A GENERAL APPROACH TO THE TOTAL SYNTHESIS OF YUEHCHUKENE AND ITS ANALOGUES. A NOVEL ANTI-IMPLANTATION AGENT*

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Abstract - A versatile synthetic strategy has been developed for the synthesis of the interesting dimeric indole natural product yuehchukene (17) and its epimer, 6a-epi-yuehchukene (22). Due to the anti-implantation activity associated with 17, it is important to develop a synthetic route *not only to* 17, *but to a family of yuehchukene analogues* with better chemical stability and/or elevated biological activity. The strategy described here and which utilizes the readily available and inexpensive isophorone (1) satisfies these requirements.

Yuehchukene (17) (its name derives from the word yueh-chu, which is the name of the plant in Chinese), an interesting dimeric indole natural product isolated initially from Murraya paniculata[1] and subsequently from other Murraya species[2,3] has attracted considerable attention due to its significant anti-implantation activity. Its racemic nature has led to the speculation that its biosynthesis involves a non-enantioselective Diels-Alder cycloaddition of two units of 3-isoprenyl indole. Although direct evidence for the biosynthetic pathway is lacking, this proposal was considered for its chemical synthesis and a low yielding acid-induced dimerization of 3-isoprenylindole has been achieved to afford the natural product[5,6]. More recently, another synthesis of yuehchukene, employing a different approach, has been published[7].

It is well known that the sensitivity of 17 towards oxidation, facile decomposition in acidic media and solvents, for example, creates considerable difficulties in the essential formulation studies required for biological evaluation. As a result, search for yuehchukene

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* This article is dedicated to Sir Derek Barton on the occasion of his 70th birthday. The authors express to Sir Derek their sincere wishes for continued good health so that he may continue his excellent chemical career for many more years.

analogues with higher stability and/or elevated anti-implantation activity is highly desirable. The synthetic strategy described herein is directed to that end, that is, an approach with sufficient versatility to provide not only the natural product, but also routes to closely related structural analogues.

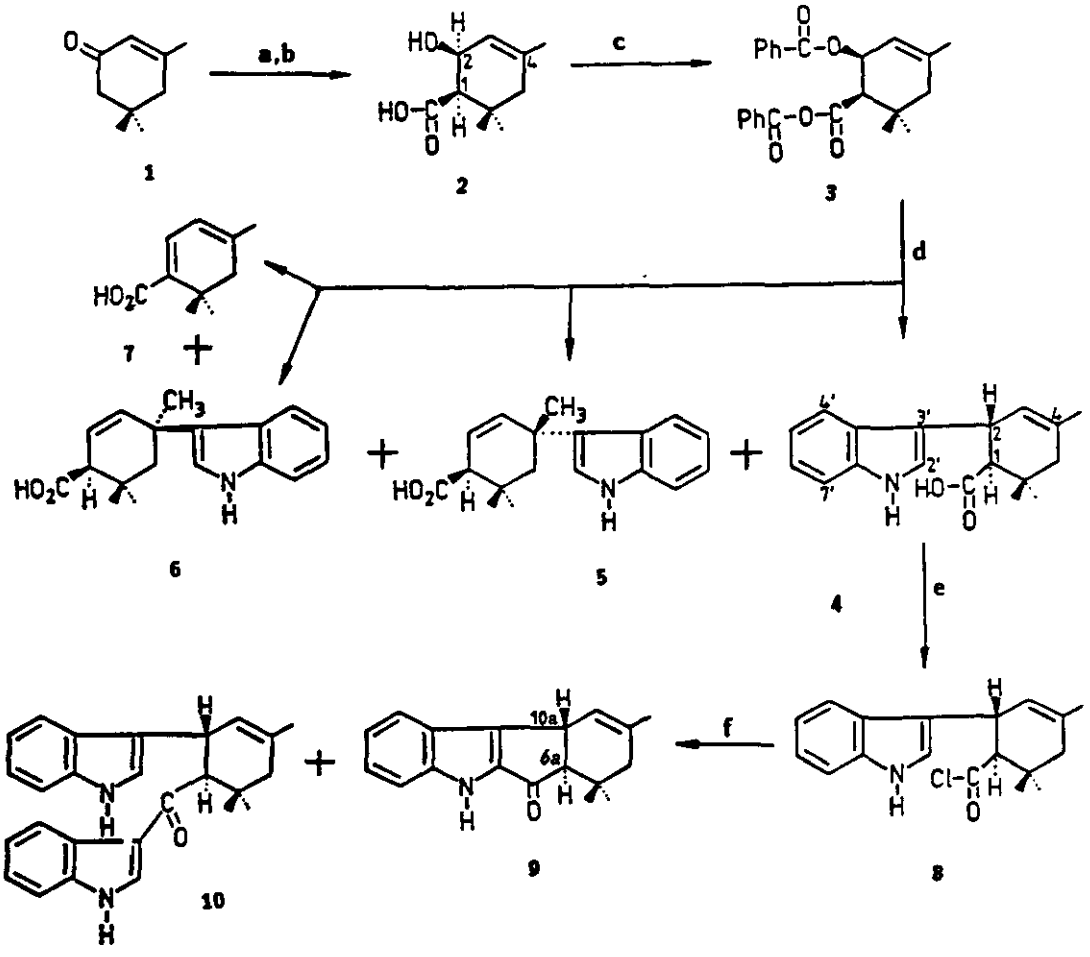
The starting material for our synthetic strategy is the readily available and inexpensive isophorone (1, Scheme 1). Kinetic carboxylation of 1 with lithium 2,6-di-tert-butyl-4-methylphenoxide and CO_2[8] afforded an unstable keto-acid which was directly reduced in situ ($NaBH_4$, MeOH) to the crystalline cis-hydroxy acid 2, (mp 115-116°C) in excellent overall yield (>95%, based on recovered starting material)[9]. The coupling constant of 6 Hz between H_1 (δ 4.45) and H_2 (δ 2.69) established the stereochemistry presented. The isomeric trans-hydroxy-acid ($J_{H_1-H_6}$ = 10Hz) was formed in only trace amounts.

