Pergamon

Tetrahedron Letters, Vol. 35, No. 22, pp. 3749-3752, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)E0678-Q

A Total Synthesis of Magallanesine *via* [1, 2]-Meisenheimer Rearrangement

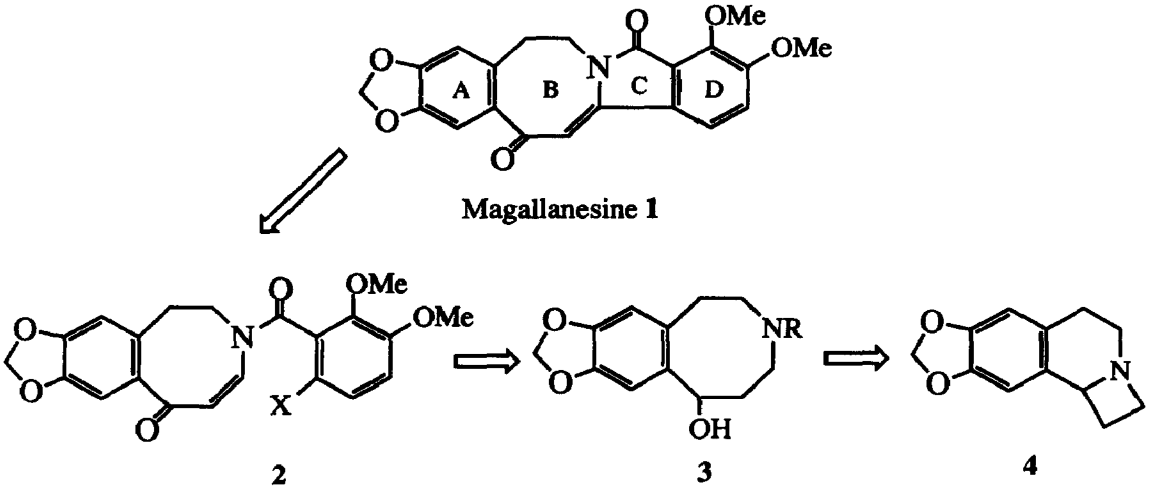
Ryuji Yoneda, Yasuhiko Sakamoto,# Yoshifumi Oketo, Kayoko Minami, Shinya Harusawa, and Takushi Kurihara*

Osaka University of Pharmaceutical Sciences, 2-10-65 Kawai, Matsubara,
Osaka 580, Japan

Abstract: A straightforward synthesis of magallanesine **1** from azetoisoquinoline **4** has been accomplished *via* [1,2]-Meisenheimer rearrangement and an intramolecular Heck cyclization as the key reactions.

Members of the plant family *Berberidaceae* have long been known to contain a number of alkaloids, and recently the first example of a new class of isoindolobenzazocine alkaloid, magallanesine **1**, was isolated from *Berberis Darwinii* Hook, collected in southern Chile.[1,2] The only total synthesis, in 1989, was reported by Danishefsky using an amide acetal-mediated intramolecular cyclization of a methylketone thioimide with activated phthalimide.[3] The unique structure of **1** including the medium-ring nitrogen heterocycles, azocine ring, which are generally the most difficult to prepare by the use of conventional cyclization methods,[4] was of synthetically interest. As an extension of our program to assess the feasibility of preparing oxa-bridged, fused azocine ring based on rearrangement of fused azetopyridine *N*-oxide,[5] we report herein a straightforward synthesis of magallanesine **1**.

Our synthetic strategy is designed mainly aiming at that isoindolobenzazocine skeleton might be constructed from *N*-benzoyl enaminone **2** *via* palladium mediated 5-*exo-trig* cyclization.[6,7] The substrate **2** may be obtained from azetoisoquinoline **4** *via* [1,2]-Meisenheimer rearrangement of the corresponding *N*-oxide followed by standard chemical transformations through intermediate **3**.



