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A simple approach for the synthesis of azocine alkaloids: The total synthesis of megallanesine

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ABSTRACT

A new three step synthetic route to construct azocine ring system using anion chemistry and intramolecular Friedel-Craft reaction of an ester is presented. This method allows synthesis of azocine ring analogues in excellent overall yields. The designed strategy was applied for the synthesis of naturally occurring magallanesine.

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Introduction

Nitrogen heterocycles are most abundantly found in nature.[1] Azepine and azocine are seven and eight membered ring system containing a nitrogen atom, forms an important class of organic compounds showing interesting conformational structure and wide range of biological activities.[2] For example isoindolobenzapines alkaloids like chilenine **1**, lennoxamine **2** and deoxychilenine **3** (Fig. 1) are isolated from genus *Berberis* are known for their potent activities against cancerous cells of the lungs, colon, prostrate, etc.[3] Magallanesine **4a** a tetracyclic fused ring system is the first isoindolobenzazocine class alkaloid isolated from *Berberis darwinii*.[4]

It is often challenging to synthesize a medium ring size molecule and only a few reports are available for the synthesis of magallanesine or its azocine containing analogues.[5–9] Shamma et al.[6] achieved the synthesis of magallanesine prior to its isolation from plant *Berberis darwinii* from a natural product oxyberberine (Scheme 1). Danishefsky et al.[7] achieved first synthesis of **4a** after its isolation using intramolecular aldol condensation in 6 steps with a 56% overall yield. Kurihara et al.[8a,b] synthesized magallanesine by [1,2]-Meisenheimer rearrangement to construct an azocine ring and modified intramolecular Heck cyclisation as the key steps over 11 synthetic steps in 24% overall yield. The same group[8c] later extended the above strategy to synthesize the indole analogue of magallanesine using methyl 2-(9-(phenylsulfonyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)acetate which was

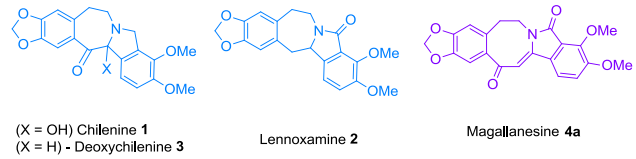
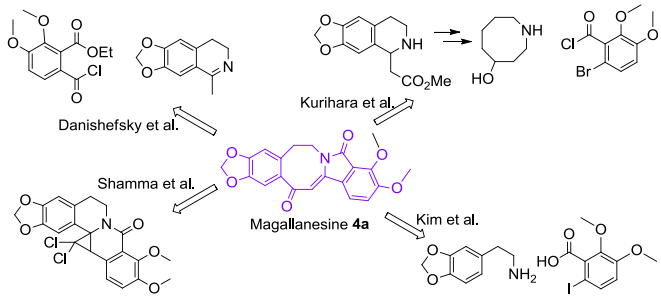


Fig. 1. Biologically important azepine and azocine ring system.



Scheme 1. Reported route for synthesis of **4a**.

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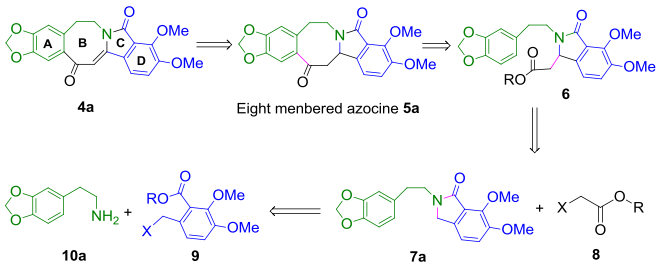


Scheme 2. Retrosynthesis for construction of azocine ring.

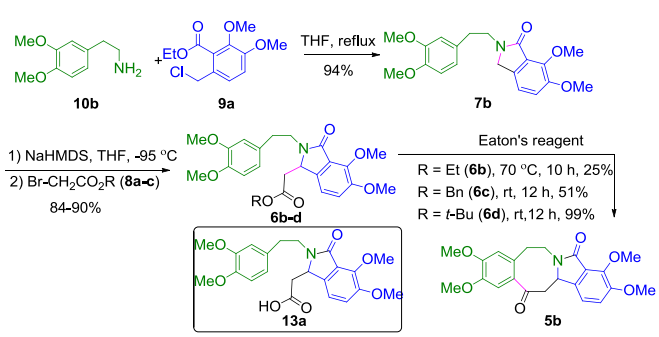
synthesized from tryptamine. Recently, Kim et al.[9] synthesized **4a** using intramolecular Heck and Friedel-Crafts cyclisation reaction in seven steps with a 33% overall yield. Our aim was to synthesize this azocine ring system efficiently in fewer steps.