Dibenzoylation of 2 afforded 3 and the latter upon treatment with indolylmagnesium iodide afforded the desired crystalline indoleacid 4 (mp 173-174°C, 40% yield), the oily byproducts 5 (26%), and 6 (3%) and the crystalline unsaturated carboxylic acid 7 (mp 115-117°C, 15%). Clearly 5 and 6 arise via displacement of the C_2-benzoate function in a SN_2-like manner or alternatively via reaction of the indolylmagnesium halide with the resultant resonating allylic carbocation formed when the C_2-benzoate function is cleaved (SN_1 mechanism). In view of the observed stereochemistry in the major byproduct (5) and considering the established stereochemistry in 2, the latter mechanism appears preferable. The stereochemistry of 4 at C_1 and C_2 was determined by nmr ($J_{H_1-H_2}$ = 10 Hz).

The next objective in our synthetic strategy involved cyclization of 4 into a tetracyclic ketone, for example, 9, since through subsequent epimerization at C-6a (see 9), this intermediate could allow an entry into both the natural yuehchukene (17) and 6a-epi-yuehchukene (22) series. For this purpose, various conditions (polyphosphoric acid[10], polyphosphate ester[11]) for direct cyclization of 4 to 9 were attempted without success. In similar manner, the acid chloride 8, obtained upon treatment of 4 with oxalyl chloride, also failed to undergo an intramolecular Friedel-Crafts acylation ($ZnCl_2$ in nitrobenzene)[12]. However slow addition of indolylmagnesium iodide in ether-dichloromethane at -15°C furnished the crystalline trans ketone 9 (mp 129-131°C, 46% yield) and the indole ketone 10 as a byproduct (14% yield). This reaction was studied extensively (varying equivalents of Grignard reagent, reaction temperature and time of addition). It was shown that if the addition is

reversed, that is, addition of 8 to a solution of the Grignard reagent, the ratio of undesired 10 to the desired ketone 9 was increased. The stereochemistry of 9 was established by X-ray analysis data.

Scheme 1



(a) Lithium 2,6-di-tert-butyl-4-methylphenoxide (3 equiv.), CO_2 gas, ether; (b) $NaBH_4$, MeOH, 10°C; (c) PhCOCl (2.1 equiv.), DMAP, CH_2Cl_2, 5°C; (d) Indolylmagnesium iodide (4 equiv.), ether-CH_2Cl_2, 5°C; (e) $(COCl)_2$ (3 equiv.), benzene; (f) Indolylmagnesium iodide (3.2 equiv.), ether-CH_2Cl_2, -15°C → r.t., 46% overall yield of 9 from 4.

