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A NEW TOTAL SYNTHESIS OF (±) STEGANONE

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As part of a program pertaining to the total synthesis of antileukemic bis-benzocyclooctadiene lignans, we have shown the feasibility of preparing highly substituted diphenyl compounds by means of an ULLMANN reaction between two hindered halides (1). We have also shown that inter- and intramolecular α-hydroxyalkylation of γ-butyrolactones could be carried out in excellent yields using lithium hexamethyl disilylamide (LHDS) as a basic agent (2,3). We have used both these reactions in the following total synthesis of (±) steganone 14.

An ULLMANN reaction between bromo-6 piperonal 1 and the aromatic iodide 2 (1) at 225°C for 35 mn, afforded the diphenyl 3, m.p. 154-165°C in 59 % yield. Treatment of the latter with LHDS (3.5 equ.) in benzene/hexane 4/1 at 15°C gave an amorphous solid in quantitative yield. Column chromatography of this solid yielded two stereoisomeric bis-benzocyclooctadienols 4, m.p. 218-225.5°C ($CHCl_3/Et_2O$) (head fraction) and 5, m.p. 196-198.5°C ($CHCl_3/Et_2O$), whose stereochemistry was not elucidated. JONES's oxidation of the alcohol 4 afforded the enol 6, m.p. 220°C (positive $FeCl_3$ test), whereas the alcohol 5, under the same conditions, presumably gave an unstable β-keto lactone 7, which spontaneously isomerized into the enol 6. The crude mixture of the alcohols (4 + 5) was oxidized (JONES's reagent) to give a mixture of 6 and 7 in quantitative yield (crude). Crystallization of this mixture from methanol afforded the enol 6 in 52 % yield. Alternatively, column chromatography on silica of the crude mixture of (6 + 7), followed by spontaneous isomerisation at room temperature, gave the enol 6 in 65 % yield.

On treatment with aqueous $Ba(OH)_2$, the crude mixture of 6 and 7 underwent decarboxylation to give a mixture of β-hydroxymethyl ketones 8 and 9 in 80 % yield (not isolated ; two spots in TLC). The same mixture of isomers 8 and 9 was also obtained by decarboxylation of the purified enol 6. The crude mixture of 8 and 9 was oxidized with JONES's reagent, and the resulting mixture of acids 10 and 11 was esterified with BF_3/MeOH, to give the γ-ketoesters 12 and 13 which could be separated and purified by column chromatography with a total yield of 41 % from the diphenyl 3. The head ester 12 had m.p. 130-134°C ($CHCl_3/Et_2O$), whereas its isomer 13 had m.p. 131-134.5°C ($CHCl_3/Et_2O$). Both esters were identified by comparison with authentic samples.

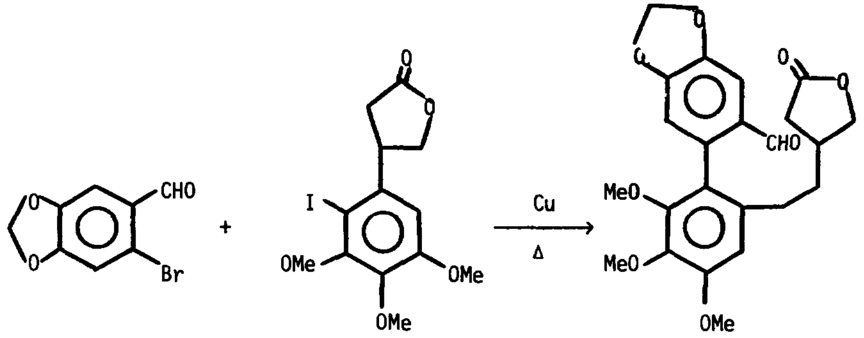
Synthesis of (±) steganone 14.

