Palladium Catalysed Cross-Coupling Reaction With Indolylborate : A Concise Access to Ellipticine Derivatives

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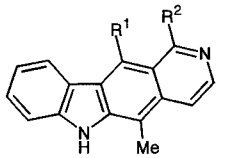
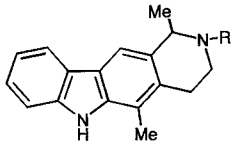
Abstract : A novel approach to ellipticine derivatives is described. The palladium catalysed cross-coupling reaction of indolylborate **1** with vinylbromides **4** gives hexatrienes **5**, which are subsequently converted to pyrido[4,3-b]carbazoles. In addition, the acid promoted spiroannelation reaction of hexatrienes **5** is observed to give spiroindoles **9**.

Compounds possessing pyrido[4,3-b]carbazole nucleus, such as ellipticine and olivacine, are known to have the remarkable antitumor activity, which has stimulated a large number of synthetic efforts, culminating in several total synthesis of these alkaloids as well as their unnatural derivatives.[1]

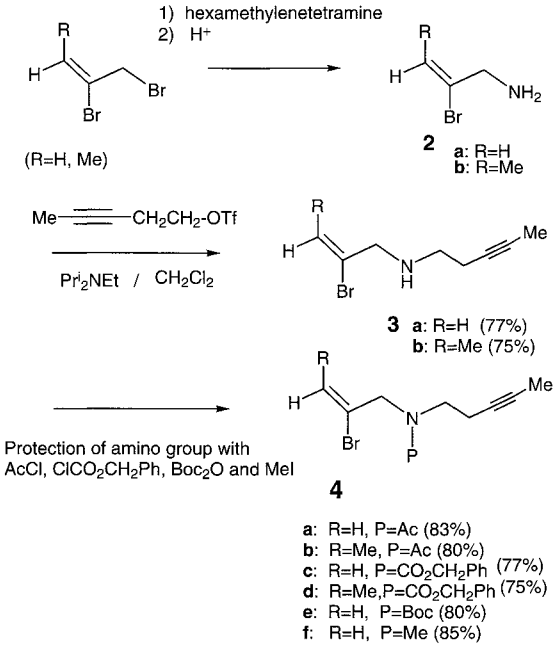


R^1=Me R^2=H Ellipticine
R^1=H R^2=Me Olivacine



R=Me Guatambuine
R=H Janetine

As a part of our ongoing studies of the synthetic use of indolylborate,[2] we describe here the preliminary results of our studies of the palladium catalysed cross-coupling reaction with indolylborate **1** resulting in a concise access to ellipticine derivatives, which comprises hexatriene **5** as a key intermediate for constructing pyrido[4,3-b]- carbazole system.



Scheme 1

Vinylbromides **4** readily available from allylamines **2**,[3] according to the conventional steps [i) alkylation of **2** (2 equiv.) with 3-pentynyl trifluoromethanesulfonate ii) protection of the amino group of **3**] as shown in Scheme 1, were subjected to the cross-coupling reaction with ca. 2 equiv. of borate **1** (generated *in situ* from 1-methylindole and tert-butyllithium, followed by treatment with triethylborane in THF) in the presence of a palladium complex (5 mol %) at 60°C under an argon atmosphere for 30 min, which provided hexatriene **5a,c,e** and vinylindole **6a-c** from **1** and **4a,c,e**, and **5b,d** from **1** and **4b,d.** Initially, $Pd(OAc)_2$ was used for the present reaction on the basis of our previous results.[2] When the reactions of **1** with **4b** and **4d** were performed, the yields of **5b** and **5d** were much lower and significant amounts of **4b** and **4d** were recovered even under the condition of the prolonged reaction time. It proved effective in these cases to use $PdCl_2(PPh_3)_2$ so as to generate **5b** and **5d** in adequate yields. However, on the reaction with **4f** having a basic amino group, there was no detectable trace of any cross-coupling products and hence, a substantial amount of unchanged **4f** was recovered, where a stabilizing Pd-N interaction by the intramolecular coordination of the amino group to palladium may hamper the catalytic cycle.

