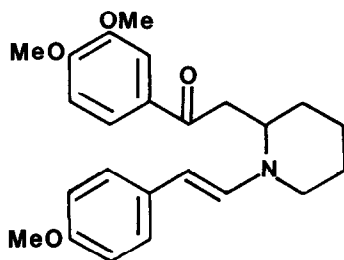


SYNTHESIS OF THE ALKALOIDS JULANDINE AND
IPALBIDINE - USE OF SILICON (IV) CHLORIDE

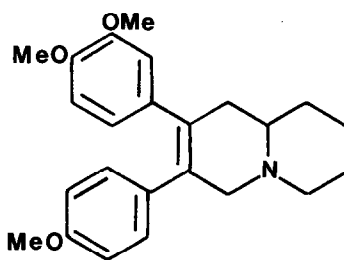
John E. Cragg, Stuart H. Hedges, and Richard B. Herbert,*
Department of Organic Chemistry, The University, Leeds LS2 9JT

Summary: Titanium (IV) chloride and silicon (IV) chloride with high oxygen affinity are the best Lewis acid catalysts, of a number tested, for cyclisation of an enamine-ketone (1) leading to the alkaloid, julandine (2); cyclisation of (6) in methanol solution without catalyst yields O-methylipalbidine (7).

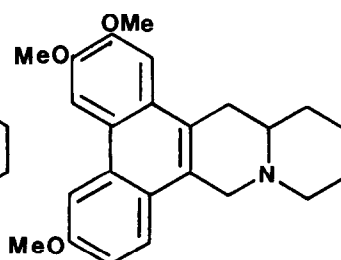
An economical, biogenetically patterned, synthesis of the cytotoxic alkaloid, cryptopleurine (3), involves formation of the enamino-ketone (1) as the key intermediate by condensation of 3,4-dimethoxyphenacylpiperidine with 4-methoxyphenylacetaldehyde. Cyclisation of (1) has been achieved with titanium (IV) chloride to give, after reduction, the alkaloid julandine (2) (yield: 29%). Thallium (III) trifluoroacetate oxidation of (2) gave cyrptopleurine (3).¹



(1)



(2)



(3)

Table: Yields of Julandine with various Lewis Acids

<u>Lewis Acid</u>	<u>No. of Moles</u>	<u>Solvent</u>	<u>Yield (%)</u>
TiCl ₄	1	CH ₂ Cl ₂	29 ^a
"	1	C ₆ H ₆	35 ^a
"	3	"	35
"	0.5	"	18
SiCl ₄	1	"	42 ^a
"	3	"	17
"	0.5	"	16
SnCl ₄	1	"	18
BF ₃ .Et ₂ O	1	"	13
Zr Cl ₄	1	"	12
AlCl ₃	1	C ₆ H ₆ ; Et ₂ O	11
FeCl ₃	1	Et ₂ O	5

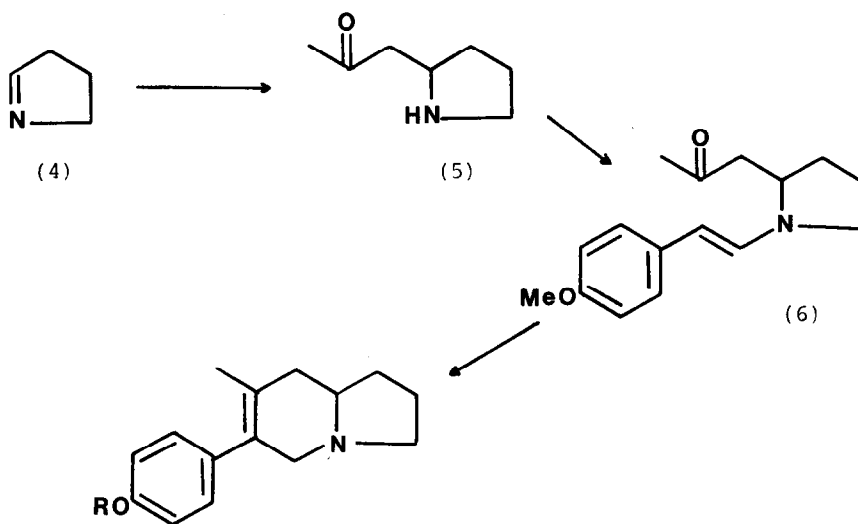
^aCrystallized yield; others: yield after chromatography

We have now examined a range of Lewis acids, in varying proportions, as catalysts for the cyclisation of (1) (Table). With one notable exception, silicon (IV) chloride, all were less effective catalysts than titanium (IV) chloride; 1 molar equivalent of catalyst was optimal. Importantly, the yields of julandine (2) show a direct, though rough, correlation with recorded metal-oxygen bond strengths:² those for silicon, titanium, boron and zirconium are high, the others low. The yield with zirconium (IV) chloride was low, probably for solubility reasons. Complexation of boron trifluoride as its etherate clearly prevented effective complexation to the ketone in (1) and a low yield resulted.

In the cyclisation of (1) reaction will be favoured by metal coordination to the ketonic oxygen and hindered by coordination to the enamine system. The former is clearly most favourably achieved with the silicon and titanium chlorides. The latter has found useful application in synthesis as a reagent which favours coordination to oxygen

and is an effective dehydrating agent.³ The successful, and novel, use of silicon (IV) chloride as a Lewis acid in the cyclisation of (1) (and in the subsequent dehydration) suggests that the reagent may find application in other reactions as an alternative to titanium (IV) chloride.

An enamo-ketone with an alkyl carbonyl group, *e.g.* (6), would be expected to cyclise more readily than the corresponding, less electrophilic, aryl analogue (1), and this should be reflected in a higher yield of cyclised product. We have found this to be true for the synthesis of *O*-methylipalbidine (7) from (6); cyclisation occurs in methanol solution and without Lewis acid catalysis [demethylation of (7) affords ipalbidine (8)⁴]. Norhygrine (5) is one starting material for the preparation of (6) and it is prepared simply, and in our hands, uniquely, by condensation of acetoacetic acid with Δ^1 -pyrroline (4), generated from 1,4-diaminobutane by pea seedling diamine oxidase.⁵ Norhygrine has been conveniently used without purification for the synthesis of *O*-benzylipalbidine (9),⁶ but use of purified material (Whatman 3MM; 4 parts *n*-BuOH : 1 part HOAc : saturated with water; R_f 0.5; blue colour with isatin) significantly improved the yield (68%) of, in this case, *O*-methylipalbidine (7).



- (7) R = Me
 (8) R = H
 (9) R = CH₂Ph

We thank the Science Research Council for a Studentship (S.H.H.) and a CASE Studentship (J.E.C.), and Glaxo Research, Greenford, for financial support.

References

1. R. B. Herbert, J. Chem. Soc., Chem. Commun., 1978, 794.
2. cf. L. Brewer and G. M. Rosenblatt, 'Advances in High Temperature Chemistry'. vol. II, Academic Press, New York, 1969.
3. T. Mukaiyama, Angew. Chem. Int. Ed. Engl., 1977, 16, 817.
4. T. R. Govindachari, A. R. Sidhaye, and N. Viswanathan, Tetrahedron, 1970, 26, 3829.
5. A. J. Clarke and P. J. G. Mann, Biochem. J., 1959, 71, 596.
6. S. H. Hedges and R. B. Herbert, J. Chem. Res. (S), 1979, 1; (M), p. 410.

(Received in UK 19 March 1981)