Tetrahedron Letters,Vol.26,No.16,pp 1963-1966,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

METHODS FOR INDOLE ALKALOID SYNTHESIS. A HIGHLY CONVERGENT STRATEGY FOR THE SYNTHESIS OF A 3-METHYL-6,7-DEHYDROASPIDOSPERMIDINE SYSTEM.

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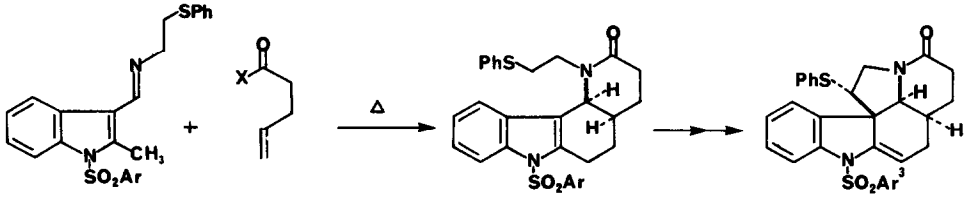
SUMMARY: The $\underline{N}^1$-CO_2Me derivative of 2-ethyl-3-formylindole has been converted into the highly functionalized aspidospermidine-type alkaloid 12 in four steps.

During the course of our recent investigations of the indole-2,3-quinodimethane cyclization strategy for the synthesis of indole alkaloids the $\underline{N}^1$-nitrogen atom has been inductively deactivated as an arylsulfonamide, and the 3-position has been unsubstituted. SCHEME 1.[1]



1 2

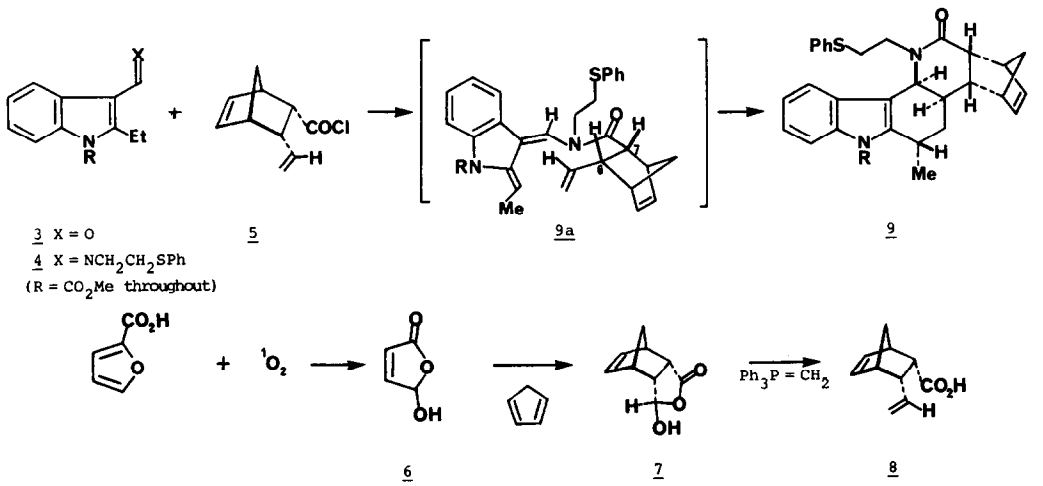
SCHEME 1

Here we report that the yields in the key cyclization can be improved by replacement of the $\underline{N}^1$-SO_2Ar by $\underline{N}^1$-CO_2Me, and a 3-Me group can be carried through the sequence. Furthermore, the 6,7-double bond can be masked in the form of a cyclopentadienyl Diels-Alder adduct, and released by a thermal retro-Diels-Alder reaction.

2-Ethyl-3-formylindole[2] *was treated with $ClCO_2Me$/5 mol% $PhCH_2\overset{\oplus}{N}Et_3Cl^{\ominus}$/aqueous 6N NaOH/$CH_2Cl_2$ to give the $\underline{N}^1$-CO_2Me derivative 3 (75%), m.p. 84-86°C (EtOH), which was converted into the imine 4 by treatment with $PhSCH_2CH_2NH_2/CH_2Cl_2$/4A° molecular sieves.*

The dienophilic component 5 was made by photooxygenation of 2-furoic acid[3] to give 6, which was treated with cyclopentadiene to give the lactol 7. Methylenation of 7 using $Ph_3\overset{\oplus}{P}CH_3I^{\ominus}$/BuLi/THF/0°C gave the acid 8 (70%), m.p. 72-74°C (EtOAc/hexane), which on treatment with oxalyl chloride/benzene/pyridine (cat.) gave 5.[4]

To a solution of the imine 4 in toluene at 0°C was added NPr^i_2Et (1 equiv.), followed by the acid chloride 5 (1.1 equiv.). The mixture was heated at reflux for 2h. to give the adduct 9 (44%), m.p. 161-164.5°C (EtOAc), as a single stereoisomer.[5] *The relative stereochemistry*

