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Synthesis of nitrogen-containing benzoannulated eight- and nine-membered heterocycles from methyl 4-amino-3-iodobenzoate

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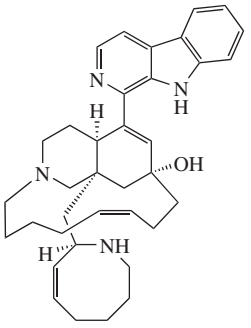
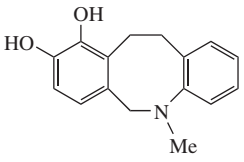
Dibenzo[*b*,*f*]azocin-6(5*H*)-one and dibenzo[*b*,*g*]azonin-6(13*H*)-one were prepared in five steps from methyl 4-amino-3-iodobenzoate.

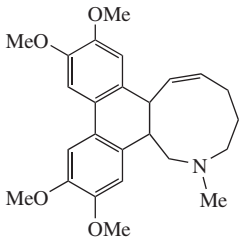
Nitrogen-containing heterocycles are widely distributed in nature and play important role in medicinal chemistry.[1] The eight- and nine-membered nitrogen-containing scaffolds are found in numerous alkaloids such as apogalanthemine, manzamine A and tylophorinemethine B.[2] Some of the N-substituted dibenzoazocine derivatives possess hypotensive and antiserotonin properties.[3] Some dibenzoazonine derivatives are used as NO synthase inhibitors.[4] Numerous methodologies have been reported for the synthesis of five- and six-membered ring systems. However, few syntheses of eight- and nine-membered heterocycles were published.[5] The main obstacle behind their formation are entropy factors and transannular interaction.[6] Larock and coworkers reported the synthesis of tetrahydrobenzo[*d*]azocine derivatives bearing exocyclic double bond by palladium-catalyzed heteroannulation of allenes.[7] Majumdar and coworkers have performed the palladium catalyzed intramolecular Heck coupling for the synthesis of dibenzoazocinone with endocyclic double bond.[8]



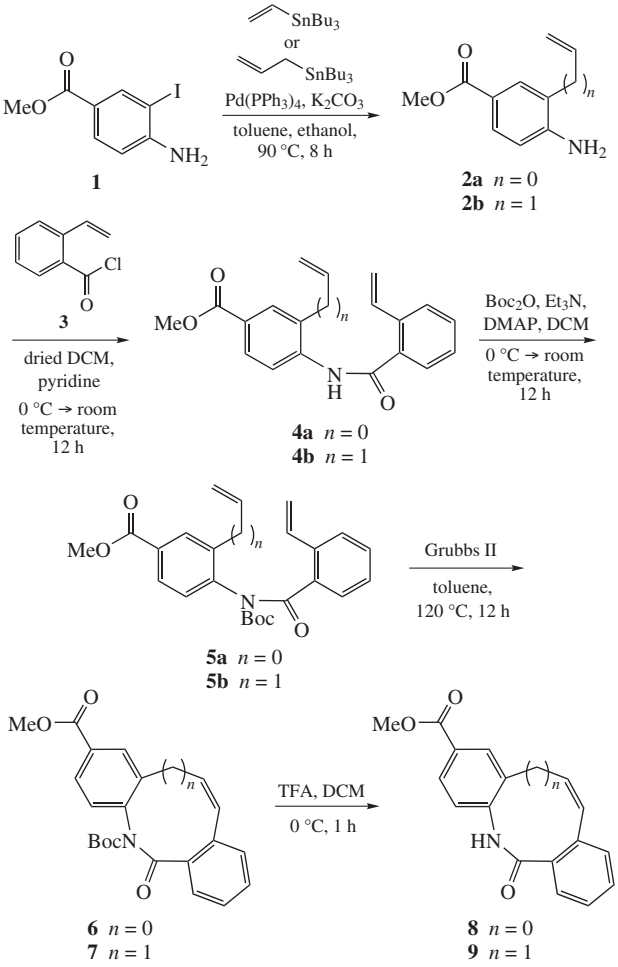
Manzamine A



Apogalanthemine



Tylophorinemethine B



Scheme 1

Herein, we report a concise synthesis of dibenzoazocinone and dibenzoazoninone using ring closing metathesis (Scheme 1). The Stille coupling of methyl 4-amino-3-iodobenzoate **1** with tributyl(vinyl)stannane and allyl(tributyl)stannane in the presence of tetrakis(triphenylphosphine)palladium gave compounds **2a** and **2b**, respectively. The reaction between 2-vinylbenzoyl chloride **3** and compounds **2a**,**b** in the presence of pyridine afforded corresponding amides **4a**,**b**. The amide NH group of compounds **4a**,**b** was Boc-protected to give compounds **5a**,**b**. Ring closing metathesis of compounds **5a**,**b** using Grubbs II generation catalyst resulted in eight- and nine-membered cyclic products **6** and **7**. Boc-deprotection in compounds **6**, **7** was performed using trifluoroacetic acid and led to the target compounds **8**, **9** in good yield.†

† NMR spectra were recorded on Bruker AVA300, AVIII400 or AV500 instruments. High resolution mass spectra were recorded on a Bruker Daltonics spectrometer.

