Novel Total Syntheses of (±)-Yohimbine and (±)-Alloyohimbine

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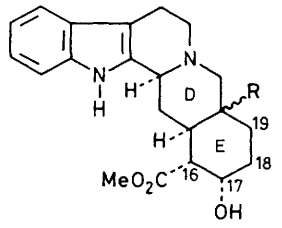
The total synthesis of two alkaloids, (±)-yohimbine (**1a**) and (±)-alloyohimbine (**1b**) was completed by the regioselective functionalisation of 18,19-didehydroyohimbones (**3a** and **b**) which were readily prepared from harmalane by enamide reductive photocyclisation.

Although there have been extensive investigations of the synthesis of yohimbine alkaloids,[1] attempts to introduce groups directly at C-16 in the yohimbine skeleton (D/E-*trans*) have resulted in preferential substitution at C-18.[2] We now report syntheses of (±)-yohimbine (**1a**) and (±)-alloyohimbine (**1b**) from the didehydroyohimbone (**2**).

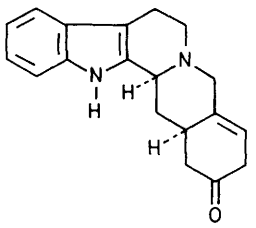
Although the unconjugated enone (**2**) was shown to undergo isomerisation into the D/E-*cis*-enone (**3b**) simply by treatment with silica gel, and (**3b**) was used[3] as a key intermediate for the synthesis of alloyohimbone, treatment of the enone (**2**) with tartaric acid[4] in dioxane at 80 °C gave the D/E-*trans*-enone (**3a**) stereoselectively in 75% yield. The structure was established from spectral data [ν ($CHCl_3$): 3480 and 1680 cm^{-1}; δ_H ($CDCl_3$): 6.80 (1H, dd, *J* 10 and 1.5 Hz, 19-H) and 6.08 (1H, dd, *J* 10 and 3 Hz, 18-H)] and also from the conversion of (**3a**) into the known yohimbone. Catalytic hydrogenation of the enone (**3a**) over 10% palladium on carbon afforded the saturated ketone (**4e**) in 95% yield which was identical (i.r. and n.m.r. comparison) with authentic yohimbone, prepared[5,6] from natural yohimbine.

Metallation of 18,19-didehydroyohimbone (**3a**) with lithium di-isopropylamide (LDA; 5.2 equiv.) in tetrahydrofuran at −78 °C under conditions of kinetic control,[7] followed by addition of methyl chloroformate (5.2 equiv.) and catalytic hydrogenation on platinum dioxide gave a mixture of the *N,C*-diacylated product (**4b**), the saturated ketone (**4a**), and the *N,O*-diacylated compound (**5**) in 14, 15, and 29% yields respectively, which were readily isolated by preparative t.l.c. (p.l.c.) and characterised by their spectral data.

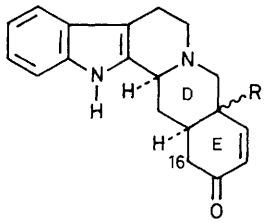
On the other hand, acylation of the corresponding magnesium enolate which was prepared *in situ* from the lithium enolate of the enone (**3a**) by treatment with anhydrous magnesium bromide, with the same acylating agent followed by catalytic reduction under the same conditions as above afforded the desired *C*-acylated product (**4c**) exclusively in



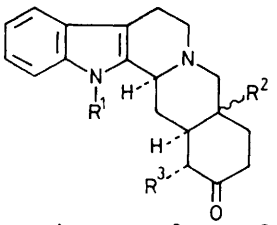
(1) a; R = —H
b; R = ---H



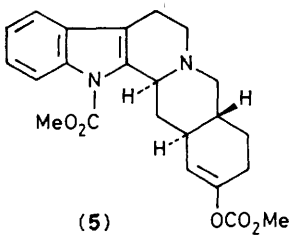
(2)



(3) a; R = —H
b; R = ---H



(4) a; $R^1 = CO_2Me$, R^2 = —H, R^3 = H
b; $R^1 = R^3 = CO_2Me$, R^2 = —H
c; R^1 = H, R^2 = —H, $R^3 = CO_2Me$
d; R^1 = H, R^2 = ---H, $R^3 = CO_2Me$
e; $R^1 = R^3$ = H, R^2 = —H



(5)

67% yield. This enhanced *C*-acylation relative to *O*-acylation by the use of the magnesium enolate is in good accord with the results of House *et al.*[8] who explained this preference in terms of contact ion pairs which would exist for the magnesium enolate. This *C*-acylated product (**4c**) was also prepared from the *N*,*C*-diacylated product (**4b**) by treatment with potassium carbonate[9] in methanol and identified as (±)-yohimbinone by comparisons with an authentic sample kindly provided by Professor Szántay. Since yohimbinone had already been converted into (±)-yohimbine (**1a**) by two groups,[6,10] we also reduced the keto ester (**4c**) with sodium borohydride, thus achieving a total synthesis of (±)-yohimbine.

By the same methodology, (±)-alloyohimbine (**1b**) was also synthesised from the D/E-*cis*-enone (**3b**). Lithiation of 18,19-didehydroyohimbone (**3b**) with LDA followed by conversion of the lithium enolate into the magnesium enolate, addition of methyl chloroformate, and then catalytic hydrogenation yielded (±)-alloyohimbinone (**4d**) in 68% yield, which was identical (i.r. and n.m.r.) with an authentic sample.[11] Since alloyohimbinone (**4d**) had been converted into (±)-alloyohimbine (**1b**),[11] this completes the formal total synthesis of (±)-alloyohimbine (**1b**).

These new syntheses of (±)-yohimbinone (**4c**) and (±)-alloyohimbinone (**4d**) consist of seven conventional steps with overall yields of 34 and 41% from harmalane respectively.

Thus, coupled with a practical preparation of the indole alkaloid skeleton by reductive photocyclisation of enamides,[3] the present method involving the direct functionalisation of the basic skeleton of enones provides a practical synthetic route to various indole alkaloids, and its application directed to the synthesis of reserpine type alkaloids is in progress.

We thank the Ministry of Education, Science, and Culture (Japan) for a research grant and Professor Cs. Szántay for a gift of yohimbinone and alloyohimbinone and encouragement.

Received, 4th July 1983; Com. 898

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