Tetrahedron Letters, Vol.31, No.22, pp 3195-3198, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

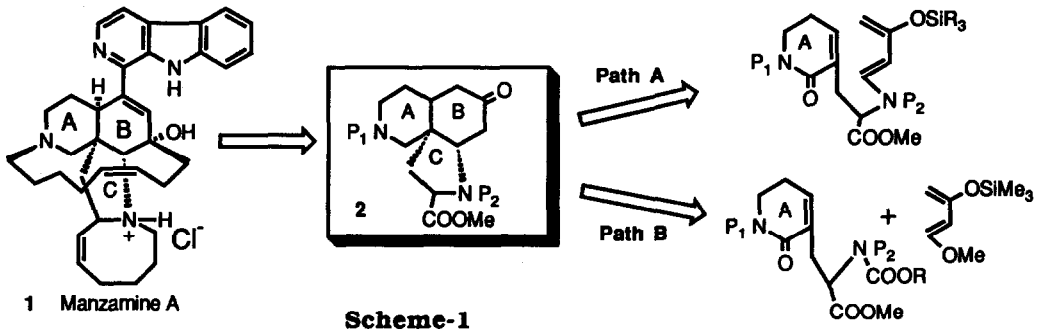
SYNTHETIC STUDIES ON MANZAMINE A II;[1] A NOVEL DIELS-ALDER APPROACH TO THE PYRROLO[2,3-j]ISOQUINOLINE SKELETON

Yasuhiro Torisawa,[a] Masako Nakagawa,[a]* Hitoe Arai,[a] Ziping Lai,[a] and Tohru Hino[a]*
Tadashi Nakata[b] and Takeshi Oishi[b]
Faculty of Pharmaceutical Sciences, Chiba University,[a] 1-33, Yayoi-cho, Chiba-shi 260, Japan
The Institute of Physical and Chemical Research (RIKEN),[b] Wako-shi, Saitama 351-01, Japan

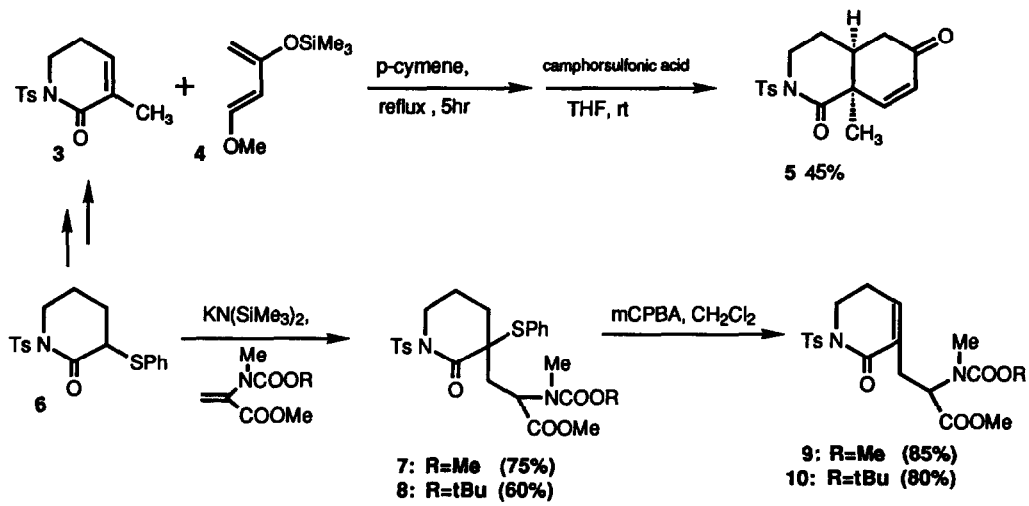
Summary: *An expeditious preparation of the central pyrroloisoquinoline skeleton of manzamine A (1) was achieved via the high-pressure Diels-Alder reaction of 3-alkyl-5,6-dihydro-2-pyridinone (10) with Danishefsky diene followed by deprotection and spontaneous pyrrolidine ring clousure.*

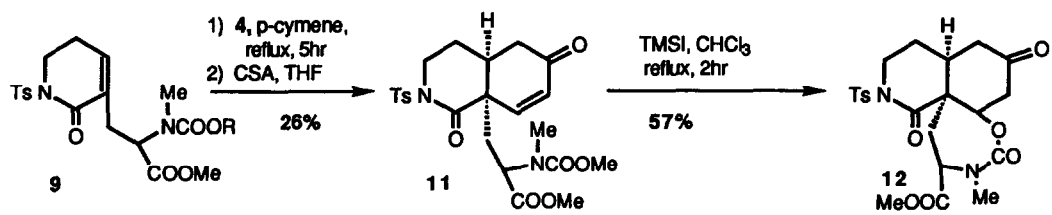
Since the first isolation and structural elucidation of manzamine A (1) from Okinawan marine sponge by Higa[2] and subsequent characterization of the five congeners (manzamine B~F)[3] coupled with the independent isolation of the same alkaloids as keramamines,[4] there have been widespread interests in the structure and synthesis of these oncolytic marine alkaloids. While the simplest congener manzamine C has recently been synthesized in this laboratory,[5] the more complex manzamine A (1) is truely a challenging target for total synthesis, and three groups have reported their own synthetic studies in this area. Brands and Pandit[6] described an approach to the central pyrroloisoquinoline framework of **1** *via* the intramolecular Diels-Alder reaction of the dihydropyrrole derivative. Another strategy for this substructure through a radical cyclization process has been announced by Hart and Mckinney.[7] On the other hand, Imbroisi and Simpkins[8] have recently reported a more general and versatile approach to the functionalized *cis*-hydroisoquinolines. Described herein is our own access to the pyrroloisoquinoline key intermediate for **1**, which is featured by the utilization of a ultra-high-pressure Diels-Alder reaction of 3-alkyl-5,6-dihydro-2-pyridinone.