*Methyl (Z)-5-*tert*-butoxycarbonyl-6-oxodibenzo[*b,f*]azocine-2-(6H)-carboxylate* **6**. Grubb's second generation catalyst (0.35 g, 0.41 mmol) was added to a solution of compound **5a** (1.0 g, 2.5 mmol) in dry toluene (50 ml) under argon and reaction mixture was refluxed for 12 h. The reaction mass was concentrated under reduced pressure and subjected to column chromatography using hexane–ethyl acetate (80 : 20) to give 0.65 g of product **6** (69%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.38 (s, 9H), 3.84 (s, 3H), 6.93–7.02 (m, 3H), 7.18–7.28 (m, 2H), 7.33 (d, 1H, *J* 8.4 Hz), 7.53 (dd, 1H, *J* 7.6 and 0.8 Hz), 7.80–7.86 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 27.8, 52.3, 83.6, 127.8, 128.1, 128.3, 129.0, 129.2, 129.4, 129.9, 130.5, 133.3, 133.6, 135.6, 136.0, 141.2, 150.6, 165.9, 170.2.

In summary, we have used ruthenium-mediated ring closing metathesis for the construction of eight- and nine-membered frameworks of dibenzoazocinone and dibenzoazoninone, respectively, in good yield. The results demonstrated here should pave the way for the preparation of diverse eight- and nine-membered nitrogen containing heterocycles.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2014.04.011.

Methyl 5-tert-*butoxycarbonyl-6-oxo-5*H-*dibenzo[*b,g*]azonine-2(6*H,*13*H)-*carboxylate* **7**. Yield 0.77 g (55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.13 (s, 9H), 3.23 (dd, 1H, *J* 14.8 and 6.5 Hz), 3.33 (dd, 1H, *J* 14.8 and 11.6 Hz), 3.91 (s, 3H), 5.77 (td, 1H, *J* 11.6 and 6.5 Hz), 6.57 (d, 1H, *J* 11.6 Hz), 7.29 (d, 1H, *J* 7.6 Hz), 7.39 (td, 1H, *J* 7.6 and 1.2 Hz), 7.44 (d, 1H, *J* 8.8 Hz), 7.53 (td, 1H, *J* 7.6 and 1.2 Hz), 7.82 (dd, 1H, *J* 7.6 and 1.1 Hz), 8.01–8.03 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 27.5, 33.6, 52.3, 83.0, 127.4, 127.7, 128.9, 128.9, 129.6, 130.0, 130.1, 130.8, 131.7, 132.8, 134.2, 134.6, 136.9, 144.8, 151.5, 166.5, 174.6.

Methyl (Z)*-6-oxo-5,6-dihydrodibenzo[*b,f*]azocine-2-carboxylate* **8**. TFA (1.0 ml, 13 mmol) was added to a solution of compound **6** (0.65 g, 1.7 mmol) in dichloromethane (DCM) (5.0 ml) at 0 °C, and the mixture was stirred for 1 h. Then it was concentrated, the remaining slurry was co-evaporated with chloroform to provide 0.35 g of compound **8** (73%), mp 135 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.87 (s, 3H), 6.85 (d, 1H, *J* 11.6 Hz), 7.02 (d, 1H, *J* 11.6 Hz), 7.05 (d, 1H, *J* 7.5 Hz), 7.22 (d, 1H, *J* 8.2 Hz), 7.26 (dd, 1H, *J* 7.5 and 1.0 Hz), 7.32 (td, 1H, *J* 7.5 and 1.1 Hz), 7.45 (dd, 1H, *J* 7.5 and 1.1 Hz), 7.82 (d, 1H, *J* 1.6 Hz), 7.85 (dd, 1H, *J* 8.2 and 2.0 Hz), 8.23 (s, 1H), ^{13}C NMR (125 MHz, $CDCl_3$) δ: 52.4, 126.3, 128.0, 128.2, 128.5, 128.9, 129.2, 129.5, 130.0, 131.1, 133.8, 134.0, 134.5, 135.1, 139.5, 166.2, 173.6. HRMS, *m*/*z*: 273.0894 $[M]^+$ (calc. for $C_{17}H_{13}NO_3$, *m*/*z*: 273.0895).

*Methyl 6-oxo-6,13-dihydro-5*H-*dibenzo[*b,g*]azonine-2-carboxylate* **9**. Yield 0.185 g (71%), mp 182–184 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.51 (dd, 2H, *J* 14.8 and 11.8 Hz), 3.89 (s, 3H), 5.78 (td, 1H, *J* 11.8 and 7.3 Hz), 6.57 (d, 1H, *J* 11.8 Hz), 7.24–7.42 (m, 4H), 7.70 (s, 1H), 7.91 (d, 1H, *J* 6.5 Hz), 7.97 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 34.4, 52.3, 127.6, 128.5, 129.3, 129.4, 129.4, 130.3, 131.2, 131.5, 132.4, 134.4, 135.5, 135.6, 144.8, 144.8, 166.5, 173.8. HRMS, *m*/*z*: 292.0973 $[M-H]^-$ (calc. for $C_{18}H_{14}NO_3$, *m*/*z*: 292.0974).

For synthesis and characteristics of compounds **2a**,**b**, **4a**,**b** and **5a**,**b**, see Online Supplementary Materials.

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