A CONCISE APPROACH TO ANTIFERTILITY AGENTS; STRUCTURAL ANALOGUES OF YUEHCHUKENE

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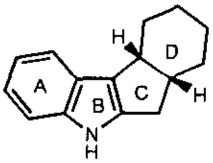
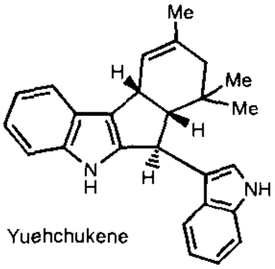
Abstract - Palladium catalyzed carbonylative cross-coupling reaction using lithium triethyl-(1-methylindol-2-yl)borate (**1**) was applied in a concise formation of structural analogues of yuehchukene.

Yuehchukene, bis-indole alkaloid isolated from the root bark of *Murraya paniculata* (L.) Jack,[1] exhibits strong anti-implantation activity in rats, mice and pigs.[2] Due to their potent biological activity, hexahydroindeno[2,1-*b*]indole nucleus common to yuehchukene and related compounds has recently received considerable attention.[3] There are several studies of synthetic approaches to yuehchukene and its analogues,[4] and their structure-activity relationships as well.[5] Mostly, hitherto known synthetic strategies can be grouped into those that use Diels-Alder process with dehydroprenylindoles, not well in yields, and those that involve the formation of unsaturated 2-acylindoles and their subsequent cyclization into hexahydroindeno[2,1-*b*]indoles.



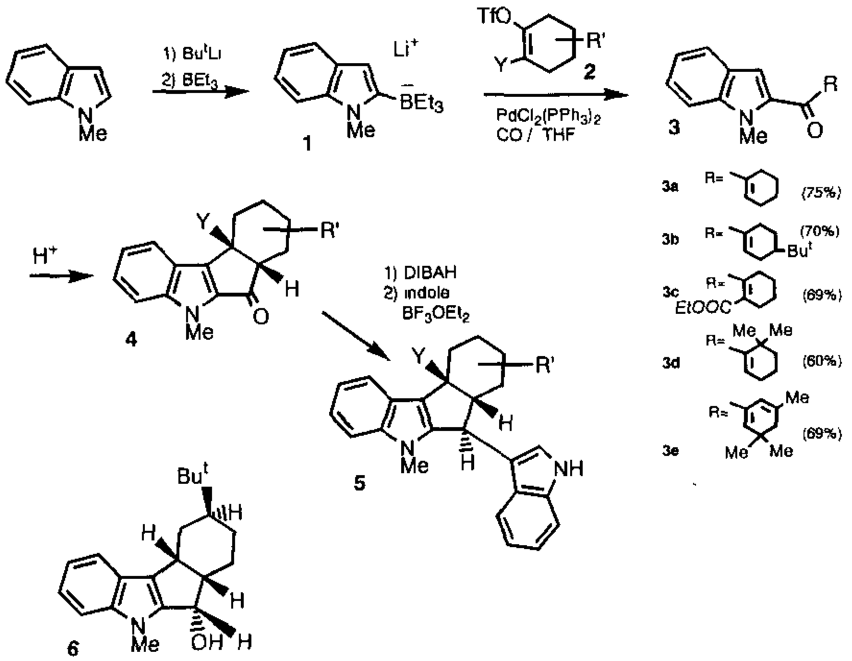
Hexahydroindeno[2,1-*b*]indole



Yuehchukene

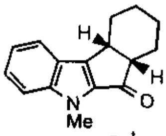
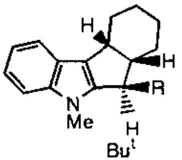
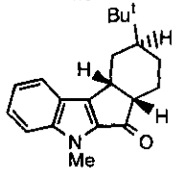
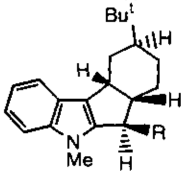
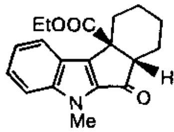
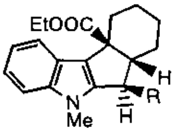
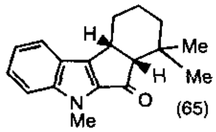
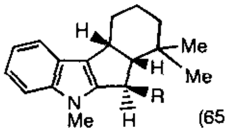
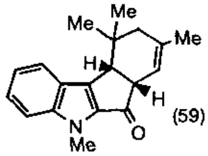
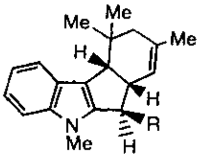
In conjunction with our continuing interest in synthetic use of indolylborate,[6] palladium catalyzed carbonylative cross-coupling reaction with indolylborate (**1**) proved to be a useful procedure for the formation of 2-acylindoles difficult to obtain by the conventional methods,[7] whose application in a simple approach to structural analogues of yuehchukene was pursued. These results are described in this paper.

