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INTEGRATED AROMATIC METALATION - CROSS COUPLING METHODOLOGIES. A CONCISE SYNTHESIS OF THE AZAFLUORANTHENE ALKALOID IMELUTEINE

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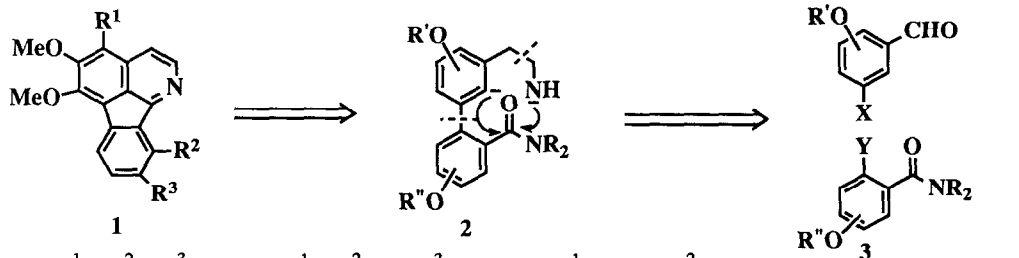
Summary: An efficient synthesis of imeluteine (**1e**) by a combinational metalation (ortho and remote) - cross coupling approach **2** is described.

As part of comprehensive studies in natural product structure and synthesis, Cava and coworkers discovered[1a] rufescine (**1d**) and imeluteine (**1e**), representing a small but biogenetically unusual group of azafluoranthene alkaloids isolated from several Menispermaceae species.[1] Synthetic efforts to date have provided routes to telitoxine (**1b**), norrufescine (**1c**), rufescine (**1d**),[1] and imeluteine (**1e**) based on Pschorr cyclization and inverse electron demand Diels-Alder strategies.[1-3] Herein we present an efficient and concise synthesis of imeluteine (**1e**) based on an approach which integrates benzamide ortho[4] and remote metalation[5] tactics with the Suzuki cross coupling protocol[6] as depicted by retrosynthetic scheme **1** → **2** → **3**.



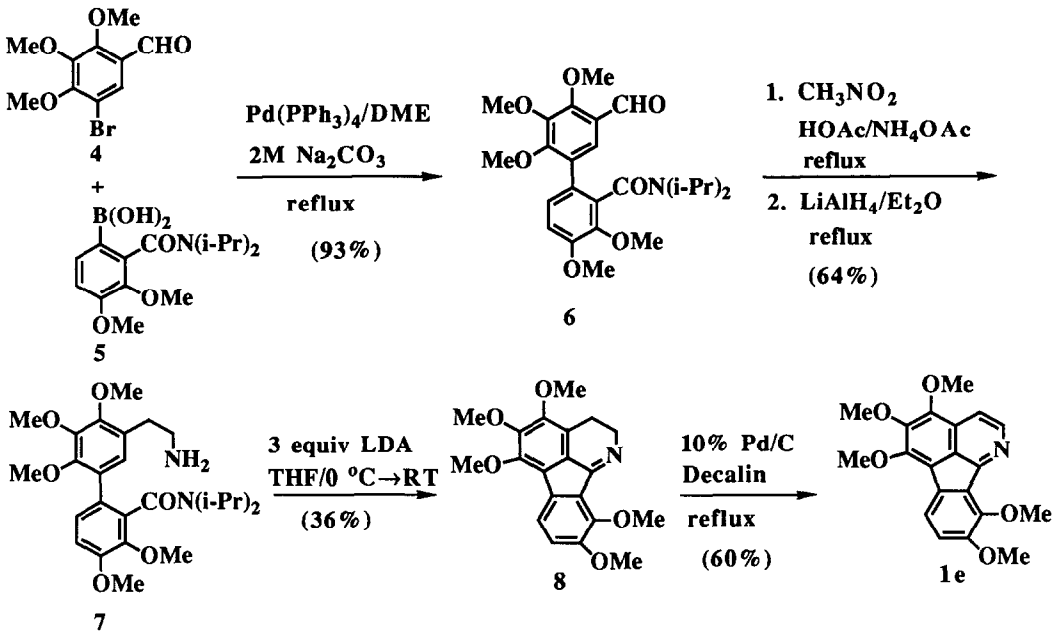
1 **2** **3**

1a: $R^1 = R^2 = R^3 = H$; **1b**: $R^1 = R^2 = H$, $R^3 = OH$; **1c**: $R^1 = OMe$, $R^2 = H$, $R^3 = OH$; **1d**: $R^1 = R^3 = OMe$, $R^2 = H$; **1e**: $R^1 = R^2 = R^3 = OMe$

X, Y = Br, B(OH)$_2$

Cross coupling of the boronic acid **5**[7] with readily available bromobenzaldehyde **4**[8] under modified Suzuki conditions gave the biaryl **6** in excellent yield. Standard nitromethane aldol chain extension[9] and $LiAlH_4$ reduction[10] afforded the phenethylamine **7**. Exposure to LDA (excess) resulted in the formation of dihydroimeluteine **8**[1a] in modest (unoptimized) yield The order of steps in this remote metalation - double cyclization process (**2**) as well as the potential weak directed metalation effect of the lithio ethyl amide side chain[11] is presently unknown. Dehydrogenation of **8** with Pd/C concluded the synthesis of imeluteine (**1e**)[12] in 6 steps and 13% overall yield.[13]

This work demonstrates the emerging value of combinational aromatic metalation (ortho and remote) and cross coupling regimens to achieve synthetic efficiency and brevity. The finding of anionic lynchpin cyclization to form **8** may complement existing Bischler-Napieralski[14] methodology for isoquinoline ring construction.[15,16]



References and Footnotes

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7. Prepared from the corresponding 2,3-dimethoxybenzamide according to the procedure described in Alo, B.I.; Kandil, A.; Patil, P.A.; Sharp, M.J.; Siddiqui, M.A.; Josephy, P.D.; Snieckus, V. *J Org. Chem.* **1990**, in press.
8. Prepared by bromination (Br_2/HOAc/RT, 70%) of commercially available 2,3,4-trimethoxybenzaldehyde, see Worden, L.R.; Kaufman, K.D.; Smith, P.J.; Widiger, G.N. *J. Chem. Soc (C)* **1970**, 227.
9. See, for example, Kubota, S.; Masui, T.; Fujita, E.; Kupchan, S.M. *J. Org. Chem.* **1966**, *31*, 516.
10. Model experiments showed that di-isopropyl benzamides are stable to these conditions.
11. For ortho metalation studies of tertiary phenethylamines, see Vaulx, R.L. Jones, F.N.; Hauser, C.R. *J. Org. Chem.* **1965**, *30*, 58.
12. Mp 146-147 °C, lit[1a] mp 146-147 °C and identical IR, ^{1}H NMR, MS to those reported.[1a]
13. Comparisons: 14% (4 steps) from 2,3-dimethoxy-6-nitrobenzoic acid;[1a] 4.9% (15 steps) based on 2,3,4-trimethoxybenzyl bromide.[3]
14. Fodor, G.; Nagubandi, S. *Tetrahedron* **1980**, *36*, 1279.
15. Analytical and normal spectral data fully corroborate structures of all new compounds.
16. We are grateful to NSERC Canada for financial support of our synthetic programs.

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