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Synthesis of an octahydroindolinone scaffold for a diversity-based chemical compound library

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Abstract—The synthesis of a chemical compound library using diversity-oriented synthesis (DOS) is discussed. The library is structurally inspired by the *Amaryllidaceae* alkaloids, a family of natural products which has been known to demonstrate potent antiviral and antineoplastic activity. Highlights of this work include the rapid, high-yielding construction of the octahydroindolinone core and the solid-phase diversification of the lactam using a neutral phosphazene base.

The octahydroindolinone ring system is a structural motif which is frequently observed in the Amaryllidaceae family of natural products. These natural products have demonstrated a wide range of biological activities including antiviral, antitumor, acetylcholinesterase inhibitory, immunostimulatory, and antimalarial activities.[1] Representative members of the Amaryllidaceae family, mesembrine (**1**) and obliquine (**2**), are shown in Figure 1.

In pursuit of synthesizing novel chemical structures using our diversity-oriented synthesis (DOS) platform, we became interested in the octahydroindolinone framework as a scaffold for a chemical compound library. Using a chemistry-driven approach, we aimed to develop an efficient, solution-phase route to an octahydroindolinone core, which contained three diversity sites that could be elaborated on solid-phase into a diverse, multi-thousand member compound library.

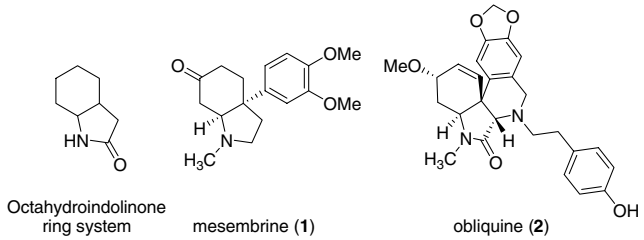

Figure 1. Octahydroindolinone ring system and Amaryllidaceae natural products.

Recently, Padwa et al. have developed an elegant method to access the hexahydroindolinone framework via an oxabicyclic intermediate using an intramolecular Diels–Alder furan/ring-opening sequence.[2–8] This oxabicycle, rich in stereochemical complexity and exhibiting an array of versatile functional groups, was recognized as a potential starting point for a diversity-based chemical compound library.

In accordance with a literature procedure, acylation of-*tert*-butyl *N*-(2-furyl)carbamate (**3**) provided an intermediary imidofuran which underwent spontaneous [4+2] cyclization at room temperature to provide 7-oxabicyclo[2.2.1]heptene **4** (Scheme 1).[6] Initial efforts to install diversity were focused on opening the oxa-bridge in an S_N2' fashion using nitrogen (sulfonamides, anilines, imides, amines, etc.) and oxygen (primary alcohols and phenols) nucleophiles in the presence of Rh^I catalyst.[9,10] However, in all cases, the starting material was recovered unchanged, perhaps due to reversible addition of the nucleophile. Alternatively, it was found that treatment of **4** with acetone or *para*-anisaldehyde in the presence of tin chloride cleanly provided the corresponding acetals **5** and **6** in excellent yields.[11] Irreversible trapping of the oxonium ion by the newly generated alkoxide likely accounts for the high regio- and diastereoselectivity was observed in the isolated products.[12]

Due to substrate compatibility issues encountered while advancing the *para*-methoxybenzylidene acetal series,

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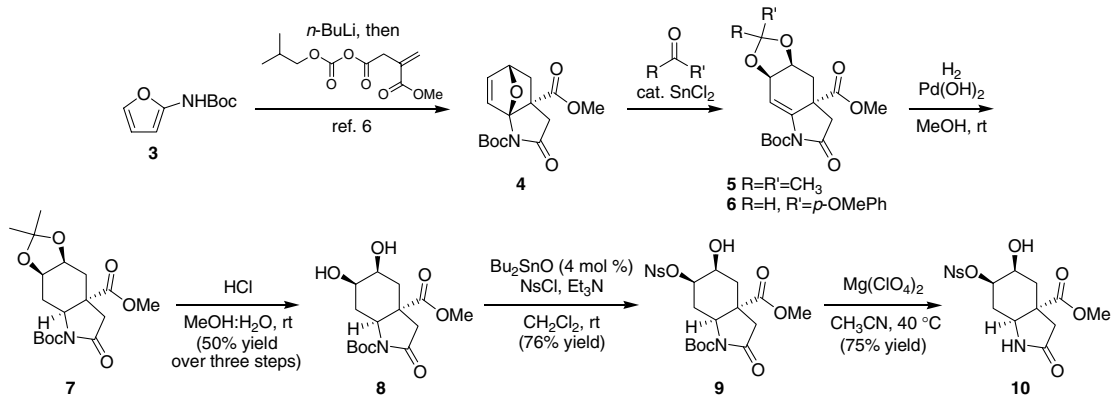


Scheme 1. Synthetic route to the core.