We have been interested in developing an efficient route to the tricyclic intermediate (**2**)*via* the Diels-Alder reaction of 3-substituted dihydropyridinones either in an intramolecular (path A) or intermolecular (path B) fashion as breifly shown in **Scheme-1**. Our initial studies along path A revealed that N-alkyl protected (i.e. P_1=alkyl) dihydropyridinones were quite sluggish towards dienes even in an intramolecular case and electron-withdrawing character of N-protecting group was essential for the successful intermolecular cycloadditions.[1] Further insight into these thermal transformation led us to select the N-*p*-toluenesulfonyl (Ts) dihydropyridinones (eg. **3**) as a dienophile in view of the thermal stability of the Ts group. In the model study using a simple N-Ts-dihydropyridinone (**3**), it was found that under conventional thermal conditions, **3** reacted smoothly with the siloxy diene (**4**) to furnish, after acid treatment, the hydroisoquinolines (**5**, mp 175~178°C, AcOEt/n-hexane) in moderate yield (**Scheme-2**). The *cis*-ring fusion in **5** was unequivocally assigned based on NOE experiments which showed an enhancement (4.1%) of the signal corresponding to the angular H upon irradiation of the angular methyl group, in accord with the literature precedented.[7,8]



Scheme-1





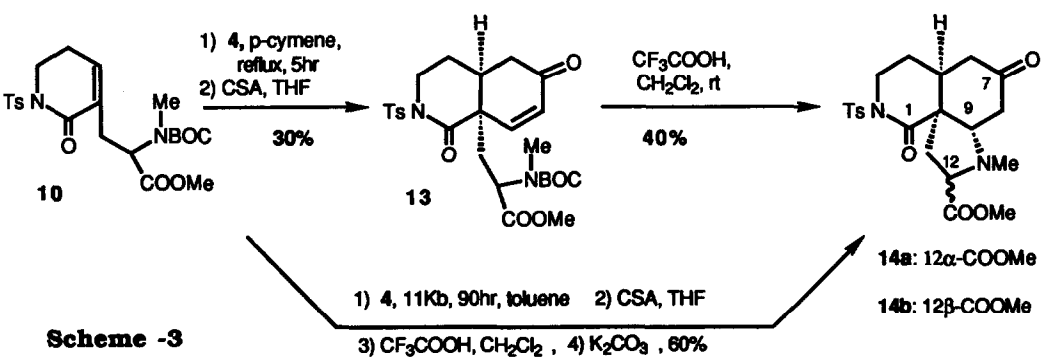
Scheme-2

With these results in mind, we next examined the Diels-Alder reaction of the two functionalized dihydropyridinones (**9** and **10**) bearing proper amino acid side chain at C-3 for further elaboration toward **2**. These dienophiles (**9** and **10**) were prepared from N-tosyl-2-piperidone (**6**) through the sequence as shown in **Scheme -2.** In contrast to the previous unsuccessful results with the N-*p*-nitrobenzoyl derivative,[1] the reaction of **9** with excess diene (**4**) (*p*-cymene, reflux 5hr) afforded, after acid treatment, the desired enone (**11**) in 26% yield along with the recovered **9** (60%). Attempted improvement in yield by carring out this reaction under the influence of various Lewis acids as well as ultrasound sonication gave unsatisfactory results. Toward the key intermediate (**2**), we next examined the deprotection of the carbamate group (NCOOMe) by the use of TMSI.[9] To our disappointment, however, the reaction of **11** with excess TMSI in $CHCl_3$ at reflux gave the unexpected cyclic carbamate (**12**)[10] in 57% yield instead of the pyrroloisoquinoline (**14**) .

We next turned our attention to the N_b-BOC derivative (**10**) because deprotection of N-BOC group could be achieved much more easily than the previous N-COOMe group. Thus, the same Diels-Alder reaction with N_b-BOC derivative (**10**) gave the corresponding enone (**13**) in a slightly better yield (~30%) but the purification of the product was proved to be quite difficult. To our delight, however, treatment of the crude **13** with CF_3COOH in CH_2Cl_2 at r.t. followed by quenching with aqueous K_2CO_3 furnished the desired tricyclic pyrroloisoquinoline (**14 a** and **14b**) in ~40% yield as a diastereomeric mixture.

