Total synthesis of yuehchukene

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Abstract: Various methods for synthesis of the bis-indole alkaloid yuehchukene are discussed with special emphasis on methods based on tetracyclic 2-acylindoles as intermediates.

The bis-indole alkaloid, yuehchukene (1), was isolated (1985) from the roots of Murraya paniculata in small amounts, (as a racemate) and later also from an other species. The compound was reported to possess strong anti-implantation activity in rats as well as in mice. For example, at a dosage of 3 mg/kg given orally on pregnancy day 2, 1 totally prevented implantation in a group of rats. A moderate anti-implantation activity in Guinea pigs has also been reported. The novel structure and the interesting anti-implantation activity has triggered several synthetic studies. The earliest approaches were based on acid-induced dimerization of 2, which gave surprisingly high yields (10-25%) of 1. Understandably chromatography purification was necessary.

Obviously the scope of the approach based on dimerization of 2 is rather limited, particularly if analogues are considered. Most of the alternative approaches center around tetracyclic 2-acylindoles (e.g. 3) as outlined in Scheme 1 (where 7 is 2,2,4-trimethyl-2,3-dihydrobenzaldehyde) and 2. It might be added that Grieco has condensed the alcohol 4 with indole in lithium perchlorate-diethyl ether in a yield of 86% and that analogues of 1 are readily available via other nucleophiles (e.g. N,N-dimethylaniline) in the last step.
In a related approach (Scheme 2) Kutney has converted isophorone to the dibenzoate of 2,2,4-trimethyl-6-hydroxy-2,3,5,6-tetrahydrobenzoic acid which with the indole Grignard reagent gave the acid (together with two isomers). After separation was transformed to benzoylated yuehchukene, plus some interesting isomers, as indicated in Scheme 2. the total yield of yuehchukene, however, is quite low (4%). An interesting aspect of this methodology is that 6a-epi-yuehchukene can be made via the ketone 8.
A third variant is due to Cheng et al. who reacted the diene 14 with acrylic acid in refluxing benzene, which gave a 4:1 epimeric mixture of the adducts 15 and 16 in 79% yield. Treatment of 15 with polyphosphate ester (PPE) in refluxing chloroform gave the ketone 17 which was subsequently reduced and benzoylated. Reaction of 18 with the indole Grignard reagent and deosylation gave the yuehchukene analogue 19.

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\begin{align*}
\text{14} & \xrightarrow{\text{CO}_2\text{H}} \text{15} \text{ and } \text{16} \\
\text{15} & \xrightarrow{\text{PPE}} \text{17} \\
\text{18} & \xrightarrow{\text{IndolylMgBr, Red., CsHsCOCI, DMAP}} \text{19}
\end{align*}
\]

Scheme 3

This approach has a limited scope and yuehchukene itself cannot be prepared by this route because p,p-dimethylacrylic acid fails to react with 14. Thus in conclusion to date our method outlined in Scheme 1 is the method of choice for the synthesis of yuehchukene as well as several of its analogues.
References and Notes


(9a) Bergman, J.; Venemalm, L., Tetrahedron Lett., 2993 (1988);


