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 cardiovascular toxicity and hemolysis, interest 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-methyldindolylborate (2a) was previously developed for a concise construction of 6-methylellipticines 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.

\[
\begin{array}{ll}
\text{Z} = \text{H} & \text{ellipticine} \\
\text{Z} = \text{Me} & 6\text{-methylellipticine}
\end{array}
\]

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 Pd₂(dba)₃•CHCl₃ and Ph₃P, producing hexatriene (4)7 in 64%
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\(_2\)Cl\(_2\) afforded 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\(_2\) in 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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REFERENCES AND NOTES


7. Hexatriene (4) as (E)/(Z) mixture: $^1$H-NMR (CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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$_3$): $\delta$ 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$_3$): $\delta$ 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 $\lambda$ 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.).