Synthetically desirable 2-acylindole (**3**) was readily obtained from the carbonylation reaction of indolylborate (**1**) [generated *in situ* from 2-lithio-1-methylindole and triethylborane] with vinyl triflate (**2**) in the presence of $PdCl_2(PPh_3)_2$ (5 mol%) under carbon monoxide atmosphere (15 atm) in THF at 60°C (Scheme; yield of **3** is based on 1-methylindole). On heating of 2-acylindole (**3**) with acid (10% HCl or BF_3 etherate), closure of C ring could be effected to give indeno[2,1-*b*]indole (**4**) as a single isomer (Table), whose C/D ring cis configuration was confirmed by a NOE experiment. Conversion of **4** to yuehchukene analogue (**5**) was successfully attained through sequential steps; 1) reduction of **4** with DIBAH in THF at -78°C provided intrinsically unstable product that was used for the next step without purification, and 2) it was treated with indole (2 equiv.) in the presence of BF_3 etherate (2 equiv.) in ether (Table). On the reduction of **4b**, hydride attack from the least hindered side produced isolable alcohol (**6**) in 74% yield as a single isomer, being successufully characterized. NOE spectra were consistent with the assigned structure of **6**.



Scheme

Table Formation of yuehchukene analogues (**4**)[a]

3	condition[b]	4 (Yield %)[c]	5[d] (Yield %)[e]
3a	A	 **4a** (70)	 (70)
3b	A	 **4b** (60)	 (70)
3c	B	 **4c** (58)	 (68)
3d	A	 **4d** (65)	 (65)
3e	B	 **4e** (59)	 (60)

[a] All products gave satisfactory spectral data and elemental analysis [b] A; 10% HCl in dioxane at 100°C B; BF_3 etherate in benzene at 80°C [c] Isolated yield based on **3** [d] R = indol-3-yl [e] Isolated yield based on **4**

The palladium catalyzed carbonylative cross-coupling process could be well applied in a simple approach to structural analogues of yuehchukene (**5**), which has the advantages over preceding strategies in simplicity of the procedure, easy availability of 2-acylindole and inclusion of an additional functionality in **5**.

REFERENCES

1. Y. C. Kong, K. F. Cheng, R. C. Cambie, and P. G. Waterman, *J. Chem. Soc., Chem. Commun.*, 1985, 47; , 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. Systems Ecol.*, 1986, **14**, 491; 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. Ethnopharmacol.*, 1986, **15**, 195.
2. Y. C. Kong, K. H. Ng, K. H. Wat, A. Wong, I. F. Saxena, K. F. Cheng, P. P. But, and H. T. Chang, *Planta Med.*, 1985, **44**, 304; M. Hammarstrom, L. Venemalm, J. Bergman, and P. Eneroth, *Am. J. Chin. Med.*, 1990, **18**, 1.
3. C. Riche, A. Chiaroni, G. Dubois, R. Hocquemiller, M. Leboeuf, and A. Cave, *Planta Med.*, 1980, **39**, 206; F. Tillequin, M. Koch, M. Bert, and T. Sevenet, *J. Nat. Prod.*, 1979, **42**, 92.
4. E. Wenkert, P. D. R. Moeller, S. R. Piettre, and A. T. McPhail, *J. Org. Chem.*, 1988, **53**, 3171; J. Bergman and L. Venemalm, *Tetrahedron Lett.*, 1988, **29**, 2993; K. F. Cheng, T. T. Chan, and T. F. Lai, *J. Chem. Soc., Perkin Trans. 1*, 1988, 3317; J. P. Kutney, F. J. Lopez, S. P. Huang, and H. Kurobe, *Heterocycles*, 1989, **28**, 565; K. F. Cheng, T. Y. Chen, T. T. Wong, and T. F. Lai, *J. Chem. Soc., Perkin Trans. 1*, 1990, 1555; K. F. Cheng, K. P. Chan, and T. F. Lai, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2461; K. F. Cheng, K. P. Chan, Y. C. Kong, and D. D. Ho, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2955; J. H. Sheu, Y. K. Chen, and Y. L. V. Hong, *Tetrahedron Lett.*, 1991, **32**, 1045; J. P. Kutney, F. J. Lopez, S. P. Huang, H. Kurobe, R. Flogaus, K. Piotrowska, and S. J. Retting, *Can. J. Chem.*, 1991, **69**, 949; J. Bergman and L. Venemalm, *Tetrahedron*, 1992, **48**, 759; K. J. Henry and P. A. Grieco, *J. Chem. Soc., Chem. Commun.*, 1993, 510; J. H. Sheu, Y. K. Chen, and Y. L.V. Hong, *J. Org. Chem.*, 1993, **58**, 5784; K. F. Cheng, G. A. Cao, Y. W. Yu, and Y. C. Kong, *Synth. Commun.*, 1994, **24**, 64.
5. W. L. Chan, D. D. Ho, C. P. Lau, K. H. Wat, Y. C. Kong, K. F. Cheng, T. T. Wong, and K. P. Chen, *Eur. J. Med. Chem.*, 1991, **26**, 387; K. F. Cheng, T. T. Wong, K. P. Chan, and T. C. Kong, *Eur. J. Med. Chem.*, 1992, **27**, 121.
6. M. Ishikura, *J. Chem. Soc., Chem. Commun.*, 1995, in press; M. Ishikura, *Yuki Gosei Kagaku Kyokaishi* , 1995, **53** (4), in press.
7. M. Ishikura and M. Terashima, *J. Org. Chem.* 1994, **59**, 2634.

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