

SYNTHETIC APPLICATIONS OF 2-(1,3-DITHIAN-2-YL)INDOLES. III¹.
A NEW ROUTE TO TETRACYCLIC [ABCD] INTERMEDIATES IN THE
SYNTHESIS OF *ASPIDOSPERMA* INDOLE ALKALOIDS

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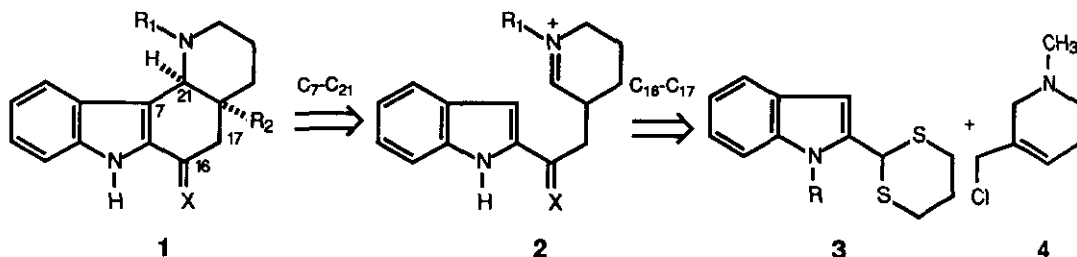
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Abstract - The synthesis of tetracyclic [ABCD] framework of *Aspidosperma* alkaloids has been achieved via allylamine-enamine isomerization using $(\text{Ph}_3\text{P})_3\text{RhCl}$ in hot aqueous acetonitrile of the 1,2,5,6-tetrahydro-3-(indolyloethyl)-pyridine (**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 reactivity⁵ 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**) ($\text{R}_1=\text{CH}_3$; $\text{R}_2=\text{H}$; $\text{X}=\text{H}$, H).



Scheme 1

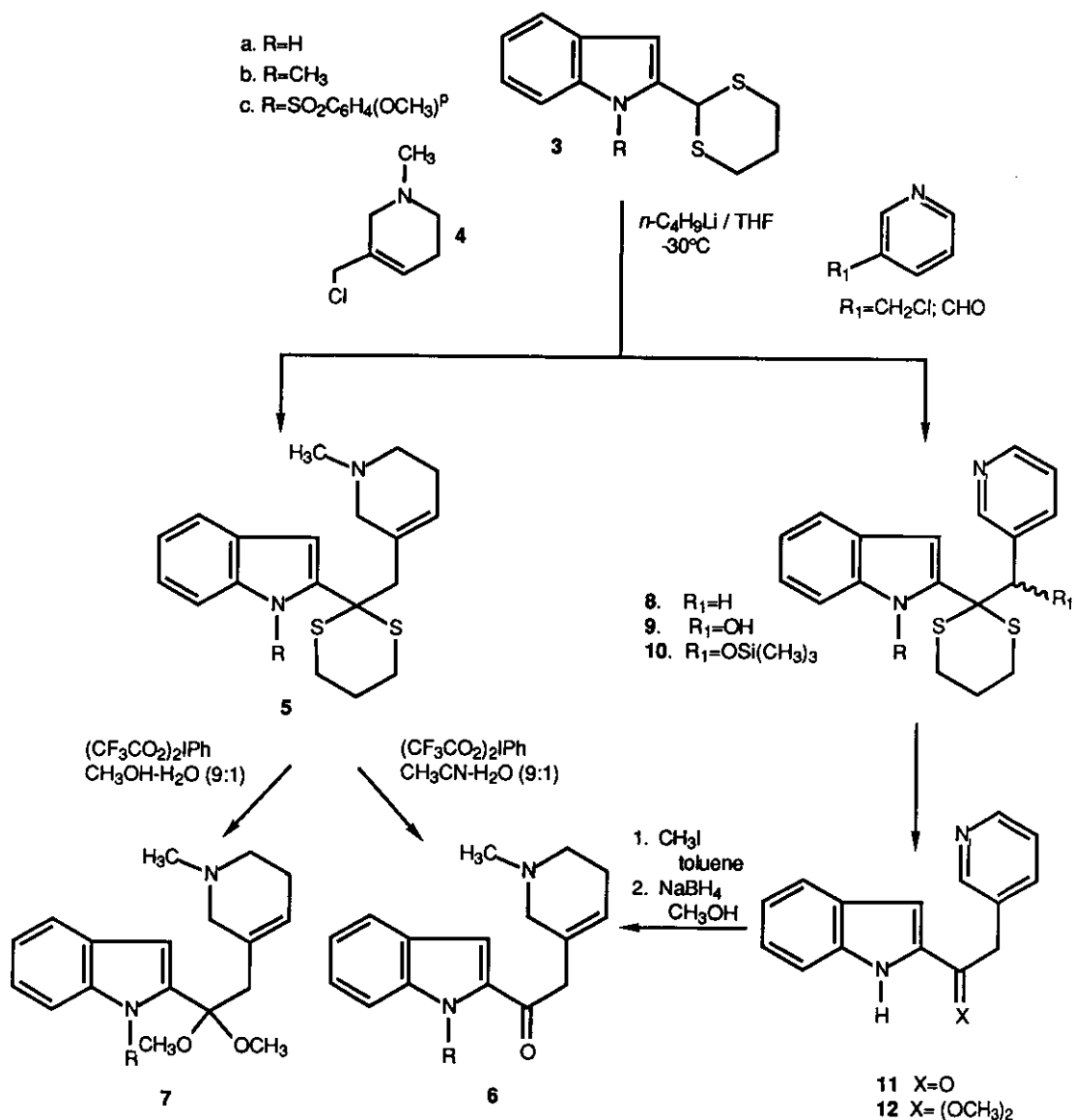
In the present work the C7-C₂₁ bond⁷ is formed in the last step through cyclization of the iminium ion (2), generated by an allylamine-enamine isomerization⁸ and further treatment with acid.