Having developed the construction of hexatrienes **5**, the conversion of **5** to pyrido[4,3-b]carbazoles **7** was then examined. Previously, Hibino, et al. have utilized an analogous hexatriene intermediate for this purpose; e.g., the thermal electrocyclic reaction of pyridine 3,4-quinodimethane generated *in situ* from 2-[α-(3-ethylpyridin-4-yl)vinyl]indole at high temperature (480-500°C).[4] In our case, the well known photocyclisation protocol of styrylindole systems producing carbazoles[5] was envisioned as an attractive procedure for the pyrido-[4,3-b]carbazole construction. Therefore, **5** was firstly irradiated [450W high-pressure Hg vapor lamp] in benzene under an ice-cooling, providing tetrahydropyrido[4,3-b]carbazoles **7** as an oxidized form accompanied by the photochemical isomerisation forming **8** except in the case of **5d**.

Otherwise, on exposure to 2 equiv. of BF_3•OEt_2 or trifluoroacetic acid (TFA) in CH_2Cl_2 at room temperature, **5** readily underwent spiroannulation to furnish the spiroindole **9** whose structure was established by X-ray crystallography (Figure).[6]

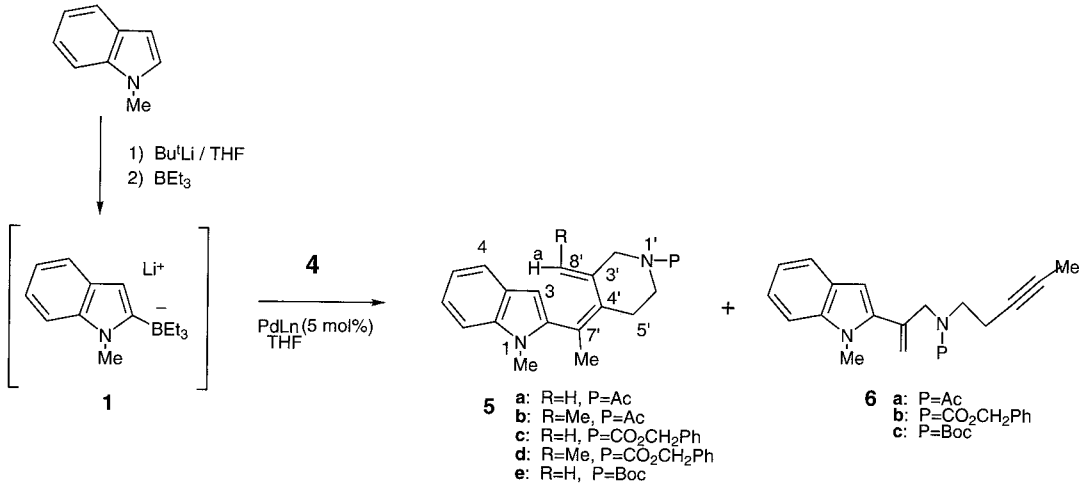
An analysis of the nmr data of **5e**, particularly noe experiments [distinctive enhancements of N1-Me, C3-H and C5'-2H on irradiation of C7'-Me, and C3-H, N1-Me and C8'-R (R=H) on irradiation of C8'-Ha (the atomic numbering is shown in the structure of **5** in Scheme 2)], reveals the distorsion of the conjugated hexatriene system, which may be ascribable to the steric repulsion between N1-methyl and C7'-methyl groups. This reflects the greater tendency of the photoisomerisation of **5** (especially, in the case of **5a** and **b**) to **7**, and the acid promoted spiroannelation of **5** to **9** through the iminium **A** (Scheme 3).

Finally, **7c** and **d** were subjected to the removal of N-carbobenzyl-oxycarbonyl group under a hydrogen atmosphere in the presence of $Pd(OH)_2$ in THF, giving amines **10a** and **b**, having a structural resemblance to Janetine and Guatambuine,[7] in 60% and 63% yields, respectively.

The present results demonstrate the further scope for the palladium catalysed cross-coupling with indolylborate **1**. Although the yields are not optimised, pyridocarbazole derivatives could be prepared in short steps, and from readily available starting material.

