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A TOTAL SYNTHESIS OF MAGALLANESINE: DMF ACETAL MEDIATED CYCLODEHYDRATION OF A METHYL KETONE THIOIMIDE

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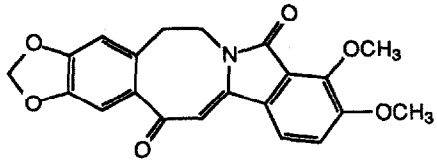
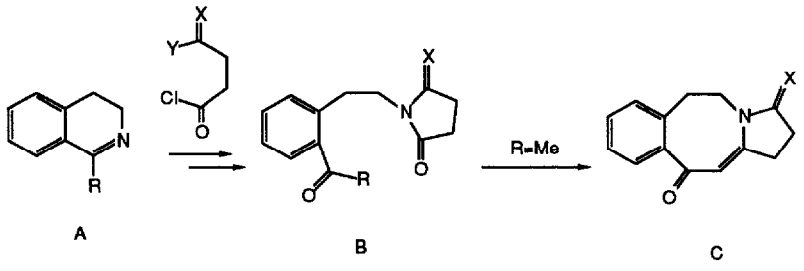
Abstract An amide acetal-mediated intramolecular condensation of a methylketone with a regioselectively activated unsymmetrical phthalimide resulted in the total synthesis of the isoindolobenzazocine alkaloid magallanesine (**1**).

South American members of the botanical genus *Berberis* have proven to be an abundant source of novel isoquinoline and isoindolobenzazepine bases.[1] Recently magallanesine (**1**), the first known isoindolobenzazocine alkaloid, was isolated from *Berberis Darwinii*.[2,3,4]

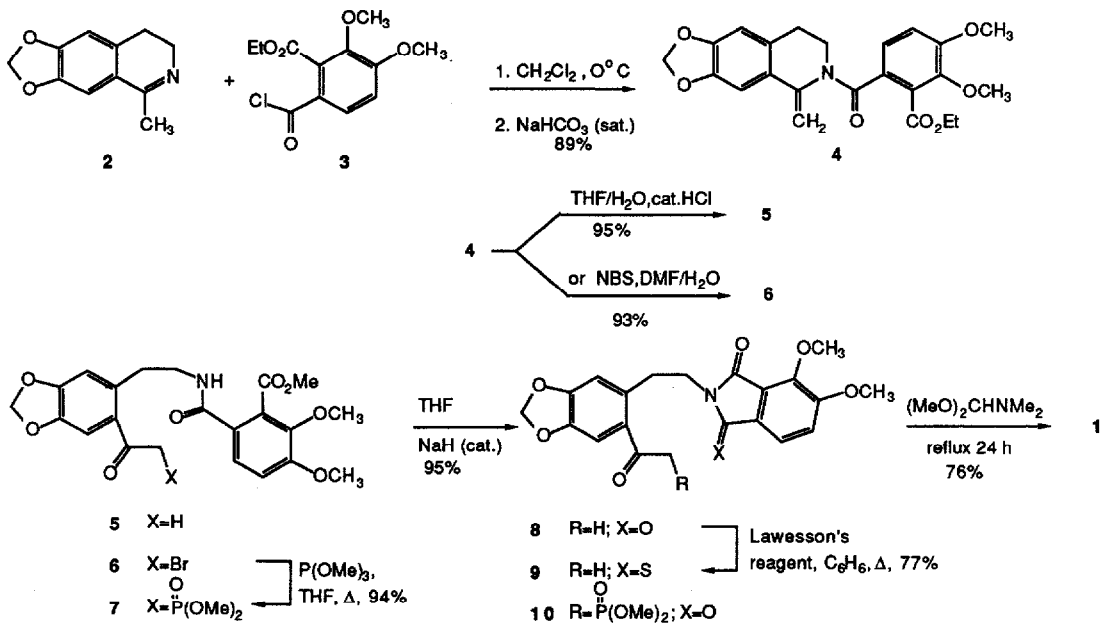


1 magallanesine

In conjunction with a larger program directed at exploring the feasibility of carbon-carbon bond forming cyclizations to amide and imide like carbonyl linkages, we have investigated the total synthesis of magallanesine(**1**). An important element of our strategy involved acylative opening of readily available dihydroisoquinolines (cf. A) as a concise route to cyclization substrates (cf. B). It was hoped that means could be found to allow for closure of the novel benzazocine ring from a precursor such as B. Both suppositions have been realized. In this Letter we describe the total synthesis of **1**.



Treatment of methyl-β-hydrastine (**2**) [5] with known acid chloride **3** [6] in methylene chloride at 0° C followed by addition of saturated sodium bicarbonate solution provided enamide **4** in 89% yield. Acid catalyzed hydrolysis of **4** to methyl ketone **5** proceeded in 95% yield. The secondary amide in **5** was cyclized onto the adjacent carboethoxyl group under base catalysis to afford a 95% yield of imide **8**. Attempts to achieve the cyclization of **8** to magallanesine (**1**) under a variety of basic conditions were unsuccessful.



