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AN EFFICIENT TOTAL SYNTHESIS OF ELLIPTICINE

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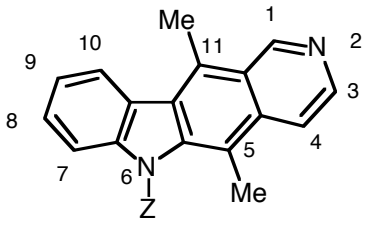
Abstract - A total synthesis of ellipticine could be attained through the palladium catalyzed tandem cyclization-cross-coupling reaction of indolylborate (**2b**) with vinyl bromide (**3**) as a key reaction.

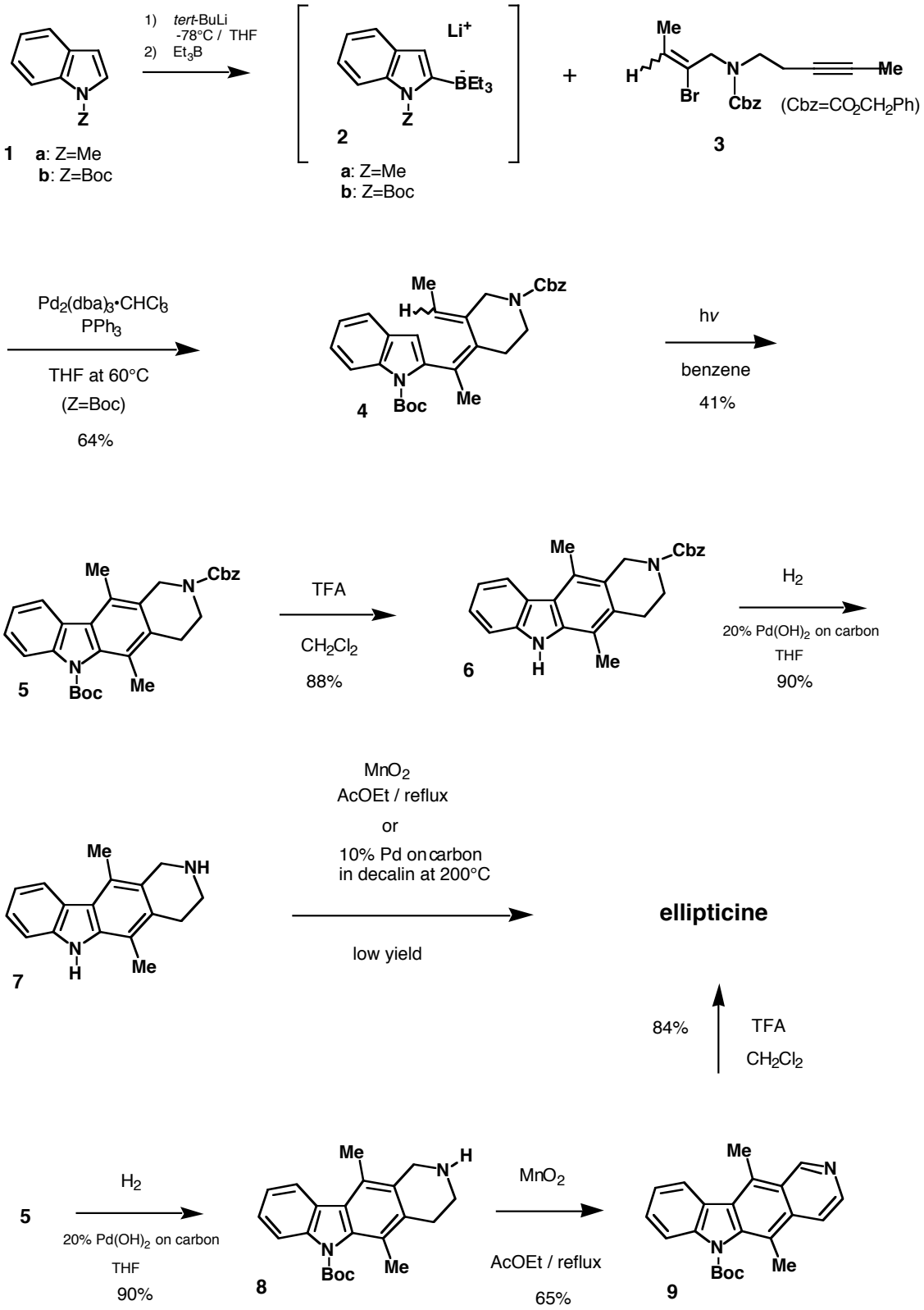
Ellipticine, first isolated from *Ochrosia elliptica* Labill in 1959,[1] is a member of pyrido[4,3-*b*]carbazole, which displays potent antitumor activity.[2] Because of its cardiovasuclar toxicity and hemolysis, interst was shifted to the investigation of the structure-activity relationships of structural analogues of ellipticine, which promoted the pronounced development of synthetic methodologies to pyrido[4,3-*b*]carbazoles.[3] As a part of our ongoing studies of synthetic application of indolylborate,[4] the palladium catalyzed tandem cyclization-cross-coupling reaction with 1-methylindolylborate (**2a**) was previously developed for a concise construction of 6-methylellipticine derivatives.[5] At this point, use of pyrido[4,3-*b*]carbazole bearing a removable protecting group at the 6-position (indole-1-N) is indispensable to complete the synthesis of ellipticine. This paper describes a successful use of this protocol for the total synthesis of ellipticine.



