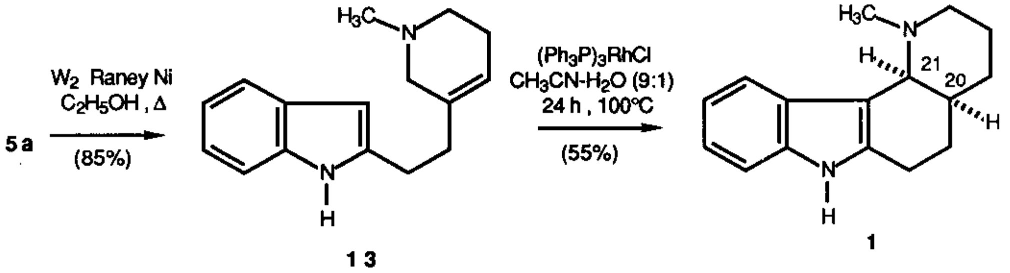
Unfortunately, isomerization and cyclization of **6a** to the tetracyclic (ABCD rings) intermediate (**1**) (X=O, R_1=CH_3, R_2=H) was not observed under either acid (50% AcOH) or base (*n*-BuLi in THF at - 30°C, ^{t}BuOK in THF at 0°C, or NaH in refluxing THF) conditions.

Therefore, at this point, we studied the reactivity of tetrahydropyridine (**13**), which was obtained by W_2 Raney nickel desulfurization of dithiane (**5a**) in refluxing ethanol. It is worth mentioning that long reaction times led to the saturated piperidine together with the desired tetrahydropyridine (**13**)[12] in a 1:1 ratio. Allylamine (**13**) was directly converted into the tetracyclic *Aspidosperma* alkaloids intermediate (**1**) in 55 % yield by treatment with tris(triphenylphosphine) coupling rhodium(I) chloride in aqueous acetonitrile at 100°C (Joule's procedure).[13] Formation of **1**[14] was evident from the disappearance of the indole proton at 3-position (δ 6.20 in **13**) as well as that of the olefin proton (δ 5.50 in **13**) in the ^{1}H nmr spectrum. The formation of the cyclization



Scheme 2

product was confirmed by the presence of two aliphatic methine carbons at δ 35.1 and 60.2 assigned to C-20 and C-21, respectively. The *cis* C/D ring junction was determined by the constant between the protons on positions 20 and 21, the latter being observed as a broad singlet at δ 3.50 ($W_{1/2}$=6 Hz), which is in accordance with other analogous tetracyclic compounds.[2]



Scheme 3

ACKNOWLEDGEMENT

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9. **5a**: ^{1}H Nmr (CDCl$_3$, 200 MHz) 2.09 (s, 3H, NCH$_3$), 2.67 (s, 2H, =CCH$_2$), 5.40 (br s, 1H, =CH), 6.74 (s, 1H, In-3H), 7.10 and 7.15 (2t, *J*=8 Hz, 1H each, In-5H and In-6H), 7.34 (d, *J*=8 Hz, 1H, In-7H), 7.57 (d, *J*=8 Hz,1H, In-4H), 8.80 (br, 1H, NH). ^{13}C Nmr (CDCl$_3$) 23.8 (SCH$_2$*C*H$_2$), 25.1 (SCH$_2$), 27.2 (=C*C*H$_2$) , 44.7 (NCH$_3$), 49.6 (NCH$_2$), 50.4 (=CCH$_2$), 52.8 (SCS), 57.4 (N*C*H$_2$C=), 103.4 (In-3C), 110.2 (In-7C), 119.0, 119.8, 121.1 (In-4C, In-5C, In-6C), 125.3 (=CH), 128.1 (In-3aC), 129.3 (In-C2), 135.3 (In-7aC), 138.2 (=C).
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11. **6a**: Ir (NaCl) 1660 (C=O).^{1}H Nmr (CDCl$_3$) 2.40 (s, 3H, NCH$_3$), 2.56 (t, *J*=8 Hz, 2H, NCH$_2$), 3.06 (br s, 2H, COCH$_2$), 3.64 (s, 2H, =CCH$_2$N), 5.73 (br s, 1H, =CH), 7.17 (t, *J*=7 Hz, 1H, In-5H), 7.28 (s, 1H, In-3H), 7.32 (t, *J*=7 Hz, 1H, In-6H), 7.49 (d, *J*=7 Hz, 1H, In-7H), 7.72 (d, *J*=7 Hz, 1H, In-4H), 10.3 (br , 1H, NH). ^{13}C Nmr (CDCl$_3$) 24.7 (NCH$_2$*C*H$_2$), 44.2 (=C*C*H$_2$CO), 44.3 (NCH$_3$), 56.0 (=CCH$_2$N), 109.6 (In-3C), 111.8 (In-7C), 120.2, 122.4, 123.2 (In-4C, In-5C, In-6C), 125.7 (=CH), 126.8 (In-C3a), 129.2 (In-C2), 134.3 (In-C7a), 137.2 (=C), 190.2 (C=O).
12. **13**: ^{1}H Nmr (CDCl$_3$) 2.1-2.4 (m, 4H, NCH$_2$CH$_2$), 2.46 (s, 3H, NCH$_3$), 2.64 and 2.87 (2 t, *J*=8 Hz, 2H each, In-CH$_2$CH$_2$), 3.00 (br s, 2H, NCH$_2$), 5.50 (br s, 1H, =CH), 6.20 (s, 1H, In-3H), 6.9-7.1 (m, 2H, InH), 7.35 (d, *J*=7 Hz, 1H, In-7H), 7.50 (d, *J*= 7 Hz, 1H, In-4H), 8.90 (br s, 1H, NH). ^{13}C Nmr (CDCl$_3$) 24.9 and 26.4 (=CCH$_2$), 34.7 (In-CH$_2$), 45.0 (NCH$_3$), 51.3 (NCH$_2$), 56.2 (N*C*H$_2$C=), 99.2 (In-3C), 110.7 (In-7C), 119.4, 119.7, 120.8 (In-4C, In-5C, In-6C), 120.2 (=CH), 128.7 (In-3aC), 133.8 (In-2C), 135.9 (In-7aC), 139.4 (=C).
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14. **1**: ^{1}H Nmr ($CDCl_3$) 2.40 (s, 3H, NCH_3), 3.50 (br s, $W_{1/2}$=6 Hz, 1H, 21-H), 7.0-7.1 (m, 1H, InH), 7.2-7.35 (m, 2H, InH), 7.55 (br d, 1H, In-4H), 8.60 (br, 1H, NH). ^{13}C Nmr ($CDCl_3$) 20.9, 22.8, 29.5, 30.1, 35.1 (20-C), 44.6 (NCH_3), 57.2 (NCH_2), 60.2 (21-C), 109.9, 110.8 (In-7C), 118.2, 119.6, and 121.1 (In-4C, In-5C, In-6C), 126.9, 129.0, 135.9 (In-7aC).

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