Scheme 2 outlines the remaining steps of the synthetic route to natural yuehchukene. Epimerization of 9 with sodium methoxide in refluxing methanol afforded the crystalline cis ketone 11 (mp 220-223°C) in quantitative yield. It was of interest to note that in their nmr spectra, the proton signals of the C-6a and C-10a carbon centers were different in the two isomeric ketones (in 9: δ 2.84 (d) C-6a and 3.99 (m) C-10a; in 11: δ 2.89 (d) C-6a and 4.05 (m) C-10a), but the coupling constant $J_{H_{6a}-H_{10a}}$ was identical (6 Hz) in both compounds, thereby requiring X-ray analysis to settle the stereochemistry, as noted above.

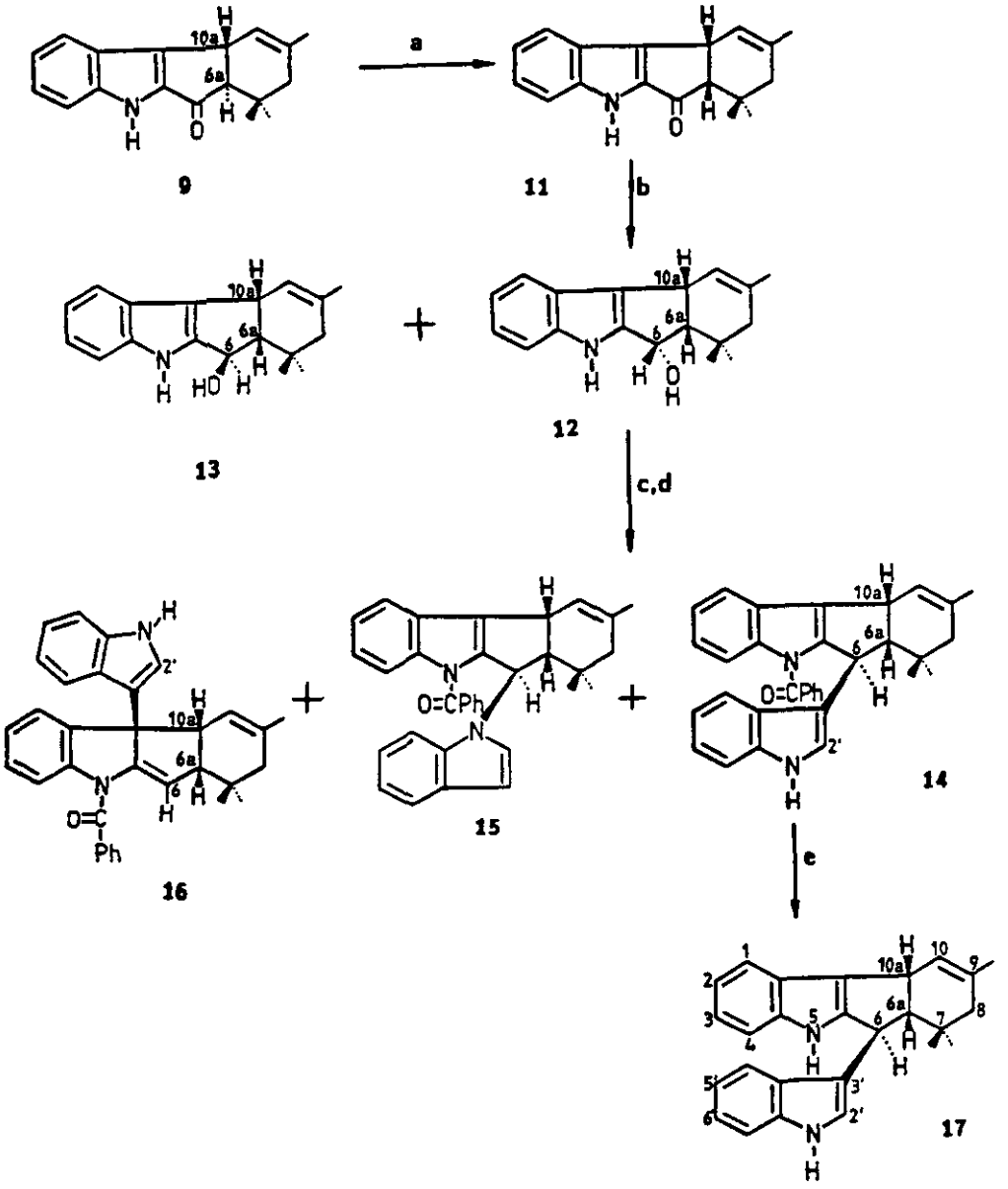
Hydride reduction of the cis ketone (11) to the corresponding alcohol depended upon the reagent employed. With lithium aluminum hydride, the desired crystalline alcohol 12 (mp 159-162°C), bearing the alcohol function in the α-orientation, was obtained in 65% yield while the β-isomer 13, (mp 149-150°C) was obtained in 35% yield. On the other hand, with L-selectride, the reduction proceeds to 12 as the exclusive product albeit in lower yield (50%). nmr experiments, involving deuterium exchange and NOE, were employed to establish the stereochemistry at C-6 in these isomeric alcohols.