The sequence to the required **3** starts from unsaturated ester **5**, prepared from piperonal.[8] Catalytic hydrogenation of **5** followed by $LiAlH_4$ reduction gave alcohol **7**, which could be converted to chloride **8** in 90% overall yield from **5** (chart 1). Base catalyzed cyclization[9] of **8** gave **4**[10] (72% yield), which was oxidized with H_2O_2 followed by quenching with PtO_2[11] to give the corresponding *N*-oxide **9**. Refluxing of **9**, without purification, in THF gave the best result to lead the [1,2]-Meisenheimer rearrangement product **10**[10] in 64% yield. Catalytic hydrogenation of **10** gave hydroxybenzazocine **11** quantitatively.

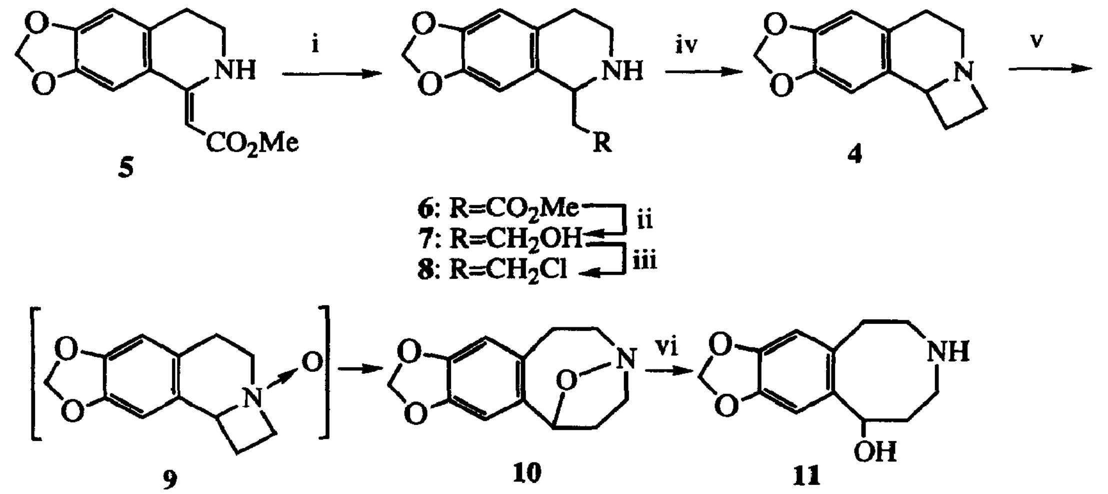


Chart 1

i: 10% Pd-C/H_2, AcOH-MeOH (1:1), 4 Kg/cm^2, R.T., 100%; ii: $LiAlH_4$, THF, 0°C, 10 min, 93%;
iii: $SOCl_2$, CH_2Cl_2,reflux, 2 h, 97%; iv: NaOMe (1.5 equiv.), MeOH, reflux, 1.5 h, 72%; v: 35% H_2O_2, MeOH-$CHCl_3$ (1:1), R.T., 16 h; PtO_2 (0.01 equiv.), R.T., 5 h, then THF, reflux, 1 h, 64%;
vi: 10% Pd-C/H_2, MeOH, 1 Kg/cm^2, R.T., 100%

Treatment of **11** with acid chloride **12**[12] afforded amide **13** (94%), which was oxidized with Dess-Martin reagent[13] in CH_2Cl_2 to give azocinone **14** in 95% yield (Chart 2). Introduction of a double bond was effected by conditions, which employ phenylsulfenylation, *m*CPBA oxidation followed by subsequent thermolysis of sulfoxide in toluene, to afford approximately a 4:1 mixture [^1H NMR of olefinic protons: δ 6.01 and 6.39 (d, J=9.3 Hz) for *cis* and δ 6.33 and 7.10 (d, J=9.3 Hz) for *trans*] of *cis*- and *trans*-*N*-benzoyl enaminone **16**[14] in 67% overall yield from **14**. Finally, construction of the C-ring of **1** was investigated by an intramolecular Heck reaction.[15] After several attempts, ring closure of **16** was successfully accomplished by means of a modified Heck cyclization[15b] with $Pd(OAc)_2$ and TlOAc in the presence of PPh_3 in DMF to provide a 93% yield of yellow powder. Its melting point (254-256°C) and spectral data (^1H-NMR, ^{13}C-NMR, IR, and UV) were identical with those reported for magallanesine **1**.[1]

