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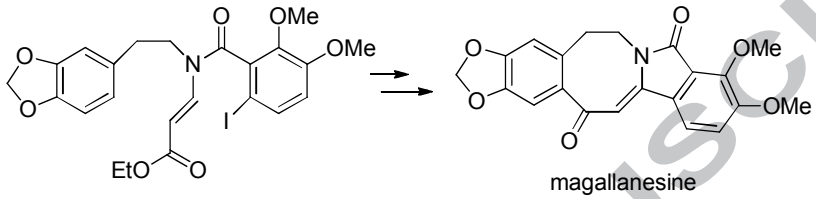


magallanesine

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# A synthetic study of magallanesine by cyclization of a benzamidoacrylate intermediate

Seong-Ye Seo and Guncheol Kim*

*Department of Chemistry, College of Natural Sciences, Chungnam National University, Daejon 305-764, Republic of Korea*

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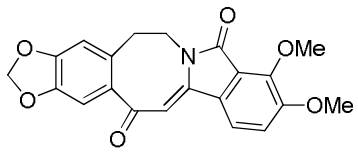
ABSTRACT

Cyclization of a benzamidoacrylate intermediate has been applied for the synthesis of magallanesine rings. Heck reaction for the 5-membered ring and the following Friedel-Crafts reaction provided the azocine central rings of the alkaloid. The precursor obtained by cyclizations from a properly funtionalized benzamidoacrylate has been converted successfully to magallanesine via the final oxidation with DDQ.



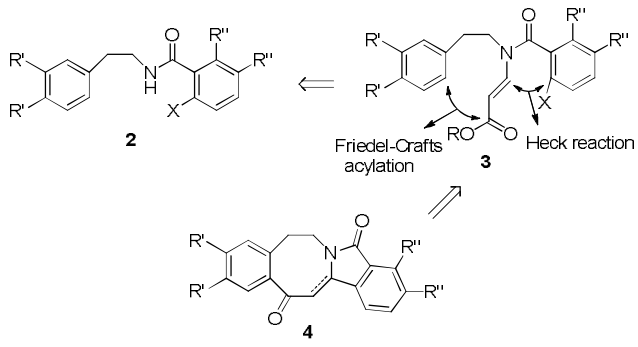
Polycyclic alkaloids are frequently encountered in natural compounds, and the structurally related products containing synthetic drugs have shown numerous physiological activities.[1] Especially, medium ring sized azocine or azepine compounds arranged with other rings around have been attracted by many synthetic chemists because of skeletal attraction as well as biological applications.[2,3] As an extension of our interests on the synthesis of the natural alkaloid products containing medium sized ring,[4] we want to explore cyclization reactions using benzamidoacrylate intermediates for the synthetic study of magallanesine containing an 8-membered ring (Figure 1). The product is the first known isoindolobenzazocine alkaloid isolated from *Berberis Darwin*,[5] which has been synthesized only by a few groups.[6] For a new synthetic approach, we wanted to explore benzamidoacrylate precursors providing proper carbon number as well as functional groups, however, these intermediates have been rarely applied in natural alkaloid synthesis.




**1: magallanesine**

**Figure 1.**

For the construction of the core skeleton of **1**, we planned to try two cyclization reactions from intermediate **3**: Heck reaction for 5-membered ring first and Friedel-Crafts acylation for 8-membered ring next. Compound **3** would be prepared by Michael type reaction of amide **2** with an alkyl propiolate. Heck reaction of aryliodide with the vinyl group of acrylate group would yield the 5-membered ring and the following Friedel-Crafts acylation reaction with or without olefin group would be tried to construct the required central ring skeleton (Scheme 1).

