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Directed *ortho* Metalation - Cross Coupling Connections. Total Synthesis of *Amaryllidaceae* Alkaloids Buflavine and 8-*O*-Demethylbuflavine

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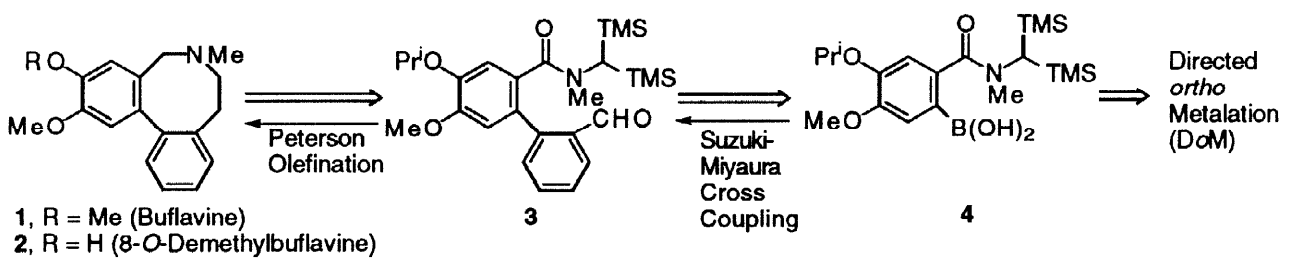
Abstract: The *Amaryllidaceae* alkaloids, buflavine (**1**) and 8-*O*-demethylbuflavine (**2**), have been synthesized by a sequence which highlights Directed *ortho* Metalation, Suzuki-Miyaura cross coupling, and intramolecular Peterson reactions. © 1998 Elsevier Science Ltd. All rights reserved.

Buflavine (**1**) and 8-*O*-demethylbuflavine (**2**) constitute *Amaryllidaceae* alkaloids isolated from *Boophane flava* bulbs[1] whose unique 5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine skeleton and potential α-adrenolytic and anti-serotonin activities[2] provide compelling reasons for synthesis. As part of continuing efforts to develop new Directed *ortho* Metalation (D*o*M) chemistry, we have previously described the α',α'-disilylated tertiary amide as dual *ortho*- and α'-carbanion synthon.[3] Herein we report a short and convergent route to buflavine[4] (**1**) and 8-*O*-demethylbuflavine (**2**) based on the application of key D*o*M and intramolecular Peterson olefination reactivity of the α',α'-disilylated tertiary amide Directed Metalation Group (DMG). Accordingly, retrosynthetic analysis of alkaloids **1** and **2** cascades to biaryl **3** with associated functional group transformations (**Scheme 1**). Biaryl **3**, in turn, may be derived from boronic acid **4** and *o*-bromobenzaldehyde following the Suzuki-Miyaura cross coupling process; the boronic acid **4** is accessible by the D*o*M protocol.



Scheme 1

Thus α',α'-disilylated amide **5**[5] was regiospecifically metalated (*t*-BuLi/TMEDA) and quenched with $B(OMe)_3$ to furnish the boronic acid **4** (**Scheme 2**). Suzuki-Miyaura cross coupling of **4** with *o*-bromobenzaldehyde gave the highly functionalized biaryl **3** in 70% yield. When **3** was subjected to CsF in anhyd DMF under high dilution (0.02M) conditions at 110°C, the Peterson olefination product **6** was obtained in 54% yield. Sequential catalytic hydrogenation, LAH reduction, and chemoselective deisopropylation with BCl_3 gave 8-*O*-demethylbuflavine (**2**) in 71% yield (27% overall yield from **5**). Methylation of alkaloid **2** using NaH/Me_2SO_4 yielded buflavine (**1**) in 84% yield (23% overall yield from **5**). Synthetic **1** and **2** were shown to be identical with the corresponding alkaloids by direct comparison of spectral data.[1]