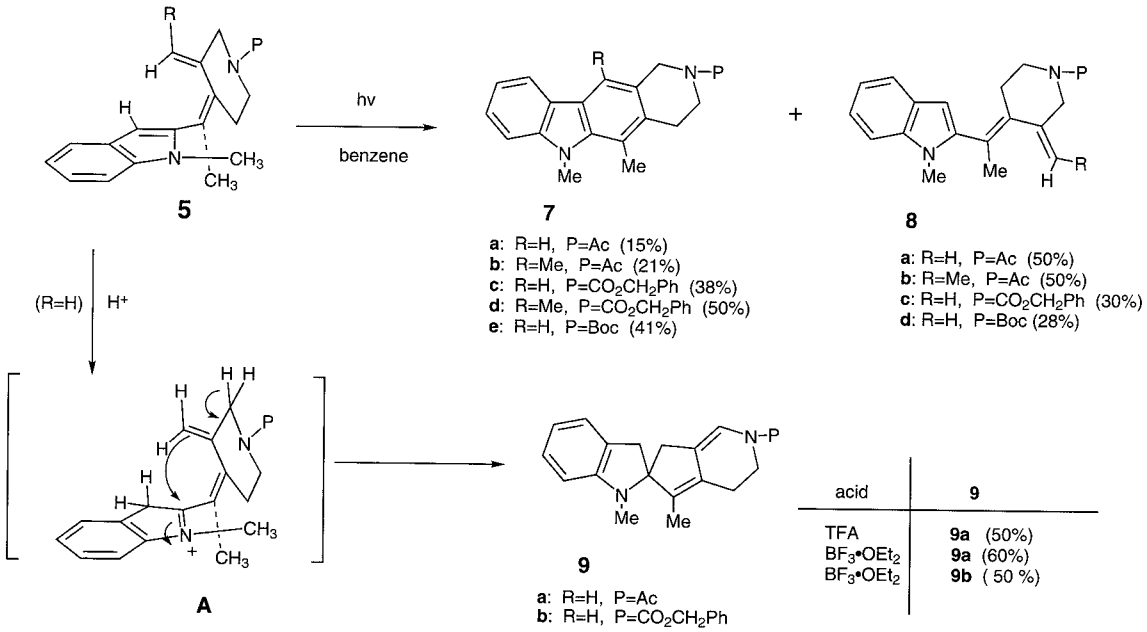
References and Notes

(1) Suffness, M.; Cordell, C. A. In *The Alkaloids*, Vol. 25; Brossi, A. Ed.; Academic Press, Inc. San Diego, 1985, p 89; Gribble, G. W. In *The Alkaloids*. Vol. 39; Brossi, A. Ed.; Academic Press, Inc. San Diego, 1990, p 239; Gribble, G. W. In *Advances in Heterocyclic Natural Product Synthesis*, Vol. 1; Pearson, W. H. Ed.; JAI Press Inc. Greenwich, 1990, p 43; Alvarez, M.; Joule, J. A. In *The Chemistry of Heterocyclic Compounds*. Supplement to part 4; Saxton, J. E., Ed.; John Wiley & Sons, Ltd, Chichester, 1994, p 261; Boese, R.; Van Sickele, A. P.; Vollhardt, K. P. C. *Synthesis*, **1994**, 1374; Blechert, S.; Knier, R.; Schroers, H.; Wirth, T. *Synthesis*, **1995**, 593.



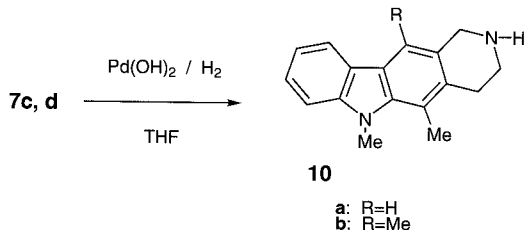
PdLn	5	6
$Pd(OAc)_2$	**5a** (39%)	**6a** (23%)
$PdCl_2(PPh_3)_2$	**5b** (53%)	—
$Pd(OAc)_2$	**5c** (38%)	**6b** (20%)
$PdCl_2(PPh_3)_2$	**5d** (55%)	—
$Pd(OAc)_2$	**5e** (40%)	**6c** (22%)

Scheme 2



acid	9
TFA	**9a** (50%)
BF_3•OEt_2	**9a** (60%)
BF_3•OEt_2	**9b** (50 %)