In continuation of our interest in synthesis of nitrogen heterocycles[10] we report herein a general route for the construction of the azocine ring system. Our retrosynthetic pathway is depicted is Scheme 2. The dihydro benzoazocine derivative **4a** could be obtained from its tetrahydro derivative **5a**. The construction of eight membered tetrahydro benzoazocine ring B of **5a** could be accomplished from the corresponding ester **6** by intramolecular Friedel-Craft acylation reaction.[11] The ester **6** could be obtained by C—C bond formation via anion chemistry of isoindolinone derivative **7a** which in turn could be prepared by a one pot alkylation-amidation step from intermediates **9** and **10a**.

Results and discussion

We started with the synthesis of dimethoxy azocine derivative **5b** (Scheme 3). The required ethyl 6-(chloromethyl)-2,3-dimethoxybenzoate **9a** was synthesized according to the procedure described by Rapoport et al.[12a]

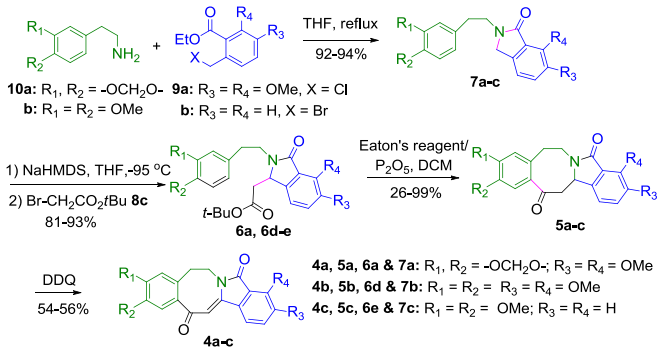
On heating **9a** with 2 equiv of commercially available 2-(3,4-dimethoxyphenyl)ethan-1-amine **10b** in THF gave the isoindolinone **7b** by one-pot alkylation-amidation sequence.[12b] Isoindolinone **7b** was deprotonated with NaHMDS at −95 °C and then alkylated with ethyl bromoacetate **8a** to get the key intermediate ethyl ester **6b**.[13] Only few reports are available in which esters are used as acylating agent.[11] The all-important intramolecular Friedel-Craft acylation with PPA (polyphosphoric acid) 110 °C for 16 h failed to deliver the expected eight membered ring compound. Hence, ethyl ester **6b** was reacted with 1:10 mixture of P_2O_5/methanesulphonic acid (Eatons reagent), which is known to be advantageous over using PPA.[14] No change in starting was observed at room temperature even after stirring for 16 h. Hence the reaction mass was heated at 70 °C for 10 h, which gave the desired product tetrahydro benzoazocine **5b** in only 25% yield. To improve the yield the corresponding benzyl ester of **6c** was prepared which gave **5b** in 51% yield at room temperature in 12 h. Further, treating *tert*-butyl ester **6d** with Eaton's reagent gave 99% yield of **5b**. To understand the reaction pathway, **6d** was treated with Eaton's reagent for 1 h at room temperature. The unreacted **6b** and product **5b** was seen in small amount along with the corresponding hydrolysed product acid **13a**. This suggested that the intramolecular Friedel-Craft reaction of ester **6d** is taking place *via* its acid. The compound **5b** was then converted to magallanesine analogue **4b** by dehydrogenation with DDQ (Scheme 4).[9]



Scheme 3. Synthesis of azocine derivative **5b**.

Having successfully synthesized the azocine ring containing **4b**, a synthetic derivative of magallanesine, we then completed synthesis of **4c** unsubstituted in ring D using starting **10b** and ethyl 2-(bromomethyl)benzoate[15] **9b** following the same protocol as shown in Scheme 4. Kim et al.[9] synthesised same compound **5c** using palladium mediated Heck coupling reaction over 6 steps in 57% overall yield, whereas our method gave the same compound in just 3 steps with an overall yield of 82% using same starting material **10b**. After this success, we then undertook the synthesis of naturally occurring magallanesine starting from 2-(benzo[*d*][1,3]dioxol-5-yl)ethan-1-amine **10a**[16] which on treatment with **9a** in refluxing THF to furnish the isoindolinone derivative **7a**. The intermediate **7a** was then alkylated with *tert*-butyl bromoacetate **8c** to give ester **6a** in 84% yield. The ester **6a** was then subjected to the Eaton's reagent in order to get cyclised compound **5a** (Table 1).