attention was focused on advancing acetonide **5**. To this end, hydrogenation of the vinyl imide of **5** led to exclusive formation of the *cis*-ring fused product.[13] Next, selective deprotection of the acetonide in the presence of the Boc group furnished diol **8**. Since one of the hydroxyl groups of **8** would serve as a handle for loading to solid support, differentiation of the two alcohols was required at this stage. Ultimately, it was found that catalytic dibutyltin oxide could be employed to facilitate a regioselective nosylation to provide nosylate **9** in 76% yield.[14–16] To our knowledge, regioselective introduction of the nosyl (Ns, *para*-nitrobenzenesulfonyl) protecting group via the stannylene acetal has not been previously reported in the literature. Deprotection of the Boc group with magnesium perchlorate completed the synthesis of the octahydroindolinone core **10**, the structure of which was confirmed by single crystal X-ray analysis (see Fig. 2).[6,17–19]

In preparation for solid-phase diversification, the octahydroindolinone core **10** was loaded onto polystyrene Lantern™ (Mimotopes L-series) with a loading level of 14.5 μmol/Lantern™. As shown in Scheme 2, cleavage of the nosyl group using the Fukuyama protocol revealed secondary alcohol **12**, which was poised for subsequent diversification.[20,21] Additionally, lactam **11** was functionalized with a series of activated electrophiles using BTPP (*tert*-butylimino-tri(pyrrolidino)phosphorane), a neutral phosphazene base recently employed by Shaw et al. in a similar transformation.[22]

In summary, we have developed a six-step route to a novel octahydroindolinone core in 16% overall yield.

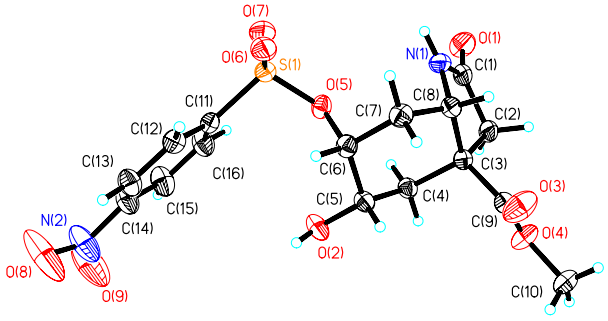
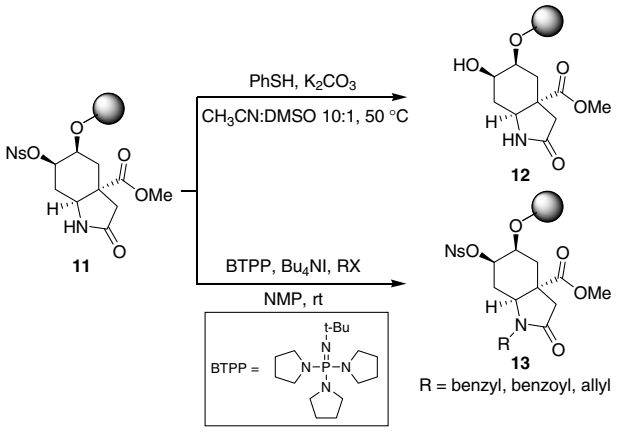


Figure 2. ORTEP diagram of compound **10**.



Scheme 2. Preliminary solid-phase diversification.

The solution-phase sequence requires only two chromatographic purifications (intermediates **4** and **9**) and has been scaled to provide multi-gram quantities of **10**. Initial solid-phase chemistry involving nosyl deprotection and lactam functionalization has enabled entry into two solid-phase diversification pathways. Further solid-phase elaboration of this core and additional work on related scaffolds will be reported in due course.

Acknowledgments

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18. Characterization data for **10**: White solid (mp 147–148 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (d, $J = 9.2$ Hz, 2H), 8.22 (d, $J = 9.2$ Hz, 2H), 4.76 (m, 1H), 3.92 (t, $J = 4.2$ Hz, 1H), 3.68 (s, 3H), 3.63 (td, $J = 3.4$, 10.2 Hz, 1H), 2.61 (d, $J = 16.2$ Hz, 1H), 2.30 (d, $J = 16.2$ Hz, 1H), 2.20 (td, $J = 4.5$, 15.5 Hz, 1H), 1.99 (ddd, $J = 3.5$, 5.2, 15.5 Hz, 1H), 1.83 (comp m, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.9, 174.0, 151.3, 142.9, 130.4, 127.9, 125.4, 124.3, 82.3, 65.5, 53.4, 52.4, 49.1, 42.7, 33.5, 30.7 ppm; IR (HATR FT-IR) 3416 (br m), 3232 (w), 2948 (m), 1695 (s), 1532 (s), 1350 (m), 1189 (m), 903 (m), 620 (m) cm^{-1}; HRMS (FAB) *m*/*z* found: 432.1070 [calcd for $C_{16}H_{20}N_2O_{10}S$ $(M+H_2O)^+$: 432.0839]; Anal. Calcd ($C_{16}H_{18}N_2O_9S$): C, 45.46; H, 4.56; N, 6.51; S, 7.01.
19. Crystal data for **10**: $C_{16}H_{18}N_2O_9S$, $M = 414.38$, $T = 193(2)$ K, triclinic, space group *P*-1, $Z = 2$, $a = 8.1740(11)$, $b = 10.9303(15)$, $c = 11.9711(17)$ Å, $\alpha = 113.496(2)°$, $\beta = 95.460(2)°$, $\gamma = 107.828(2)°$, $V = 904.4(2)$ Å^3, $D_x = 1.522$ Mg/m^3, $R_1 = 0.0475$, $wR_2 = 0.1062$. Crystallographic data for **10** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 647518. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
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