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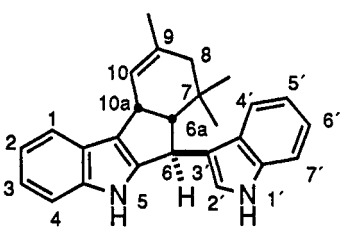
Total synthesis of yuehchukene

Jan Bergman and Lennart Venemalm

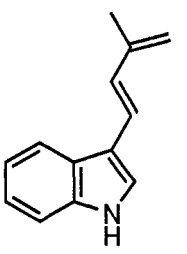
Department of Organic Chemistry, Royal Institute of Technology,
S-100 44 Stockholm, Sweden
and
Department of Organic Chemistry, CNT, Novum Research Park,
S-141 57 Huddinge, Sweden

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* [1] in small amounts,[1] (as a racemate) and later also from an other species[2]. The compound was reported to possess strong anti-implantation activity in rats[1b] as well as in mice,[3] For example, at a dosage of 3 mg/kg given orally on pregnancy day 2, **1** totally prevented implantation in a group of rats.[1b] A moderate anti-implantation activity in Guinea pigs has also been reported.[4] The novel structure and the interesting anti-implantation activity has triggered several synthetic studies. [5-14] The earliest approaches [5-8] were based on acid-induced dimerization of **2**, which gave surprisingly high yields (10-25%) of **1**. Understandably chromatography purification was necessary.

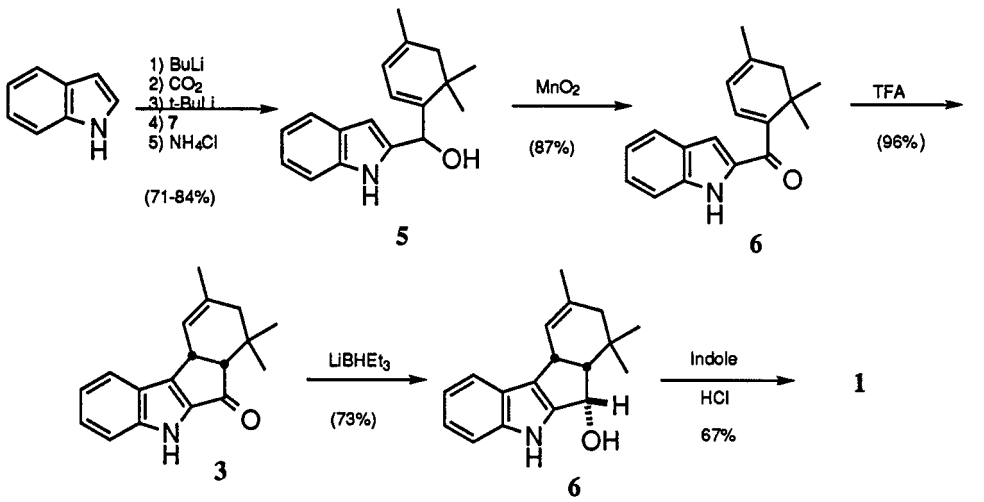


1



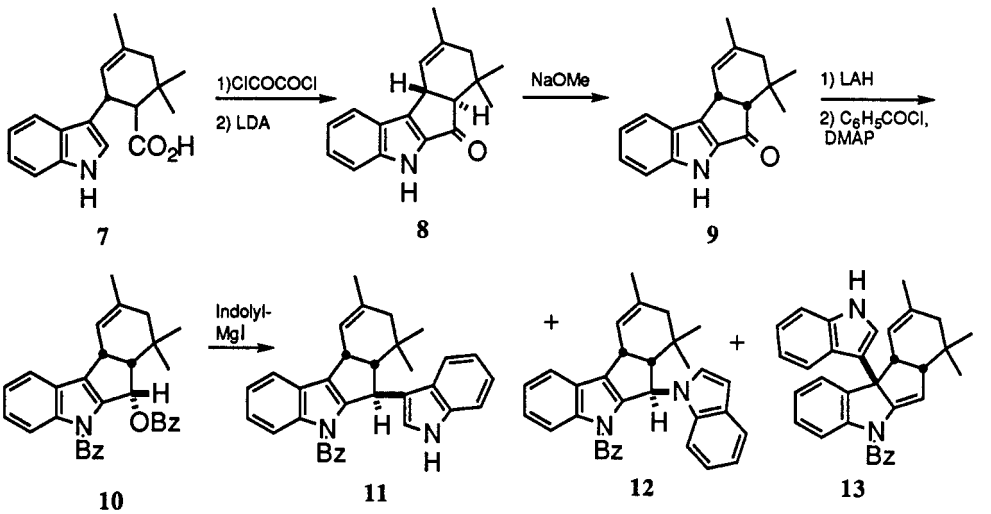
2

Obviously the scope of the approach based on dimerization of **2** is rather limited, particularly if analogues are considered. Most of the alternative approaches[9-14] 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.