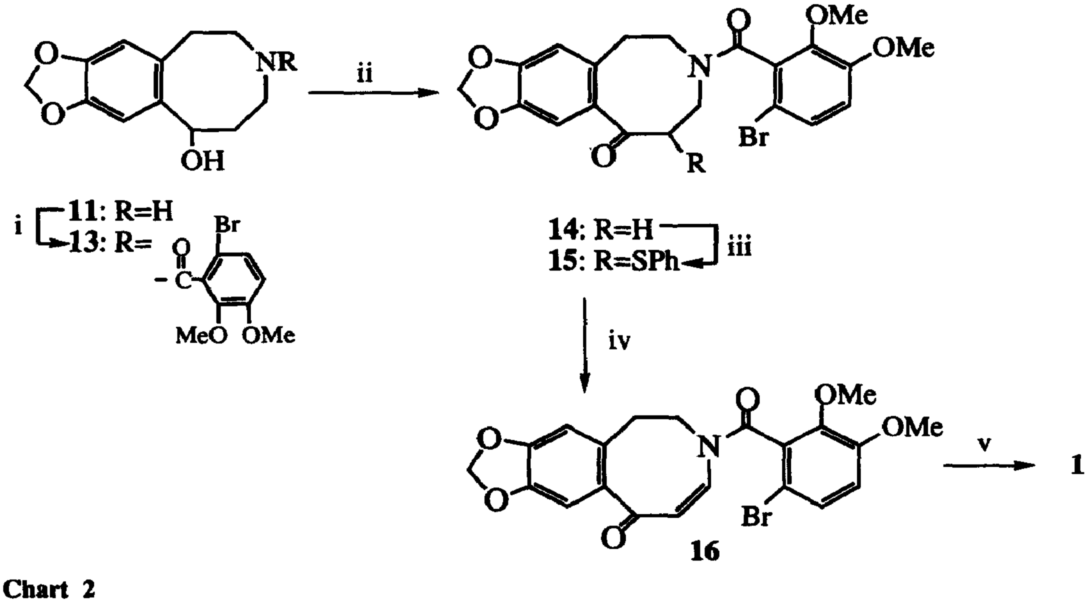


Chart 2
i: 5-Bromo-2,3-dimethoxybenzoyl chloride **12** (1.2 equiv.), 10% NaOH (1 equiv.), DME, R.T., 94%; ii: Dess-Martin Reagent (1.5 equiv.), CH_2Cl_2, R.T., 20 min, 95%; iii: $(TMS)_2NLi$, HMPA, THF, -78°C, 20 min, then $(PhS)_2$ (2 equiv.), -78°C to R.T., 1 h; iv: *m*CPBA (1 equiv.), CH_2Cl_2, R.T., then reflux in toluene, 2 h, 67% from **14**; v: $Pd(OAc)_2$ (10 mol %), Ph_3P (0.2 equiv.), TlOAc (1.2 equiv.), DMF, 130°C, 24 h, 93%

In summary, this report has demonstrated that the [1,2]-Meisenheimer rearrangement of fused azetopyridine provides a convenient entry to oxa-bridged, fused azocine systems.

Acknowledgements This work was supported finacially by *Nippon Shoji Kaisha, Ltd.* is gratefully acknowledged. We thank Mrs M. Fujitake of our university for measurements of mass spectra.

References and Notes

\# Present address: *Research Laboratories, Nippon Shoji Kaisha, Ltd, Ibaraki City, Osaka, Japan.*