Dibenzoylation of 12, followed by reaction of the latter with indolylmagnesium iodide provided N-benzoylyuehchukene (14, 40%) as a foam, the N-substituted indole system 15, (18%) as an oil and the crystalline indoline 16, (mp 250-252°C, 30%). The structure of 16 was unambiguously established by data on X-ray analysis. It is clear from these results that the Grignard reagent reveals nucleophilic character on carbon (C-3′) and nitrogen in its displacement of the benzoate group at C-6 in 12 to afford 14 and 15 respectively. The indoline structure 16 arises from a mechanistically interesting reaction.

To complete the synthesis of yuehchukene (17), the benzoyl group in 14 was removed (sodium methoxide in methanol) and the product obtained in 90% yield, was identical in every respect with the natural product kindly provided by Professor Y.C. Kong.

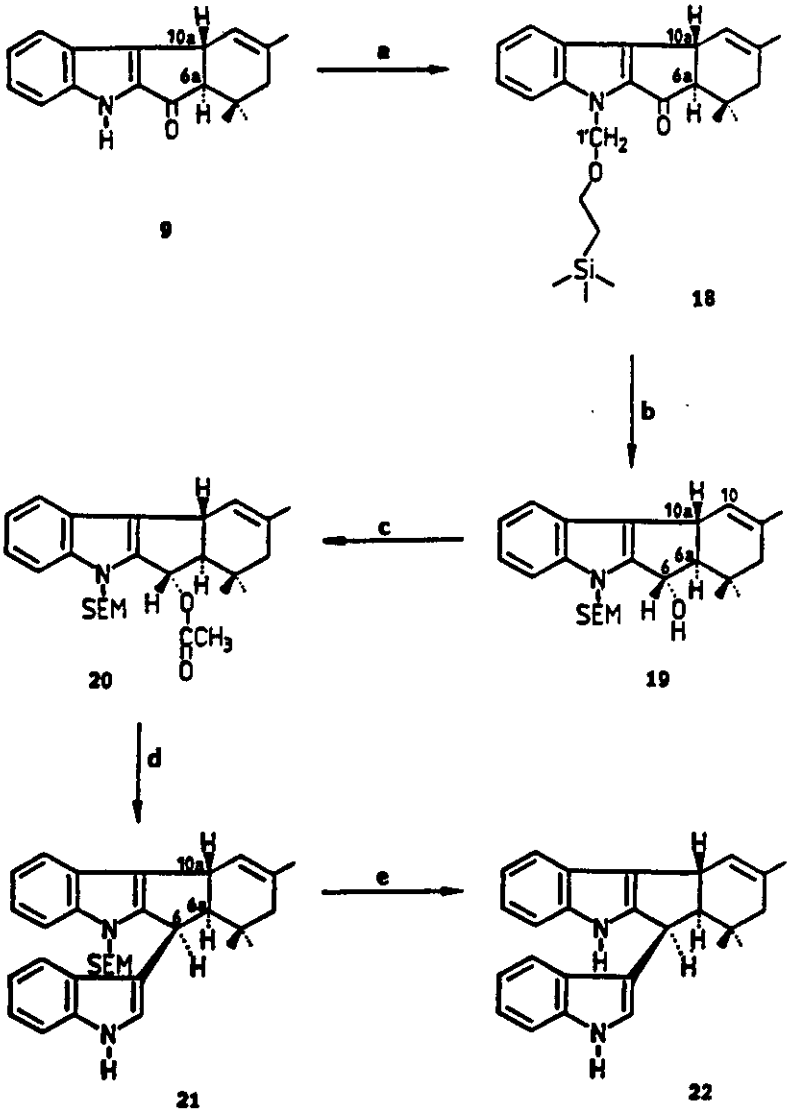
The synthesis of 6a-epi-yuehchukene (22) from the trans ketone 9 is summarized in Scheme 3. It is pertinent to note that direct elaboration of the synthetic strategy outlined above was not applicable in several aspects of the overall synthetic route. For example, the N-benzoyl protecting group employed in the synthesis of N-benzoylyuehchukene (14), that is, in the conversion, 12 → 14, proved unsuitable in the trans series. Only complex reaction mixtures and decomposition products were obtained. Of the various other protecting groups evaluated

Scheme 2



(a) MeONa/MeOH, reflux; (b) LAH, THF; (c) PhCOCl (2.1 equiv.), DMAP (1.1 equiv.) Et_3N (5 equiv.), CH_2Cl_2, reflux; (d) Indolylmagnesium iodide, ether-CH_2Cl_2, 5°C, (e) MeONa/MeOH, 5°C.