An alternative, Wittig-like olefination was pursued.[7] Treatment of enamide **4** with N-bromosuccinimide (NBS) in dimethylformamide (DMF)/water gave a 93% yield of bromoketone **6**. Arbuzov[8] reaction of **6** with trimethylphosphite afforded ketophosphonate **7** in 90% yield. Conversion of **7** to imide **10** under sodium hydride catalysis proceeded in 83% yield. Unfortunately, attempts to achieve the required cyclization of imide **10**, under a variety of basic reaction conditions were unsuccessful..

At this point we turned to activation of the phthalimide ring as a means for inducing eight-membered ring formation. Treatment of **8** with Lawesson's reagent[9] converted the apparently more accessible imide carbonyl into its thio analog, providing **9** in 77% yield. That the desired regioisomer had been obtained was demonstrated by subsequent conversion to the natural product. Thus, heating a solution of **9** in dimethylformamide dimethyl acetal at reflux for 24 h generated a yellow precipitate. This was collected by filtration and recrystallized from methanol to provide a 76% yield of a yellow powder whose spectral properties (^{1}H NMR, NOEDS, ^{13}C NMR, IR, MS) and melting point (254-256°C) were identical with the published data for magallanesine (**1**).[10]

In summary, an efficient total synthesis of magallanesine (**1**) which proceeds in five steps and 47% overall yield from methyl-β-hydrastine (**2**) has been achieved. The interesting features of the synthesis as we see them are (i) overall hydrolytic phthaloylation of a cyclic imine (see **2** → **8**) and its oxidative counterpart (see **2**→**7**), (ii) regiospecific thioimidization of **8** and (iii) use of DMF acetal as a cyclization catalyst. This novel cyclodehydration possibly occurs by concurrent activation of both the methyl ketone and thioimide functions. Further developments which build upon these findings will be reported in due course.

Acknowledgments This research was supported by PHS Grant CA 28824. A Kent Fellowship (Yale University) to F.G.F. is gratefully acknowledged. We thank Professor M. Shamma (Pennsylvania State University) for providing spectral data relating to natural **1**. We also thank John van Duzer (Yale University) for providing a sample of the carboxylic acid corresponding to **3**. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR facility at Yale University, which was supported by NSF Chemistry Division Grant CHE 7916210.

Notes and References

1 Shamma, M. "The Isoquinoline Alkaloids: Chemistry and Pharmacology", Academic Press, New York, 1972. Shamma, M.; Moniot, J.L. "Isoquinoline Alkaloids Research 1972-1977." Plenum Press, New York, 1978. Valencia, E.; Weiss, I.; Firdous, S.; Freyer, A.J.; Shamma, M.; Urzua, A.; Fajardo, V. *Tetrahedron* **1984**, *40*, 3957.

2. Valencia, E.; Fajardo, V.; Freyer, A.J.; Shamma, M. *Tetrahedron Lett.* **1985**, *26*, 993.

3. Several years prior to its isolation from natural sources, magallanesine (**1**) was obtained as the rearrangement product of the dichlorocarbene adduct of oxyberberine.: Manikumar, G.; Shamma, M. *J Org. Chem.* **1981**, *46*, 386.

4. It has recently been suggested that magallanesine (**1**) may have been obtained as an artifact of the isolation protocol.: Shamma, M.; Rahimizadeh, M. *J. Nat. Prod.* **1986**, *47*, 1.

5. Bills, J.,L.; Noller, C. R. *J. Am. Chem. Soc.* **1948**, *70*,960.

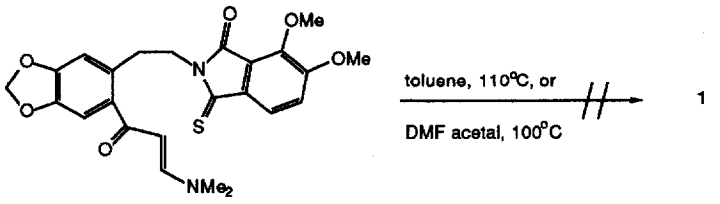
6. Wasserman, H.H.; Amici, R.; Frechette, R. H.; van Duzer, J. H. *Tetrahedron Lett.* **1989**, *30*, 869.

7. For reviews on the Wittig reaction of imides see: Murphy, P. J.; Brennan, J. *Chem Soc. Rev.* **1988**, *17*, 1-30. Flitsch, W.; Schindler, S. R. *Synthesis*, **1975**, 685..

8. Arbuzov, B. A. *Pure Appl. Chem.* **1964**, *9*, 307. Kosolapoff, G. M. *Org. React.* **1951**, *6*, 276.

9. For a review on the use of Lawesson's reagent see: Cava, M.; Levinson, M. I. *Tetrahedron*, **1985**, *41*, 5061.

10. Isolated as a minor product (ca. 10%) from this reaction was enamide **11**. That **11** does not lie along the pathway for conversion of **9** to magallanesine (**1**) was suggested by its failure to undergo cyclization to **1** in either refluxing toluene or refluxing dimethylformamide dimethyl acetal.



11

11. All new compounds were fully characterized by ^{1}H NMR, IR, MS, HREIMS and/or elemental analysis, and melting point (where appropriate): **6** (141-143°C d), **8** (173-174°C), **9** (172-173°C).

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