By carrying out the afore-mentioned reaction sequence on the crude mixture of stereoisomeric alcohols (4 + 5), without separation or purification of the various intermediates, we obtained the crude mixture of the acids (10 + 11), which we subsequently treated with 30 % aqueous formaldehyde, followed by JONES's oxidation. After removal of any residual acidic material from the reaction product, the latter was heated in refluxing xylene, to afford (±) steganone 14 in 20.7 % yield (from the purified diphenyl 3), m.p. 231-233°C after 3 recrystallizations from EtOH/CH_2Cl_2 (6).

(±) Steganone 14 was thus obtained with an overall yield of 7 % starting from trimethoxybenzaldehyde. On the other hand, esterification of the crude mixture of acids 10 + 11, followed by chromatography, gave the purified and separated esters 12 and 13 with a total overall yield of *ca.* 14.5 %. Since both these esters can be transformed into (±) steganone 14 in 75 % yield (with recycling of the unreacted starting material) (4,5), our present total synthesis of (±) steganone 14, *via* the esters (12 + 13), has an overall yield of 11 % starting from the commercially available trimethoxybenzaldehyde (7).

Conclusion.

We have developed a new total synthesis of (±) steganone 14 in eleven steps from bromo-6 piperonal and trimethoxybenzaldehyde. The overall yield of our synthesis (*ca.* 11 %) is comparable to that reported by KENDE (*ca.* 10 %) (4) and ZIEGLER (*ca.* 9 %) (8), but is



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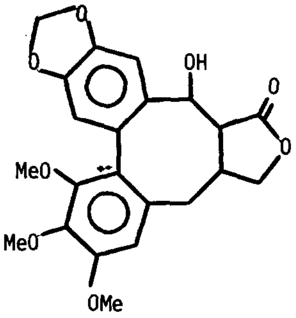
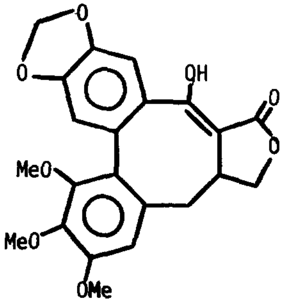


4 + 5



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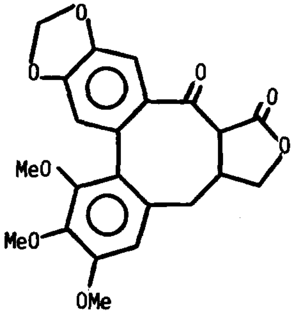

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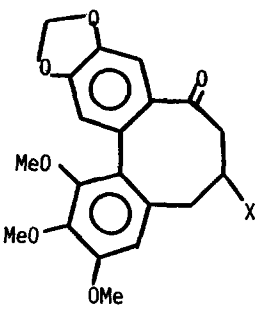
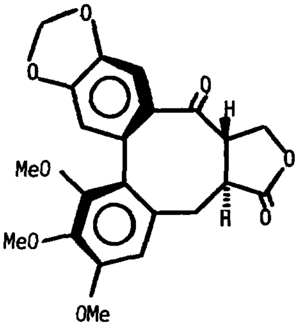


8, 9 R = CH_2OH
10, 11 R = CO_2H
12, 13 R = CO_2Me



14

twice as low as that observed by RAPHAEL (*ca.* 23%%) (5). However, it is worth mentioning that our overall yield was calculated starting from trimethoxybenzaldehyde itself, and not from some deriving intermediate, contrary to RAPHAEL, ZIEGLER or KENDE's yields. Nevertheless, RAPHAEL's total synthesis of (±) steganone **14**, which was the first one to be published, appears to be the most efficient one so far.

Acknowledgements.

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(6) We used our racemic steganone **14** to prepare the known (4,5) (±) steganol, m.p. 115-118°C (MeOH) and m.p. 155-157.5°C (Et_2O), and (±) steganacin, m.p. 222-222.5°C ($EtOH/CH_2Cl_2$).

(7) Satisfactory analytical data were obtained for all the compounds described in this paper.

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