Z = H **ellipticine**
Z = Me **6-methylellipticine**

Requisite vinyl bromide (**3**) as (*E*)/(*Z*) mixture was prepared from a mixture of *cis*- and *trans*-crotyl alcohol *via* sequences reported previously.[5]

The cross-coupling protocol was successfully extended to the reaction of 1-(*tert*-butoxycarbonyl)indolylborate (**2b**), generated from indole (**1b**) *in situ*,[6] with **3** using a 1:4 ratio of $Pd_2(dba)_3 \bullet CHCl_3$ and Ph_3P, producing hexatriene (**4**)[7] in 64%


1) tert-BuLi -78°C / THF
2) Et3B
1 a: Z=Me b: Z=Boc
2 a: Z=Me b: Z=Boc
3
(Cbz=CO2CH2Ph)
Pd2(dba)3•CHCl3
PPh3
THF at 60°C
(Z=Boc)
64%
4
hν
benzene
41%
5
TFA
CH2Cl2
88%
6
H2
20% Pd(OH)2 on carbon
THF
90%
7
MnO2
AcOEt / reflux
or
10% Pd on carbon
in decalin at 200°C
low yield
ellipticine
84%
TFA
CH2Cl2
H2
20% Pd(OH)2 on carbon
THF
90%
8
MnO2
AcOEt / reflux
65%
9

Scheme

yield (Scheme). Irradiation of **4** with high-pressure mercury lamp in benzene gave rise to pyridocarbazole (**5**) as an oxidized form[8] in 41% yield. Then, treatment of **5** with TFA in CH_2Cl_2afforded **6** in 88 % yield, and the deprotection of carbobenzyloxy group in **6** by catalytic hydrogenation using 20% $Pd(OH)_2$ on carbon produced **7** in 90% yield. To complete the sequence, dehydrogenation of **7** was examined next. However, the dehydrogenation of **7** with MnO_2in AcOEt under reflux or 10% Pd on carbon in decalin at 200°C was frustrated by fairly low yield of ellipticine, which reveals that the presence of free indole-1-NH would be problematic.[9] For successful completion of synthesis of ellipticine, **8** bearing a Boc group at the indole-1-N derived from **5** by catalytic hydrogenation was subjected to the dehydrogenation with MnO_2 in AcOEt under reflux to give **9** in 65% yield. Finally, deprotection of the Boc group in **9** with TFA provided ellipticine in 84% yield.

In summary, a novel and concise route to ellipticine was realized based on the palladium catalyzed tandem cyclization-cross-coupling reaction of indolylborate (**2b**) with vinyl bromide (**3**) as a key step.

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6. M. Ishikura, Y. Matsuzaki, I. Agata, and N. Katagiri, *Tetrahedron*, 1998, **54**, 13929.
7. Hexatriene (**4**) as (E)/(Z) mixture: ^{1}H-NMR ($CDCl_3$): δ 1.30-1.50 (m, 3H), 1.61 (s, 9H), 1.90 (s, 3H), 2.32 (br s, 1H), 2.64 (br s, 1H), 3.50-3.80 (m, 3H), 4.40-4.55 (m, 1H), 5.17 (s, 2H), 5.10-5.25 (m, 1H), 7.17 (t, 1H, J=7.3 Hz), 7.23 (t, 1H, J=7.3 Hz), 7.30-7.45 (m, 6H), 8.14 (d, 1H, J=8.3 Hz). ^{13}C-NMR ($CDCl_3$): δ 13.4, 20.3, 28.0, 30.3, 42.8, 45.6, 67.1, 83.3, 106.4, 115.3, 120.1, 122.6, 123.3, 123.9, 125.1, 127.8, 127.9, 128.4, 129.6, 133.7, 135.1, 136.4, 136.8, 142.7, 149.9, 155.4.
8. Compound (**5**): mp 145°C (recrystallized from AcOEt). ^{1}H-NMR ($CDCl_3$): δ 1.67 (s, 9H), 2.31 (s, 3H), 2.70 (br s, 3H), 2.92 (br s, 2H), 3.75-3.83 (m, 2H), 4.78 (s, 2H), 5.21 (s, 2H), 7.30-7.45 (m, 7H), 8.08 (d, 1H, J=8.3 Hz), 8.12 (d, 1H, J=7.8 Hz). ^{13}C-NMR ($CDCl_3$): δ 15.1, 17.2, 27.3, 28.1, 41.2, 44.5, 67.1, 83.7, 114.9, 117.0, 122.4, 122.9, 123.5, 124.2, 126.0, 127.3, 127.9, 128.0, 128.5, 132.7, 136.9, 138.0, 140.8, 151.3, 155.4. UV λ nm ($CHCl_3$) : 240, 270, 290.
9. The dehydrogenation of 6-methyl (indole-N-Me) derivative of **7** with MnO_2 in AcOEt under reflux produced 6-methylellipticine in 62% yield (unpublished result by M. Ishikura, *et al.*).