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TWO HIGHLY EFFICIENT SYNTHESES OF SCALEMIC AZOCINES

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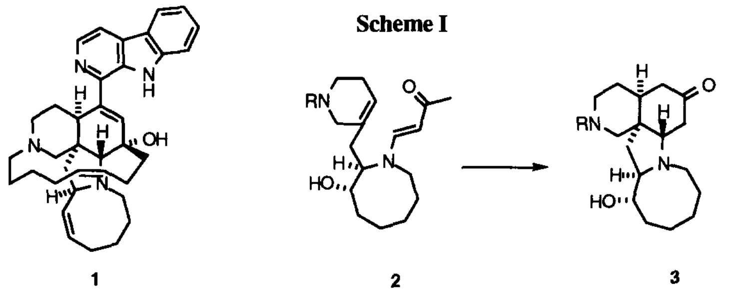
Abstract Two approaches to the synthesis of disubstituted azocines in scalemic form, via intramolecular alkylation and olefin metathesis, respectively, are described.

Our recently described photochemical approach to the synthesis of the manzamine A, **1**,[1] features the use of a trans-disubstituted azocine template, **2**, to effect highly stereoselective formation of **3** (Scheme I).[2] A striking difference in induction was observed between cis- and trans- disubsituted azocine templates. However, the desired trans-isomer could be obtained only as the minor product from reduction of the corresponding ketone. We report herein the development of two highly efficient approaches to the synthesis of the requisite azocine systems, as outlined in Scheme II.

Scheme I

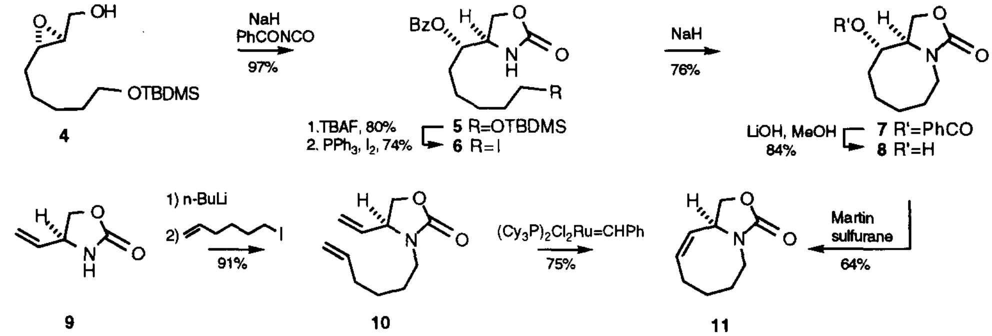


1 **2** **3**

Exposure of the Sharpless product **4**[3] to sodium hydride and benzoylisocyanate (Scheme II), based on the elegant studies of McCombie,[4] leads, via carbamate formation, intramolecular epoxide opening, and N→O benzoyl migration to the formation of oxazolidinone **5** (R=OTBDMS) in 97% yield, in which the critical vicinal stereochemical relationship for the formation of the trans-disubstituted azocine has been established. Desilylation and formation of the corresponding iodide, **6**, followed by treatment with sodium hydride leads to the formation of the requisite azocine **7** in 76% yield, the structure and stereochemistry of which were confirmed by X-ray crystallographic analysis.[5]

Alternatively, alkylation of oxazolidinone **9**,[6] which is available in three steps from Garner's aldehyde,[7] with 6-iodo-1-hexene provided the diene **10**. Exposure of **10** to the metathesis conditions recently reported by Grubbs gave the unsaturated azocine product **11** in 75% yield.[8,9] Correlation of **7** with **11** could be achieved by debenzoylation of **7** and dehydration of the resulting alcohol **8** with Martin sulfurane, $[PhC(CF_3)_2O]_2SPh_2$.[10] The azocine **11** obtained by either route was identical in all respects including optical rotation.

Scheme II



These sequences compare favorably with the seven-step protocol recently reported by Nakagawa for the formation of an azocine starting from Garner's aldehyde.[11] The synthesis and photochemical reactivity of the vinylogous amide photosubstrate derived from **11**, i.e., containing the azocine unsaturation present in manzamine is now being examined and our results will be reported in due course.

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5. All new compounds were characterized by full spectroscopic (NMR, IR, high resolution MS) data. Yields refer to spectroscopically and chromatographically homogeneous (>95%) materials. Selected spectral data---Azocine **7:** ^1H NMR (500MHz, $CDCl_3$): δ8.01-7.95(m, 2H); 7.56(t, 1H, J=7.4Hz); 7.43(t, 2H, J=7.7Hz); 5.05(t, 1H, J=7.8Hz); 4.43(t, 1H, J=9.0Hz); 4.05(dd, 1H, J=9.1, 5.3Hz); 3.95-3.88(m, 1H); 3.83-3.75(m, 1H); 3.21-3.12(m, 1H); 2.08-1.89(m, 3H); 1.82-1.72(m, 1H); 1.70-1.49(m, 4H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 165.35; 158.70; 133.41; 129.54; 129.50; 128.51; 75.88; 66.51; 59.88; 44.43; 30.39; 26.17; 24.57; 23.48; FT-IR(KBr, cm^{-1}): 3449; 2936; 2862; 1746; 1712; 1447; 1419; 1264. Exact mass calculated for $C_{16}H_{19}NO_4(M+NH_4)$: 307.1658; found: 307.1652. $[\alpha]_D^{25}$ (c 0.815, $CHCl_3$)=+37.67°. Azocine **11**: ^1H NMR (500MHz, $CDCl_3$): δ5.88-5.94 (m, 1H); 5.40-5.45 (m, 1H); 4.40-4.50 (m, 2H); 3.95-3.98 (m, 1H); 3.35-3.42 (m, 2H); 2.34-2.41 (m, 1H); 2.12-2.19 (m, 1H); 1.79-1.86 (m, 1H); 1.61-1.71 (m, 2H); 1.49-1.58 (m, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ157.7; 134.5; 127.2; 68.2; 53.9; 43.3; 27.2; 25.8; 25.6; FT-IR(neat, cm^{-1}): 1746.8; 1650.5; 1418.7; 1246.3; 1053.0. Exact mass calculated for $C_9H_{13}NO_2(M+NH_4)$: 185.1290; found: 185.1294. $[\alpha]_D^{25}$ (c 0.562, $CHCl_3$)=-85.04°.
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