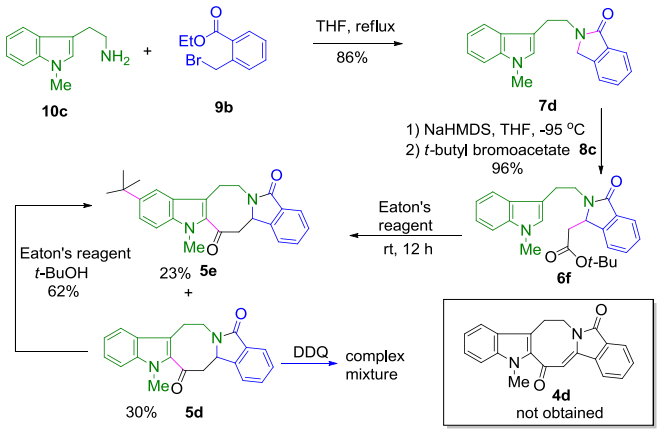
However, the only decomposition of the starting was seen at room temperature (Table 1, entry 1). We felt that use of a solvent to dilute the reaction mixture may help. Hence the reaction was attempted in dichloromethane, but similar results were obtained (entry 2). Lowering the reaction temperature also did not help (entry 3). Ester **6a** was then hydrolyzed with TFA and treated with Eaton's reagent in a one pot condition which again resulted in decomposition of the starting material. The decomposition of the starting material was attributed to the strong acidic nature of the Eaton's reagent which may be breaking the methenedioxy group. Hence, the reaction was carried out in the presence of excess of P_4O_{10} in dichloroethane during which two products, the required dihydromagallanesine **5a** and its corresponding acid **13b** were obtained. Further dehydrogenation of **5a** with DDQ provided magallanesine, the structure of which was confirmed by matching



Scheme 4. Synthesis of magallenisine and its analogues.

Table 1
Intramolecualr Friedel-Craft's cyclisation of **6a.**

Entry	Reaction condition	Results
1	Eaton reagent, rt, 2 h	Decomposition
2	1:9 (P_2O_5/methanesulphonic acid), DCM, rt, 2 h	Decomposition
3	1:9 (P_2O_5/methanesulphonic acid), DCM, −20 °C, 6 h	Decomposition
4	TFA, rt, 2 h, then Eaton reagent, 1 h	Decomposition
5	P_4O_{10}, DCE, rt, 10 h	**5a** (26%) + **13b** (20%)



Scheme 5. Synthesis of indole fused azocine ring.

with the literature spectral data.[7,8b] It is to be noted here that the reported[9] synthesis of magallanesine uses $BF_3.Et_2O$, TFAA for the intramolelcular Friedel-Craft reaction while PPA is used for the other analogues and no reason is attributed to the choice.

Having successfully synthesized magallanesine **4a** and two of its analogues we decided to extend this protocol for indole analogue **4d** (Scheme 5). Thus 2-(1-methyl-1*H*-indol-3-yl)ethan-1-amine **10c**[17] was condensed with **9b** to give 86% yield. Isoindolinone derivatives **7d** was then successfully alkylated to get **6f** in 96% yield. The ester **6f** when subjected to Eaton's reagent gave two products **5d** and **5e** in 30 and 23% yield respectively. IR spectra of these two compounds were almost similar. But the ^{1}H NMR spectrum of **5e** showed an extra peak at 1.33 ppm accounting for 9 protons. Also a substitution at 5-position of indole ring was observed based on the splitting pattern of the aromatic protons. The compound **5d** was identified to be expected tetrahydro azocine based on the spectral data. The mass spectrum of **5e** showed additional 56 a.m.u ($[M+Na]^+$ 409.1892) as compared to **5d,** which shows $[M+Na]^+$ peak at *m*/*z*. 353.1266. This suggested the presence of an additional C_4H_9 group which may be arising from *tert*-butanol, which is formed by the hydrolysis of the ester. The tetrahydro azocine derivative **5d** was then subjected to the dehydrogenation with DDQ. However, it gave a complex mixture. To account for the for the formation of **5e** we conducted a controlled experiment by treating **5d** with *t*-butanol in Eaton's reagent at room temperature. On work-up 62% of **5e** was isolated as expected, thereby confirming the formation of **5e** from **6d** during cyclisation.

Conclusion

We have successfully designed a new strategy to construct an azocine ring containing alkaloids using anion chemistry on isoindolinone and intramolecular Friedel-Craft reaction of an ester. The designed strategy was applied for the synthesis of naturally occurring magallanesine. The present method is simple, shorter and has a comparable overall yield in comparison to the reported methods.

Acknowledgments

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2018.05.055.

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