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THE TOTAL SYNTHESIS OF CANNITHRENE-2

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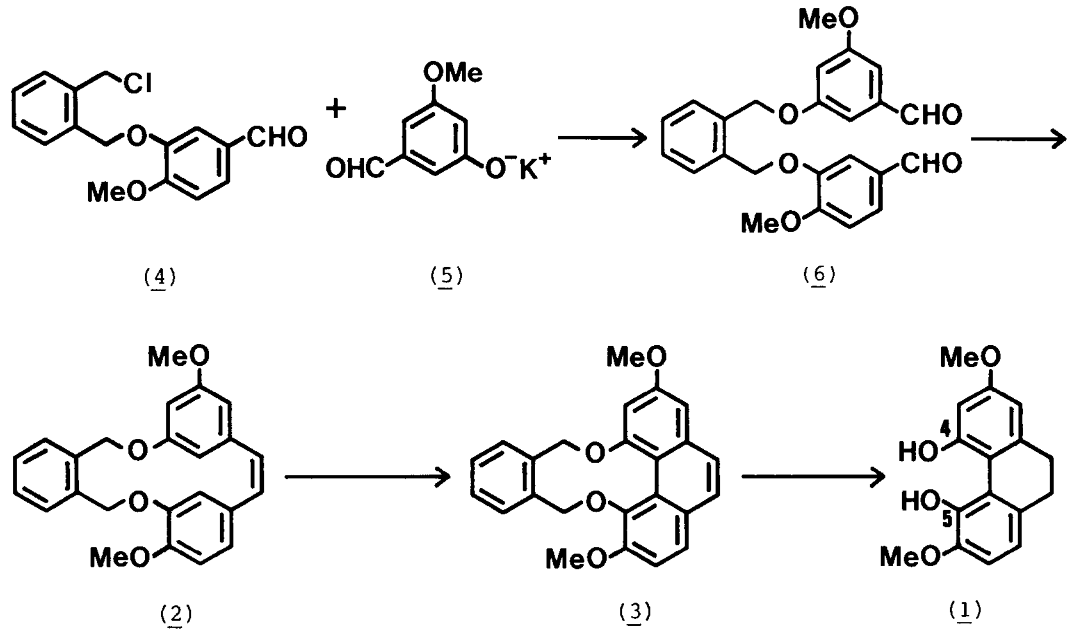
Abstract: The first total synthesis of cannithrene-2 (1), a 4,5-disubstituted phenanthrene, is reported. It is based on the regioselective cyclization of a key cyclophane (2) with a rigid cis-stilbene moiety.

Δ^1-Tetrahydrocannabinol has long been known as the main cause of the biological effects produced by the administration of the leaves of *Cannabis sativa*. However, this compound is not likely to explain, by itself, or together with other cannabinoids the complete physiological response produced by the whole mixture from the leaves[1]. This led to a recent search for minor components from the acidic fraction of the leaf extract from *Cannabis*[2]. Thus, the novel phenolic dihydrophenanthrene cannithrene-2 (1), was isolated and its structure fully confirmed by single crystal X-ray analysis of its diacetate.

Most phenanthrene syntheses are based on the formation of the biarylic bond. However, the application of this approach to the synthesis of 4,5-substituted phenanthrenes is known to give[3] low yields in the formation of the above-mentioned strategic bond due to steric repulsions between the substituents.

We wish now to report the first total synthesis of cannithrene-2, a 4,5-substituted phenanthrene. This novel approach is based on the regioselective cyclization of a suitable cyclophane (2) which, due to its rigid structure, can only afford the required phenanthrenic precursor (3).

The synthesis of the key cyclophane (2) was carried out by treating the sodium salt of 3-hydroxy-4-methoxybenzaldehyde with three equivalents of 1,2-bis(chloromethyl)benzene in DMF, to give a 73% yield of monochloride (4)[4] (m.p. 92-93°C). The potassium salt of 3-hydroxy-5-methoxybenzaldehyde (5)[5] was then reacted with compound (4) in DMF, yielding the dicarbonylic compound (6)[4] (80%, m.p. 127-129°C). This, by reductive coupling with active titanium[6] ($TiCl_3$, Zn-Cu couple, THF,reflux) under high dilution conditions afforded a 65% yield of the desired cyclophane (2)[4,7] (m.p. 151-153°C). UV irradiation of (2) (pyrex filter,Et_2O,I_2,O_2) gave a 70% yield of phenanthrene (3)[4] (m.p.215-217°C). Carefully purified (3) was then catalytically hydrogenated (10% Pd/C) in acidic dioxane-EtOH to give 90% yield of cannithrene-2 (1), whose structure was fully confirmed by direct comparison with authentic material (^{1}H-RMN, UV, MS, mixed m.p., TLC).



(4) (5) (6)

(2) (3) (1)

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3. A.J.Floyd, S.F.Dyke and S.E.Ward, Chem.Rev., 76, 509, 1976.
4. All new compounds gave satisfactory spectral and analytical data.
5. 3-Hydroxy-5-methoxybenzaldehyde was obtained in 73% yield by treating a dilute solution of commercially available 3,5-dimethoxybenzaldehyde in boiling DMF with 3 equiv. of EtSNa. Work-up should be done by pouring dil. AcOH and 26% formalin , prior to extraction with AcOEt, to avoid reaction of EtSH with the demethylated benzaldehyde. This synthesis greatly improves the previous ones. See F.Mauther, Journal für Praktical Chemie, 116, 314, 1927 and, E.Späth and K.Kromp, Chem.Ber., 74, 1424, 1941.
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7. ^{1}H-NMR(Cl_3CD,300 MHz): 7.46-7.40(sym. m,2H), 7.27-7.22(sym. m,2H), 6.92 (d,J=2.1 ,1H), 6.79 (d,J=8.3 ,1H), 6.73 (dd,J=8.3 and 2.1 ,1H), 6.50 (t, J=2.2 ,1H), 6.47-6.45(m,1H), 6.42 (d,J=12.1 ,1H), 6.35 (d,J=12.1 ,1H), 6.35-6.33(m,1H), 5.05 (s,2H), 5.03 (s,2H), 3.90 (s,3H) and 3.75 (s,3H) ppm.

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