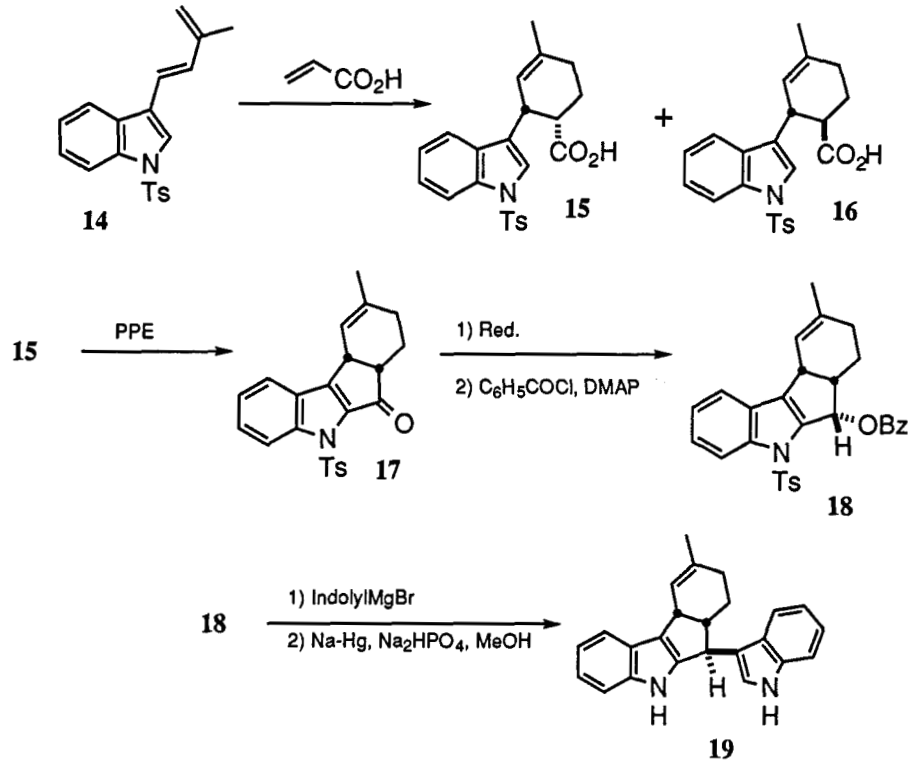
Scheme 1

In a related approach (Scheme 2) Kutney has converted[11] 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 **7** (together with two isomers). After separation **8** 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**.



Scheme 2

A third variant is due to Cheng et al.[13] 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 detosylation gave the yuehchukene analogue **19**.



Scheme 3

This approach has a limited scope and yuehchukene itself cannot be prepared by this route because β,β-dimethylacrylic acid fails to react with **14**. Thus in conclusion to date our method[9] outlined in Scheme 1 is the method of choice for the synthesis of yuehchukene as well as several of its analogues.

References and Notes

(1) Kong, Y.-C.; Cheng, K.-F.; Cambie, R.C.; Waterman, P.G.,Chem. Commun., 47 (1985),.(b) Kong, Y.-C.; Ng, K.-H.; Wat, K.-H.; Wong, A.; Saxena, I.F.; Cheng, K.-F.; But, P.P.-H.; Chang, H.-T., Planta Med., **44**, 304(1985) .

(2) Kong, Y.-C.; Cheng, K.-F.; Ng, K.-H.; But, P.P.-H.; Li, Q.; Yu, S.-X.; Chang, H.-T.; Cambie, R.C.; Kinoshita, T.; Kan, W.-S.; Waterman, P.G., Biochem. Syst. Ecol., **14**, 491.(1986)

(3) Wang, N.-G.; Guan, M.-Z.; Lei, H.-P.,Ydoxue Xuebao, **25**, 85 (1990); Chem. Abstr., **113**, 670v (1990).

(4) Hammarström, M.; Venemalm, L.; Bergman, J.; Eneroth, P., Am. J. Chinese. Med., **18**, 1 (1990).

(5) Cheng, K.-F.; Kong, Y.-C.; Chan, T.-Y., Chem. Commun., 48 (1985).

(6) Wenkert, E.; Moeller, P.D.R.; Piettre, S.R., J. Org. Chem., **53**, 3170 (1988).

(7a) Sheu, J.-H.; Chen, Y.-K.; Hong, Y.-L.V., Tetrahedron Lett., 1045 (1991).

(7b) Sheu, J.-H.; Chen, Y.-K.; Hong, Y.-L.V., J. Org. Chem., **58**, 5784 (1993).

(8) Sheu, J.-H.; Chen, Y.-K.; Hong, Y.-L.V., J.Org.Chem., **56**, 5781 (1991).

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

(9b) Bergman J.; Venemalm, L., Tetrahedron, **46**, 6067 (1990).

(9c) Bergman J.; Venemalm, L., Tetrahedron, **48**, 759 (1992).

(10) Henry Jr, K.J and Grieco, P.A., Chem.Comm., 510 (1993).

(11) Kutney, J.P.; Lopez, F.J.; Huang, S.-P.; Kurobe, H.; Flogaus, R.; Piotrowska, K.,. Can. J. Chem., **69**, 949 (1991).

(12) Cheng, K.-F.; Chan, T.-Y.; Lai, T.-F.; Kong, Y.-C., J. Chem. Soc. Perkin Trans.I, 3317 (1988).

(13) Cheng, K.-F.; Chan, T.-Y.; Lai, T.-F., J.Chem.Soc., Perkin Trans.I, 2461 (1991).

(14) Cheng, K.-F.; Wong, T.T.; Chan, K.-P.; Kong, Y.-C., Eur. J. Med. Chem., **27**,121 (1982).