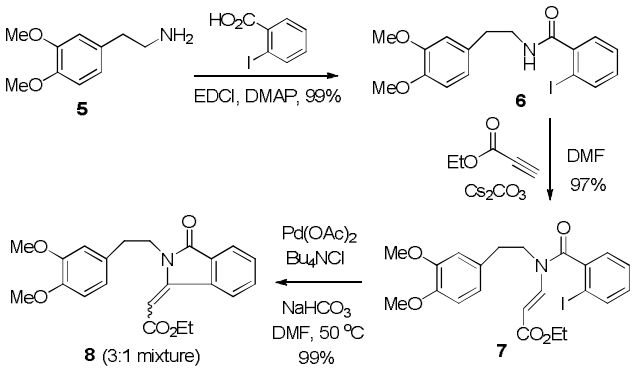



**Scheme 1.**

For the first cyclization trial using Heck reaction from **3**, we prepared iodoarylamide **6** via a coupling reaction of **5** and 2-iodobenzoic acid in 99% yield. And addition reaction of **6** with

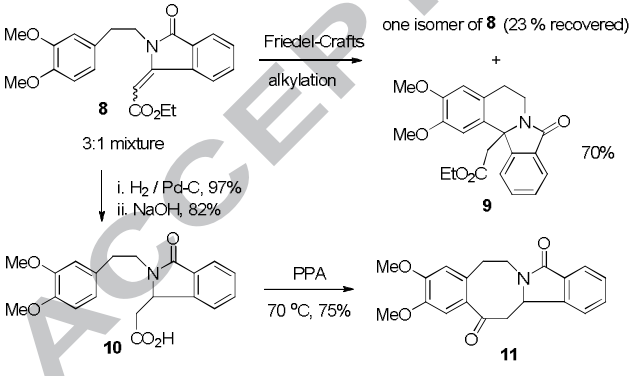
* Corresponding author. Tel.: +82-42-821-5475; fax: +82-42-821-8896; e-mail: guncheol@cnu.ac.kr

ethyl propiolate in the presence of $Cs_2CO_3$ in DMF afforded amidoacrylate **7** in 97% yield. Compound **7** under conventional Heck reaction condition using $Pd(OAc)_2$ and $Bu_4NCl$ provided a 3:1 mixture of **8** in 99% yield (Scheme 2). The mixture of **8** could be neither separated nor differentiated to show which isomer should be *E* or *Z* in NMR spectrum. However, we expect that any cyclzation attempt of **8** under acidic conditions might reveal its potential aspects to the azocine ring.



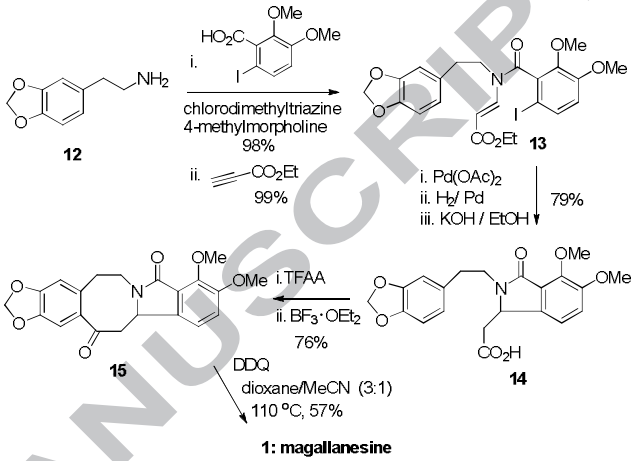

**Scheme 2.**

Friedel-Crafts reaction of **8** with acid such as $AlCl_3$, $BF_3{\cdot}OEt_2$ or HCl provided all the similar results yielding a single isomer of **8** recovered in 23% yield and **9** in 70% yield via Michael type alkylation reaction.[7] Only one isomer has been found to be reactive under the acidic condition toward Michael reaction and the stereochemistry of the isomer recovered remains still uncertain. For the formation of the 8-membered ring, the exo-C-C double bond of **8** seemed to be removed first. Accordingly, hydrogenation of **8** in the presence of Pd catalyst (97%) was followed by hydrolysis with NaOH (82%) to provide compound **10**. The azocine ring could be formed under heating a solution of **10** in polyphosphoric acid (PPA) at 70 °C in 75% yield of **11** (Scheme 3).