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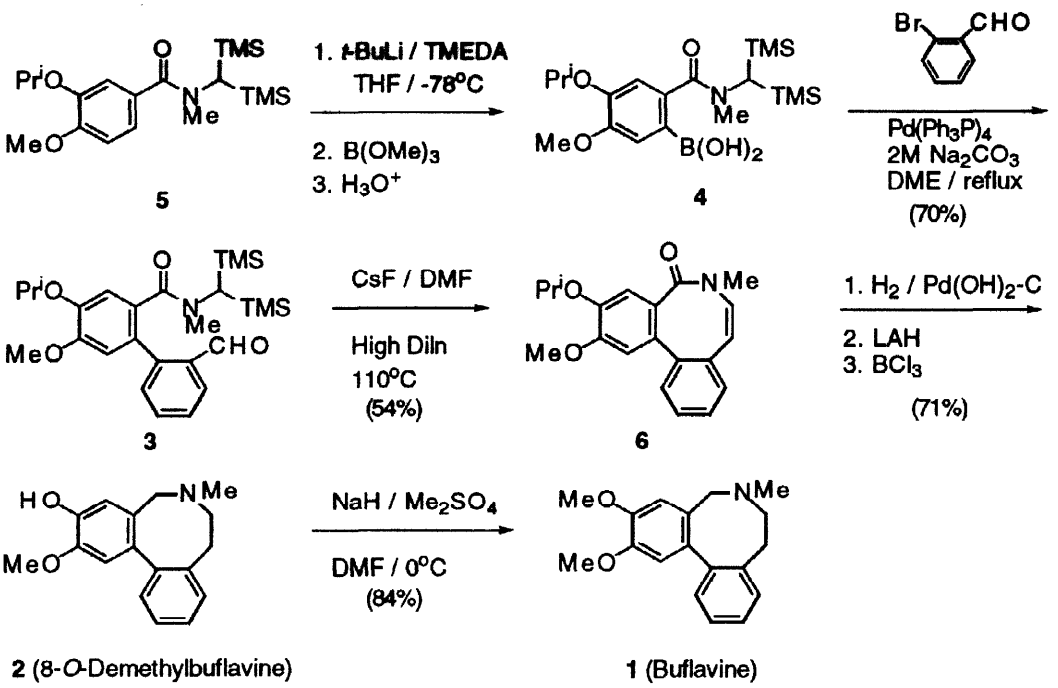

Scheme 2

In summary, we have achieved the first syntheses of buflavine (**1**) and 8-*O*-demethylbuflavine (**2**) using a combined DoM - cross coupling regimen and taking advantage of the unique *ortho*- and α'-carbanionic properties of the α',α'-disilylated tertiary amide DMG. Details and generalization of this sequence for dibenz[*c*,*e*]azocine derivatives will be reported in due course.[6]

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References and Footnotes

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2. a) Ishida, Y.; Sasaki, Y.; Kimura, Y.; Watanabe, K. *J. Pharmacobiodyn.* **1985**, *8*, 917; *Chem. Abstr.* **1986**, *104*, 45660. b) Ishida, Y.; Watanabe, K.; Kobayashi, S.; Kihara, M. *Chem. Pharm. Bull. Jpn.* **1977**, *25*, 1851.
3. Cuevas, J.-C.; Patil, P.; Snieckus, V. *Tetrahedron Lett.* **1989**, *43*, 5841.
4. The synthesis of buflavine (**1**) but not 8-*O*-demethylbuflavine (**2**) was reported by Kobayashi and coworkers (Kobayashi, S.; Kihara, M.; Shizu, S.; Katayama, S.; Ikeda, H.; Kazuo, K.; Matsumoto, H. *Chem. Pharm. Bull. Jpn.* **1977**, *25*, 3312). Since this report predates the isolation work[1] by twenty years, the present work may arguably claim the *first* total synthesis of this class of natural products.
5. N,N-dimethyl-3-isopropoxy-4-methoxybenzamide, prepared from 3-hydroxy-4-methoxybenzoic acid following standard procedures, was treated with LiTMP/TMSCl[3] to give **5** in 75% yield.
6. All new compounds show spectroscopic (^{1}H, ^{13}C NMR and HRMS) and analytical data in accordance with their assigned structures.