Scheme 3



(a) NaH (1.2 equiv.), $(CH_3)_3Si(CH_2)_2OCH_2Cl$(SEM-Cl) (1.5 equiv.), CH_2Cl_2, 5°C; (b) DIBAL (1.5 equiv.), Toluene, -78°C; (c) Ac_2O (8.5 equiv.), DMAP (1.5 equiv.), $(CH_3CH_2)_3N$ (9 equiv.), CH_2Cl_2; (d) indolylmagnesium iodide (3 equiv.), ether-CH_2Cl_2; (e) n-Bu_4NF (20 equiv.), THF-HMPA, 40°C.

(acetate, tosyl etc.) the SEM (trimethylsilylethoxymethyl) group[13] proved most desirable. Consequently 9 was treated with SEMchloride and the resulting derivative obtained in 93% yield, was reduced with Dibal to afford the desired alcohol 19 as the exclusive product (80%). The acetate derivative 20, obtained in 86% yield, proved superior to the benzoate employed in Scheme 2. Displacement of the acetate functionality by reaction with indolylmagnesium iodide furnished SEM-6a-epi-yuehchukene (21) as a pale yellow foam (36% yield). In contrast to the studies summarized in Scheme 2, the compounds corresponding to 15 and 16 were not observed in this series. Finally, removal of the SEM group was achieved with tetra-n-butyl ammonium fluoride[13,14] and the resultant product, obtained in 89% yield, as a white foam, revealed spectral properties characteristic of 6a-epi-yuehchukene (22).

In conclusion, the required versatility in the synthetic strategy, as described above, has been achieved. Functionalization in one of the indole ring systems to afford yuehchukene analogues can be readily accomplished in the coupling of ring-substituted indolylmagnesium halides with the benzoate derivative 3 (step d, Scheme 1), thereby providing intermediates for the synthesis of ring substituted analogues of 11 and, in turn, analogues of 17. On the other hand, introduction of functionality in the other indole ring system of 17 is readily accessible via the reaction of ring-substituted indolylmagnesium halides with 11 or its analogues (step d, Scheme 2). Obviously these variations can also be applied to the synthetic routes involved in the 6a-epi-yuehchukene series.

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REFERENCES

1. Y.C. Kong, K.F. Cheng, R.C. Cambie, and P.G. Waterman, Chem. Commun., 1985, 47.

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

3. Y.C. Kong, K.H. Ng, P.P. But, Q. Li, S.X. Yu, H.T. Zhang, K.F. Cheng, D. D. Soejarlo, N.S. Kan, and P. G. Waterman, J. Ethnoph., 1986, 15, 195.

4. Y.C. Kong, K.H. Ng, K.H. Wat, A. Wong, L.F. Lau, K.F. Cheng, P.P. But, and H.T. Chana, Planta Med., 1985, 304.

5. K.F. Cheng, Y.C. Kong, and T.Y. Chan, Chem. Commun., 1985, 48.

6. E. Wenkert, E.C. Angell, V.F. Ferreira, E.L. Michelotti, S.R. Pierre, J.H. Sheu, and C.S. Swindell, J. Org. Chem., 1986, 51, 2343.

7. J. Bergmann and L. Venemalm. Tetrahedron Lett., 1988, 29, 2993.

8. E.J. Corey and R.H.K. Chen. J. Org. Chem., 1973, 38, 4086.

9. All isolated products gave satisfactory elemental analyses, and spectral data (nmr, ms, ir and uv).

10. F.E. Ziegler and G.B. Bennett, J. Am. Chem. Soc., 1971, 93, 5930.

11. T. Imanishi, A. Nakai, N. Yagi, and M. Hanacka, Chem. Pharm. Bull. Japan, 1981, 29, 901.

12. Y. Langlois and P. Potier. Tetrahedron, 1975, 31, 423.

13. M.P. Edwards, S.V. Ley, S.G. Lister, B.D. Palmer, and D.J. Williams, J. Org. Chem., 1984, 49, 3503.

14. B.H. Lipshutz and J.J. Pegram. Tetrahedron Lett., 1980, 3343.

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