A NOVEL STEREOSELECTIVE SYNTHESIS OF MORPHINANS

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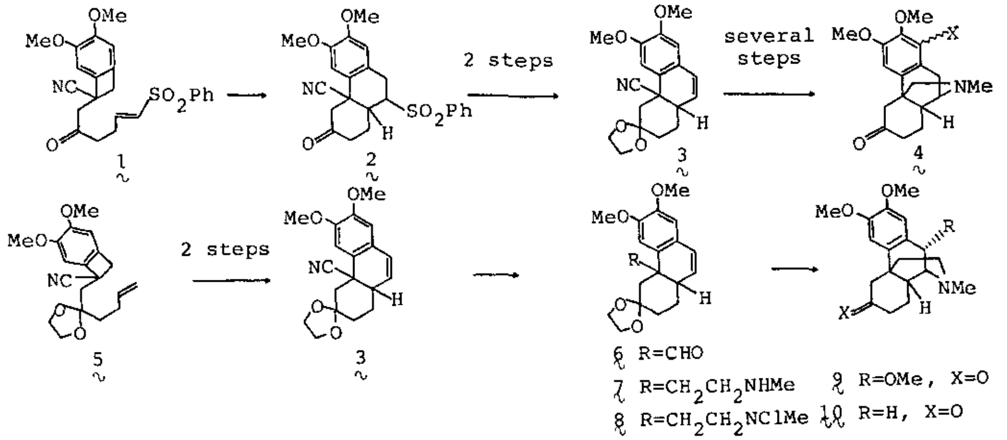
Since morphine alkaloids comprise a large and important family of natural products, the methods for their synthesis are still of interest. Many of morphine alkaloids usually possess a B/C cis-hydrophenanthrene skeleton as ABC ring system, we therefore planned to develop a general synthetic route to morphinans *via* a B/C cis-hydrophenanthrene. The B/C cis-hydrophenanthrene 2, a key intermediate, was synthesized stereoselectively by an intramolecular Diels-Alder reaction of 1-cyanobenzocyclobutene derivative 1 as a key step. The compound 2 was then converted into the olefin 3, by two steps, whose transformation to D-normorphinan 4 was succeeded by employing a cyclization of the corresponding N-chloro derivative *via* an amilynium intermediate.

Further investigation of a Diels-Alder reaction of 1-cyanobenzocyclobutene derivative 5 provided a facile synthetic route of 3. Treatment of 3 with DIBAL afforded 6, which was converted to the methylamine derivative 7 in six steps. Cyclization reaction of 8, obtained by treatment of 7 with NCS, gave the substituted morphinan 9, which was converted to the known compound 10 by reductive demethoxylation, followed by deprotection of the ketal group.

Thus, we could device a novel stereoselective synthesis of morphinans and this method would be applicable to the naturally occurring morphine alkaloids.



6 R=CHO
7 R=CH_2CH_2NHMe
8 R=CH_2CH_2NClMe
9 R=OMe, X=O
10 R=H, X=O