Scheme 3



Scheme 4

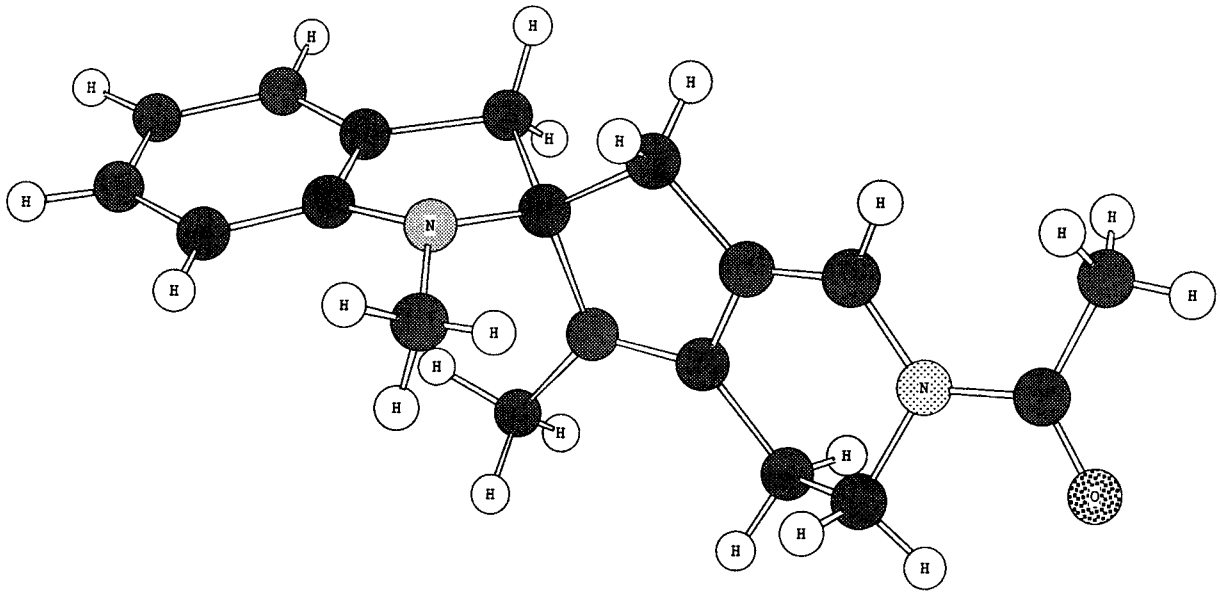


Figure. Drawing of **9a**, using parameters determined by X-ray crystallography.

(2) Ishikura, M. *J. Chem. Soc., Chem. Commun.*, **1995**, 409; Ishikura, M. *Yuki Gosei Kagaku Kyokai Shi*, **1995**, *53*, 308; Ishikura, M.; Agata, I. *Heterocycles*, **1996**, *43*, 1591; Ishikura, M.; Matsuzaki, Y.; Agata, I. *J. Chem. Soc., Chem. Commun.*, **1996**, in the press.

(3) Allylamine (**2a**) was produced accoding to the known amidation procedure (see; Bottini, A. T.; Dev, V.; Klinck, J. *Org. Synth.*, **1973**, Col. Vol. *5*, 121; By the treatment with PBr_3, a mixture of (E)-2-bromo-2-buten-1-ol and (E)-3-bromo-2-buten-1-ol (preparation see; Schlosser, M.; Hammer, E. *Helv. Chim. Acta.*, **1974**, *57*, 2547) was converted to a mixture of the corresponding dibromides, which was next subjected to the amidation to provide **2b** in 30% yield after chromatographic separation (Al_2O_3 with AcOEt - hexane 5:1).

(4) Hibino, S.; Sugino, E. *J. Heterocyclic Chem.*, **1990**, *27*, 1751; Kano, S.; Sugino, E.; Hibino, S. *Heterocycles*, **1982**, *19*, 1673.

(5) Mallory, F. B.; Mallory, C. W. *Organic Reactions*, **1984**,*30*, 1.

(6) The authors have deposited the crystal structure data with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.

(7) Azoug, M.; Loukaci, A.; Richard, B.; Nuzillard, Jean-Marc; Moreti, C.; Zeches-Hanrot, M.; Le Men-Olivier, L. *Phytochemistry*, **1995**, *39*, 1223; Marini-Bettolo, G. B.; Schmutz, J. *Helv. Chim. Acta*, **1959**, *42*, 2146.