Tetrahedron Letters No. 18, PP 1543 - 1546, 1976. Pergamon Press. Printed in Great Britain.

SYNTHESIS OF THE ANTILEUKAEMIC LIGNAN PRECURSOR (±) STEGANONE

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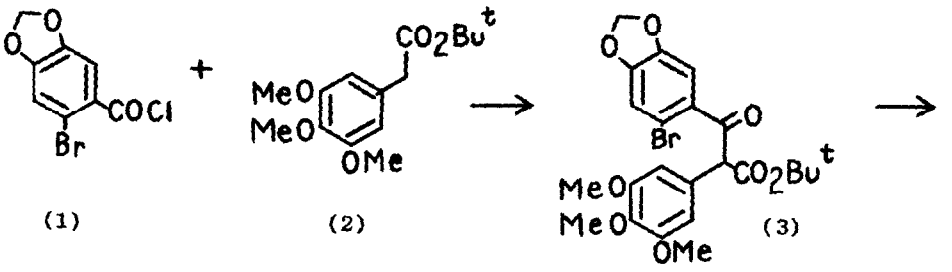
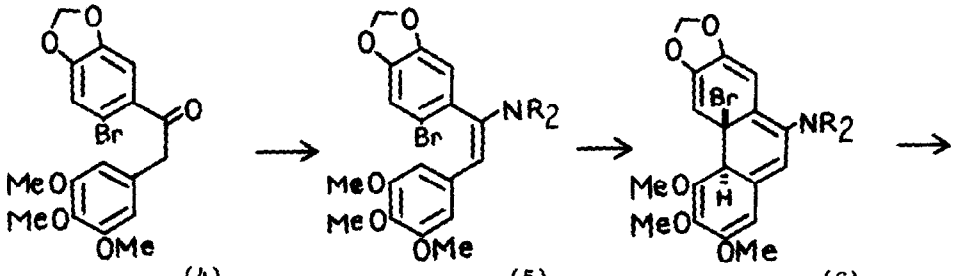
(Received in UK 9 March 1976; accepted for publication 22 March 1976)

Steganacin and steganangin are lignans isolated from Steganotaenia araliacea Hochst. which have been reported to possess significant anti-leukaemic activity in vivo.[1] Their constitutions have been shown to be respectively the O-acetyl and O-angelyl derivatives of the companion β-alcohol, steganol, which in turn is readily obtainable[1] by reduction of the co-occurring ketone steganone. (11) All the four cognate natural products are trans-fused γ-lactones[1] of the rare lignan group which contains a bisbenzocyclooctadiene structural framework.

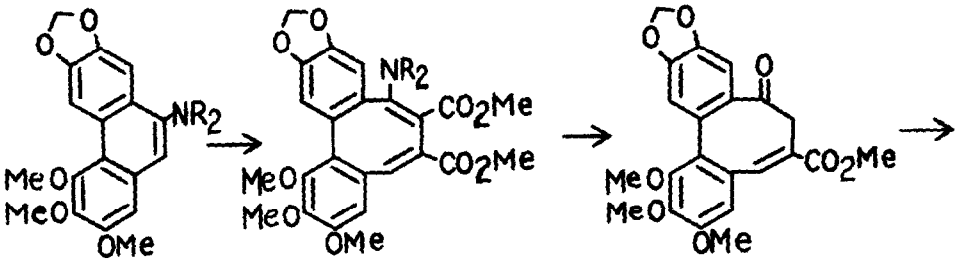
We now report the total synthesis of the racemic form of the key ketone steganone (11) by the following route. The readily obtainable 2-bromo-piperonal[2] was oxidised with silver oxide in 94% yield to 2-bromo-4,5-methylenedioxybenzoic acid. The corresponding acid chloride (1) m.p. 89-91° was then condensed with the lithio-derivative of tert-butyl 3,4,5-trimethoxyphenylacetate[3] (2) (obtained by interaction of lithium di-isopropylamide and the ester in tetrahydrofuran) to produce the corresponding β-ketoester[4](3) m.p. 97-99°. Heating this product in aqueous dimethylsulphoxide[5] resulted in hydrolysis and decarboxylation to give the ketone[4] (4) m.p. 111-112° in 74% overall yield from the acid chloride. Heating this ketone in degassed benzene with pyrrolidine and p-toluenesulphonic acid in a Dean-Stark apparatus for 18 hours gave one geometrical isomer[6] of the enamine[4](5) m.p. 148-149° in 88% yield. Irradiation of a suspension of this enamine in liquid ammonia containing a suspension of potassium tert-butoxide[7] with a medium pressure 125 watt Hanovia mercury lamp produced the required substituted amino-phenanthrene[4] (7) m.p. 133-135° in 65% yield by a conrotatory cyclisation and ready base-catalysed elimination of the elements of hydrogen bromide from the presumed intermediate trans-dihydrophenanthrene (6).