**Scheme 3.**

In order to synthesize magallanesine, we prepared the requisite precursor **13** from 3,4-methylenedioxyphenethylamine **12** through coupling with 6-iodo-2,3-dimethoxybenzoic acid using chloromethyltriazine and 4-methylmorphorine in 98% yield and the following Michael reaction in 99% yield. The same sequence, Heck reaction followed by hydrogenation and hydrolysis, has been applied to obtain compound **14** in three step 79% yield. Unlike **10**, Friedel-Crafts reaction of **14** required a particular condition, sequential treatment with trifluoroacetic anhydride (TFAA) at 0 °C and addition of $BF_3{\cdot}OEt_2$ followed by heating the resulting solution for 6 hr at 50 °C.[8] This process allowed 76% yield of **15** as a solid.[9] Final oxidative condition would result in the successful synthesis of magallanesine. Optimal dehydrogenation reaction of **15** has been found to be DDQ treatment under heating at 110 °C to yield the final product **1** in 57% yield.[10]




**Scheme 4.**

In summary, we could synthesize an azocine alkaloid, magallanesine from the useful benzamidoacrylate precursor. Two cyclization reactions, Heck and Friedel-Crafts reactions, using the intermediate have been successfully applied for a concise route to the final product.

## Acknowledgments

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7. One isomer of **8**: $^{1}$H NMR (400MHz, $CDCl_3$) 1.34 (t, 3H, *J* = 8.0 Hz), 2.87 (t, 2H, *J* = 8.0 Hz), 3.78 (s, 3H), 3.84 (s, 3H), 4.27 (q, 2H, *J* = 8.0 Hz), 4.55 (t, 2H, *J* = 8.0 Hz), 5.89 (s, 1H), 6.76 – 6.83 (m, 3H), 7.56 – 7.63 (m, 2H), 7.69 (d, 1H, *J* = 6.0 Hz), 7.82 (d, 1H, *J* = 6.0 Hz). Compound **9**: $^{1}$H NMR (400MHz, $CDCl_3$) 0.88 (t, 3H, *J* = 8.0 Hz), 2.76 (ddd, 1H, *J* = 12.0, 2.0, 2.0 Hz), 2.93 (m, 1H), 3.25 (ABq, 2H, *J* = 12.0 Hz ), 3.45 (ddd, 1H, *J* = 8.0, 2.0, 2.0 Hz), 3.81 (q, 2H, *J* = 8.0 Hz), 3.85 (s, 3H), 3.93 (s, 3H), 4.65 (ddd, 1H, *J* = 12.0, 8.0, 2.0 Hz), 6.59 (s, 1H), 7.16 (s, 1H), 7.49 (dd, 1H, *J* = 8.0, 8.0 Hz), 7.63 (dd, 1H, *J* = 8.0, 8.0 Hz), 7.84 (d, 1H, *J* = 8.0 Hz), 7.91 (d, 1H, *J* = 8.0 Hz) $^{13}$C NMR (100MHz, $CDCl_3$) 13.76, 28.87, 35.02, 45.44, 55.96, 56.36, 60.60, 64.40, 109.36, 112.24, 122.99, 123.98, 126.33, 128.84, 129.45, 131.91, 132.07, 147.83, 147.95, 148.78, 167.88, 168.27 .
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9. Compound **15**: mp 226-230 $^{o}$C, $^{1}$H NMR (400MHz, $CDCl_3$) 2.98 (dd, 1H, *J* = 14.6, 5.7 Hz), 3.26 (dd, 1H, *J* = 14.6, 1.5 Hz), 3.45 (m, dd, 1H, *J* = 14.6, 5.7 Hz), 3.72 (td, 1H, *J* = 13.7, 6.1 Hz), 3.88 (s, 3H), 3.89 (s, 3H), 4.53 (td, 1H, *J* = 13.7, 6.1 Hz), 4.83 (dd, 1H, *J* = 6.1, 1.5 Hz), 5.95 (d, 1H, *J* = 1.0 Hz), 5.97 (d, 1H, *J* = 1.0 Hz), 6.72 (s, 1H), 7.11 (d, 1H, *J* = 8.4 Hz), 7.12 (s, 1H), 7.17 (d, 1H, *J* = 8.4 Hz), 7.28 (s, 1H) $^{13}$C NMR (100MHz, $CDCl_3$) 34.84, 40.05, 47.11, 56.52, 57.14, 62.46, 101.99, 109.31, 111.44, 116.36, 117.59, 123.88, 132.78, 134.75, 136.51, 146.95, 147.39, 151.95, 152.74, 166.25, 195.69, EIMS 381.12 ($M^{+}$).
10. Spectral data of **11** were identical to those of the known.[6b]