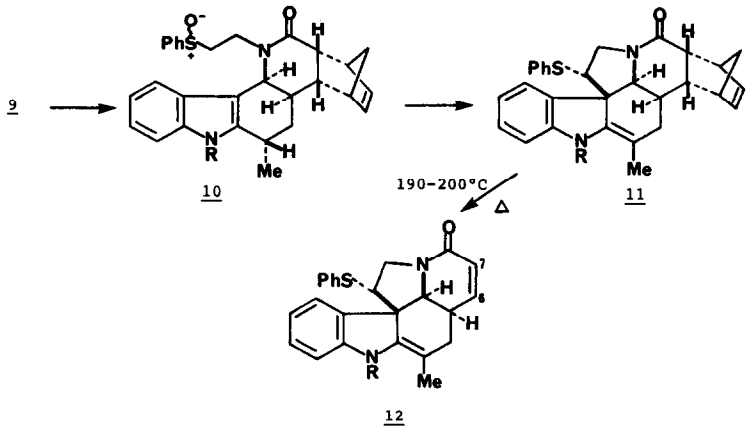


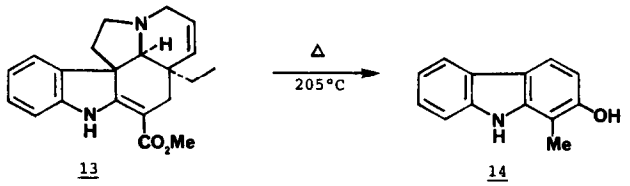
of 9 is based upon analogy with the 3-nor-methyl series, where a single crystal X-ray study verified the cis-anti-cis-stereochemistry.[6] *The postulated intermediate or transition state 9a predicts the single α-stereochemistry for the 3-sec-methyl group. In a completely analogous series N^1-SO_2Ar the yield of the adduct corresponding to 9 was 31%.*

The hexacyclic sulfide 9 was oxidized to the corresponding diastereomeric sulfoxides 10 (92%) using MCPBA/$NaHCO_3$/CH_2Cl_2. When a solution of 10 (0.92 g.) in CH_2Cl_2 (24 ml.) at 0°C was treated with TFAA (570 µl) for 1h., evaporated in vacuo, dry toluene (38 ml.) added to the

residue , and heated at reflux for 1.5h., the heptacyclic sulfide 11 *(86.5%), m.p. 202-203°C (EtOAc/hexane) was isolated.*[7]

Thermolysis of 11 *(190-200°C/ 36h.) cleanly resulted in the expulsion of cyclopentadiene and the formation of the* α,β*-unsaturated amide* 12 *(69%, after chromatography and crystallization), m.p. 230-231°C (EtOH).*[8] *It should be noted that thermolysis of tabersonine* 13 *at 205°C in xylene results in deep-seated degradation to the carbazole* 14 *and 3-ethylpyridine.*[9]





In summary, highly functionalized Aspidosperma- type alkaloids 12 *are readily available in four steps from* 4. *The* N^1*-*CO_2*Me group in general improves the yields in the indole-2,3-quinodimethane cyclization step.*[6] *Attempts to oxidize the C-3 allylic methyl group in* 11 *using a variety of procedures were not successful.*[10]

References and Footnotes

1. *For a summary of some of the main features of this strategy see: P. Magnus, T. Gallagher, P. Brown and P. Pappalardo, Acc. Chem. Res., 1984, 17, 35; P. Magnus and P. Pappalardo, J. Am. Chem. Soc., 1983, 105, 6525.*
2. *2-Ethyl-3-formylindole, m.p. 167-168.5°C (EtOAc) was made by Vilsmeier formylation of 2-ethylindole (R.L. Augustine, A.J. Gustavsen, S.E. Wanat and I.C. Pattison, J. Org. Chem., 1973, 38, 3004. The N^1-CO_2Me derivative 3 has m.p. 84-86°C (EtOH).*
3. *J.D. White, J.P. Carter and H.S. Kezar, J. Org. Chem., 1982, 47, 929.*
4. *The acid 8 has, m.p. 72-74°C (EtOAc/hexane). Anal. Calcd. for $C_{10}H_{12}O_2$ C,73.14; H,7.37. Found: C,72.86; H,7.48. ^1H NMR (360MHz) δ 1.36(1H,d,J = 8.5Hz), 1.48(1H,dt,J = 8.5,1.6Hz), 2.85(1H,bs), 3.11-3.19(2H,m), 4.95(1H,dd,J = 9.9,2.01Hz), 5.12(1H,dd,J = 16.9,2.0Hz), 5.33-5.43(1H,m), 6.14(1H,dd,J = 5.6,3.0Hz), 6.34(1H,dd,J = 5,2.9Hz), 11.1(1H,bs).*
5. *^1H NMR (360MHz) (selected signals) δ 1.27(3H,d,J = 6.5Hz), 4.06 (3H,s), 4.43(1H,dd,J = 4.2,2.1Hz).*
6. *Unpublished observations from this laboratory. P.M. Cairns.*
7. *^1H NMR (360MHz) (selected signals) δ 1.83(3H,s), 3.84(3H,s), 4.54 (1H,d,J = 4.8Hz), 4.57(1H,dd,J = 6.1,11.0Hz).*
8. *^1H NMR (360MHz) (selected signals) δ 1.87(3H,s), 3.87(3H,s), 4.49 (1H,d,J = 5.8Hz), 5.98(1H,d,J = 10.0Hz), 6.54(1H,dd,J = 10.0,5.6Hz). Anal. Calcd. for $C_{26}H_{24}N_2O_3S$ C,70.24; H,5.44; N,6.30. Found: C,70.38; H,5.66; N,6.27.*
9. *A.I. Scott and C.C. Wei, Tetrahedron, 1974, 30, 3003.*

10. *The National Institutes of Health (GM 29820) is gratefully thanked for financial support.*

(Received in USA 1 February 1985)