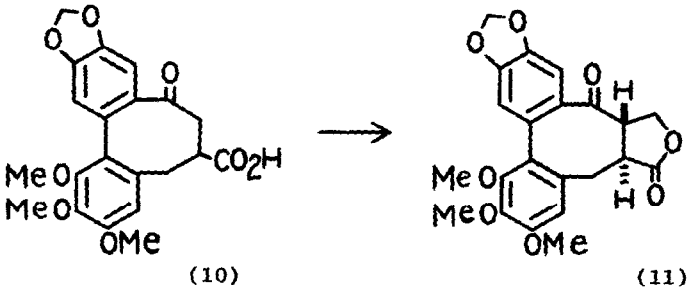
(1) (2) (3)



(4) (5) (6)



(7) (8) (9)



(10) (11)

(NR_2 = pyrrolidino)

Heating this amine in dioxan with excess of dimethyl acetylenedicarboxylate[8] gave in 91% yield the doubly ring expanded product[4] (8) m.p. 226-228°, which was transformed (90% yield) into the unsaturated ketoester[4] (9) m.p. 144-145° by refluxing with methanolic hydrochloric acid. Catalytic hydrogenation of (9) in methyl acetate with Raney nickel, followed by a Jones oxidation, produced a 95% yield of the saturated ketoester,[4] m.p. 126-128° base treatment of which gave (93%) the corresponding ketoacid[4] (10) m.p. 144-146°. Aldol reaction of this ketoacid salt in potassium hydroxide solution with excess formaldehyde, followed by a Jones oxidation[9], gave a homogeneous crystalline keto-γ-lactone[4] (11) m.p. 227-229° in 75% yield which was identical[10] chromatographically and spectroscopically with an authentic sample of (-) steganone [ν_{max} ($CHCl_3$) 1770, 1665, 1610, 1580, 1260 $cm.^{-1}$; τ ($CDCl_3$) 2.47 (1H,s,Ar-H), 3.37, 3.46 (2H,2s,Ar-H), 3.92 (2H br.s, $O-CH_2-O$), ~ 5.7 (2H, m, lactone CH_2), 6.13 (6H,s,$2OCH_3$), 6.40 (3H,s,OCH_3) ~ 6.90 (2H,m), ~7.20 (2H,m); m/e 412 (M^+), 398, 397, 381, 368, 328]

The overall yield (23 %) from the starting acid chloride (1) makes this route an attractive process for the synthesis of these pharmacologically interesting bisbenzocyclooctadiene lactones particularly in view of their low concentration in the natural plant source.[1]

After this work had been completed a preliminary communication appeared describing the synthesis of steganone by a different approach.[11]

Acknowledgements

We thank Professor S.M. Kupchan for his courtesy in providing a sample of (-) steganone and the Science Research Council and Roche Products Ltd., for financial support.

REFERENCES AND NOTES

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2. A.H. Parijs, Rec. Trav. Chim., 49, 27 (1930).

3. The parent acid is most conveniently obtained from 2,6-dimethoxyphenol by the method of J.H. Short, D.A. Dunnigan and C.W. Ours, Tetrahedron 29, 1931, (1973) followed by methylation and hydrolysis.

4. Spectroscopic properties and analytical data are in complete accord with the assigned structure.

5. A.P. Krapcho, E.G.E. Jahngen, A.J. Lovey and F.W. Short, Tetrahedron Lett.,1091, (1974).

6. The E-isomer of the enamine shown (5) is obviously that involved in the photocyclisation and would be a constituent of the photo-equilibrium mixture even if the starting enamine possessed the Z configuration. The actual stereochemistry of the starting enamine about the double bond is not yet firmly established.

7. Cf. M.F. Semmelhack, B.P. Chong, R.D. Stauffer, T.D. Rogerson, A.Chong and L.D. Jones, J. Amer. Chem. Soc., 97, 2507 (1975).

8. For model experiments see D. Becker, L.R. Hughes and R.A. Raphael, Chem. Comm., 430 (1974).

9. This process oxidises the alcohol formed by a cross-Cannizzaro process back to the required ketone.

10. The aldolisation and oxidation were carried out at room temperature. This process gave a stereoisomer of steganone which underwent ready thermal isomerisation to steganone itself.

11. A.S. Kende and L.S. Liebeskind, J. Amer. Chem. Soc., 98, 267 (1976).