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 NH₄Cl, alcohols (9) in good yield. When the reaction was quenched using trimethylsilyl chloride compound (10) was obtained in 35 % yield.

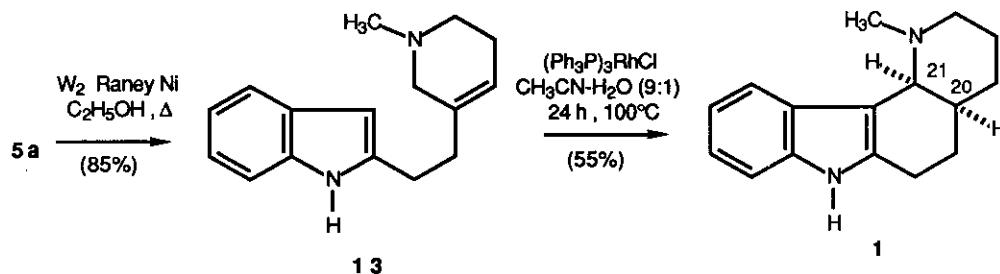
Unfortunately, isomerization and cyclization of 6a to the tetracyclic (ABCD rings) intermediate (1) (X=O, R₁=CH₃, R₂=H) was not observed under either acid (50% AcOH) or base (*n*-BuLi in THF at -30°C, ^tBuOK in THF at 0°C, or NaH in refluxing THF) conditions.

Therefore, at this point, we studied the reactivity of tetrahydropyridine (13), which was obtained by W₂ 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 1¹⁴ 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 ¹H 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**: ^1H Nmr (CDCl_3 , 200 MHz) 2.09 (s, 3H, NCH_3), 2.67 (s, 2H, $=\text{CCH}_2$), 5.40 (br s, 1H, $=\text{CH}$), 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_2CH_2), 25.1 (SCH_2), 27.2 ($=\text{CCH}_2$), 44.7 (NCH_3), 49.6 (NCH_2), 50.4 ($=\text{CCH}_2$), 52.8 (SCS), 57.4 ($\text{NCH}_2\text{C}=\text{}$), 103.4 (In-3C), 110.2 (In-7C), 119.0, 119.8, 121.1 (In-4C, In-5C, In-6C), 125.3 ($=\text{CH}$), 128.1 (In-3aC), 129.3 (In-C2), 135.3 (In-7aC), 138.2 ($=\text{C}$).
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11. **6a**: Ir (NaCl) 1660 ($\text{C}=\text{O}$). ^1H 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, $=\text{CCH}_2\text{N}$), 5.73 (br s, 1H, $=\text{CH}$), 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_2CH_2), 44.2 ($=\text{CCH}_2\text{CO}$), 44.3 (NCH_3), 56.0 ($=\text{CCH}_2\text{N}$), 109.6 (In-3C), 111.8 (In-7C), 120.2, 122.4, 123.2 (In-4C, In-5C, In-6C), 125.7 ($=\text{CH}$), 126.8 (In-C3a), 129.2 (In-C2), 134.3 (In-C7a), 137.2 ($=\text{C}$), 190.2 ($\text{C}=\text{O}$).
12. **13**: ^1H Nmr (CDCl_3) 2.1-2.4 (m, 4H, NCH_2CH_2), 2.46 (s, 3H, NCH_3), 2.64 and 2.87 (2 t, $J=8$ Hz, 2H each, In- CH_2CH_2), 3.00 (br s, 2H, NCH_2), 5.50 (br s, 1H, $=\text{CH}$), 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 ($=\text{CCH}_2$), 34.7 (In- CH_2), 45.0 (NCH_3), 51.3 (NCH_2), 56.2 ($\text{NCH}_2\text{C}=\text{}$), 99.2 (In-3C), 110.7 (In-7C), 119.4, 119.7, 120.8 (In-4C, In-5C, In-6C), 120.2 ($=\text{CH}$), 128.7 (In-3aC), 133.8 (In-2C), 135.9 (In-7aC), 139.4 ($=\text{C}$).
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14. 1: ^1H 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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