1. Valencia, E.; Fajardo, V.; Freyer, A.J.; Shamma, M., *Tetrahedron Lett.*, **1985**, *26*, 993-996.
2. Before isolation from natural sources, magallanesine 1 had already been obtained from oxyberberine *via* dichlorocarbene adduct : Manikumar, G.; Shamma, M., *J. Org. Chem.*, **1981**, *46*, 386-389.
3. Fang, F.G.; Feigelson, G.B.; Danishefsky, S.J., *Tetrahedron Lett.*, **1989**, *30*, 2743-2746.
4. For reviews of the medium-sized heterocycles, see: Evans, P.A.; Holmes, A.B., *Tetrahedron*, **1991**, *47*, 9131-9166. Glass, R.S., Ed., *Conformational Analysis of Medium-Sized Heterocycles.*; VCH Publishers, Inc., 1988.
5. Kurihara, T.; Sakamoto, Y.; Takai, M.; Ohuchi, K.; Harusawa, S.; Yoneda, R., *Chem. Pharm. Bull.*, **1993**, *41*, 1221-1225.
6. For reviews of the Heck reaction, see: Heck, R.F., in *Comprehensive Organic Synthesis*; Trost, B.M., Ed; Pergamon Press: Oxford, 1991; Vol. 4, p 833-863. Heck, R.F., *Org. React.*, **1982**, *27*, 345-390. Trost, B.M.; Verhoeven, T.R., in *Comprehensive Organometallic Synthesis;* Wilkinson, G., Ed.; Pergamon Press: Oxford, 1982; Vol. 8, p 799-938. Daves, G.D.Jr.; Hallberg, A., *Chem. Rev.*, **1989**, *89*, 1433-1445.
7. a) The palladium mediated 5-*endo-trig* cyclization of *N*-unsubstituted or *N*-alkyl enaminones to 3-substituted indoles were reported, see: Kasahara, A.; Izumi, T.; Kikuchi, T., *J. Heterocycl. Chem.*, **1987**, *24*, 1555-1556. Kasahara, A.; Izumi, T.; Murakami, S.; Yanai, H.; Takatori, M., *Bull. Chem. Soc.*, **1986**, *59*, 927-928. Iida, H.; Yuasa, Y.; Kibayashi, C., *J. Org. Chem.*, **1980**, *45*, 2938-2942; b) To our knowledge, there has been only one report about 5-*exo-trig* cyclization of *N*-benzoyl enaminone under Heck reaction conditions, see: Kraus, G.A.; Kim, H., *Synth. Commun.*, **1993**, *23*, 55-64.
8. Sano, T.; Toda, J.; Kashiwaba, N.; Ohshima, T.; Tsuda, Y., *Chem. Pharm. Bull.*, **1987**, *35*, 479-500.
9. Kóbor, J.; Fülöp, F.; Bernáth, G.; Sohár, P., *Tetrahedron*, **1987**, *43*, 1887-1894.
10. All new compounds were characterized by ^{1}H-NMR, IR, and HRMS and/or elemental analyses.
11. Rautenstrauch, V., *Helv. Chim. Acta*, **1973**, *56*, 2492-2508.
12. The acid chloride **12** was prepared from known carboxylic acid (Auerbach, J.; Weissman, S.A.; Blacklock, T.J.; Angeles, M.R.; Hoogsteen, K., *Tetrahedron Lett.*, **1993**, *34*, 931-934) by treatment with thionyl chloride.
13. Dess, D.B.; Martin, J.C., *J. Org. Chem.*, **1983**, *48*, 4155-4156. *Idem.*, *J. Am. Chem. Soc.*, **1991**, *113*, 7277-7287. Ireland, R.E.; Liu, L, *J. Org. Chem.*, **1993**, *58*, 2899.
14. The *cis* and *trans* designations of amide followed the reference: Azumaya, I.; Kagechika, H.; Fujiwara, Y.; Itoh, M.; Yamaguchi, K.; Shudo, K., *J. Am. Chem. Soc.*, **1991**, *113*, 2833-2838.
15. Recent examples of the intramolecular Heck reaction, see: a) Abelman, M.M.; Oh, T.; Overman, L.E., *J. Org. Chem.*, **1987**, *52*, 4130-4133; b) Grigg, R.; Loganathan, V.; Santhakumar, V.; Sridharan, V.; Teasdale, A., *Tetrahedron Lett.*, **1991**,*32*, 687-690; c) Ishibashi, H.; Ito, K.; Hirano, T.; Tabuchi, M.; Ikeda, M., *Tetrahedron*, **1993**, *49*, 4173-4182; d) Chida, N.; Ohtsuka, M.; Ogawa, S., *J. Org. Chem.*, **1993**, *58*, 4441-4447; e) McIntosh, M.C.; Weinreb, S.M., *ibid.*, **1993**, *58*, 4823-4832; ; f) Rice, J.E.; Cai, Z-W., *ibid.*, **1993**, *58*, 1415-1424.

(*Received in Japan* 18 *January* 1994; *accepted* 16 *March* 1994)