To overcome the sluggishness of the dienophile (**10**) toward the fairly unstable diene (**4**), we finally tried a high-pressure Diels-Alder reaction.[11] Encouradged by the initial success that the reaction of **10** with excess **4** in toluene at 10 Kb for 20 hr at r.t. resulted in a cleaner reaction affording **13** (20%) and **10** (40%) , we have then conducted the same reaction at 11Kb for 90hr. After evaporation of the excess reagents, crude products were treated with CSA in THF at r.t. to give the enone (**13**) as a major product along with small amount of **10**. Crude **13** was then directly treated with CF_3COOH to furnish **14** (**14a**: **14b**=1:1) , after treatment of a base, in 60% overall yield from **10**. The structure of **14a** and **14b** were fully characterized by the spectroscopic means,[12] including H-H COSY, NOESY, and NOEDS experiments.[13]

Further elaborations toward more advanced intermediate for **1** are currently underway.



Scheme -3

Acknowledgements

The special thanks are due to Messers. H. Omori and A. Matsumoto in Instrumentation and Characterization Center, RIKEN for their technical assistance in high-pressure Diels-Alder reaction. Financial support by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture is gratefully acknowledged. We also thank Mrs. H. Seki, Miss R. Hara, and Mr. T. Kuramochi in the Analytical Center of Chiba University for spectral data.

References and Notes

1. Part I; M. Nakagawa, Z. Lai, Y. Torisawa, and T. Hino, submitted to *Heterocycles*.
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4. H. Nakamura, S. Deng, J. Kobayashi, Y. Ohizumi, Y. Tomotake, T. Matsuzaki, and Y. Hirata, *Tetrahedron Lett.*, **28**, 621 (1987).
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7. D. J. Hart and J. A. Mckinney, *Tetrahedron Lett.*, **30**, 2611 (1989).
10. Selected data for **12**; IR νmax (KBr): 2950, 1740, 1690, 1480, 1350, 1170cm^{-1}; ^{1}H-NMR (500MHz, $CDCl_3$) δ: 7.83 (d, 2H, J=8.5Hz), 7.30 (d, 2H, J=8.5Hz), 5.05 (t, 1H, J=8.0Hz), 4.17 (m, 1H), 3.37 (s, 3H, OMe), 2.55 (s, 3H, NMe), 2.43 (s, 3H, CH_3); HR-MS observed: 479.1489 (M^+) ; Calcd for $C_{22}H_{27}N_2O_8S$: 479.1481.
11. See for example: K. Matsumoto and A. Sera, *Synthesis*, **1985**, 999.
12. Selected data for **14**: **14a** Rf: 0.45 (2 developements with CH_2Cl_2/Et_2O=15/1); m.p. 185~187°C (CH_2Cl_2 / Et_2O); IR νmax (KBr): 1735, 1710, 1675, 1345, 1160cm^{-1}; ^{1}H-NMR (500MHz, $CDCl_3$) δ: 7.90 (d, 2H, J=8.5Hz), 7.32 (d, 2H, J=8.5Hz,), 4.09 (m,1H), 3.99 (t, 1H, J=3.5Hz, H-12), 3.89 (m, 1H,), 3.78 (dd, 1H, J=8.4 and 5.6Hz, H-9), 3.66 (s, 3H, OMe), 2.44 (s, 3H, CH_3), 2.30 (s, 3H, NMe); HR-MS observed: 434.1542(M^+); Calcd for $C_{21}H_{26}N_2O_6S$: 434.1505.
14b Rf: 0.40 (2 developements with CH_2Cl_2 / Et_2O=15/1); m.p. 212~214°C (CH_2Cl_2/ Et_2O); IR νmax (KBr): 1740, 1720, 1685, 1345, 1270, 1165 cm^{-1}; ^{1}H-NMR (500MHz, $CDCl_3$) δ: 7.88 (d, 2H, J=8.5Hz), 7.33 (d, 2H, J=8.5Hz), 4.09 (m, 1H), 3.89 (m, 1H), 3.70 (s, 3H, OMe), 3.32 (t, 1H, J=4.3Hz, H-12), 3.18 (dd, 1H, J=9.2 and 6.6 Hz, H-9), 2.44 (s, 3H, CH_3), 2.29 (s, 3H, N-Me); HR-MS observed: 434.1504 (M^+) ; Calcd for $C_{21}H_{26}N_2O_6S$: 434.1505.
13. The observed NOE between H(9) and N-Me as well as H(12) and N-Me in **14a** revealed a close (*cis*) relationship of H(9), N-Me, and H(12) in **14a** . On the other hand, no NOE between H(12) and N-Me and the presence of a NOE between H(9) and N-Me indicated the stereochemical relation in **14b** as shown.

(Received in Japan 4 April 1990)