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SYNTHETIC STUDIES ON MANZAMINE A I :
DIELS-ALDER REACTION OF 5,6-DIHYDRO-2-PYRIDINONE

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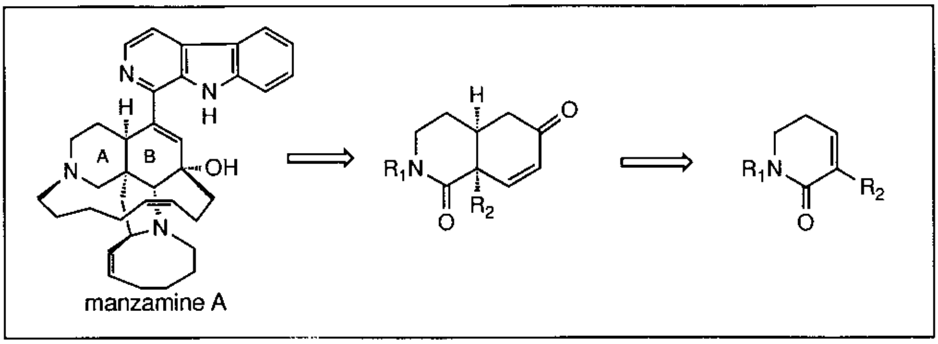
Abstract- Various hydroisoquinolines have been synthesized *via* the Diels-Alder reactions of 5,6-dihydro-2-pyridinones with Danishefsky diene.

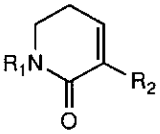
Diels-Alder reaction in synthetic organic chemistry can not be overemphasized and recent applications to the synthesis of natural products have received much attention.[1] As a program to the total synthesis of manzamine A, a novel β-carboline alkaloid isolated from the Okinawan marine sponge,[2] we have initiated a concise and stereoselective synthesis of hydroisoquinolines from 5,6-dihydro-2-pyridinone as a dienophile in the Diels-Alder reaction. Growing interests in the unique structure and antitumor activity of this compound have led to the extensive synthetic studies in this area.[3,4] We now wish to report the synthesis of functionalized hydroisoquinolines corresponding to the AB rings system of manzamine A by the Diels-Alder reaction of 5,6-dihydro-2-pyridinones as a dienophile with Danishefsky diene.

The dienophiles (**1**, **2**, and **3**) were prepared from the readily available 2-piperidone by the conventional sulfenylation and oxidative elimination sequences,[5,6] while **4** was accessible by the slight variant of the reported procedure.[7]

The first attempted Diels-Alder reaction of N-benzyl-dihydropyridinone (**1**) with the diene (**5** or **6**) failed to afford the expected adduct under the thermal or Lewis acid catalyzed conditions ($AlCl_3$, CH_2Cl_2). In order to provide a stronger electronic pertubation of the LUMO of the dienophile, 1-(*p*-nitrobenzoyl)-5,6-dihydro-2-pyridinone (**2**) was then subjected to the cycloaddition with **6** (xylene reflux, 18 h) to give the adduct (**7**). Treatment of the resulting crude **7** with KF in aqueous THF afforded the perhydroisoquinolinone (**8**) (54% from **2**). The structure of **8** was confirmed by the spectral data.[8]

On the other hand, when the 3-sulfinylpyridinone (**3**), in which the dienophile has been activated by the presence of the electron-withdrawing group at the 3-position,





1, R_1= PhCH$_2$(Bn), R_2= H

2, R_1= p-NO$_2$PhCO (p-NO$_2$Bz),
R_2=H

3, R_1=Bn, R_2 = PhSO

4, R_1= PhCO (Bz),
R_2 = ClCH$_2$CO

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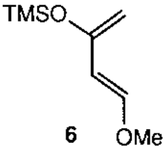

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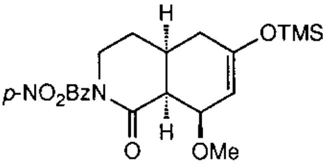

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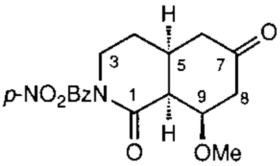

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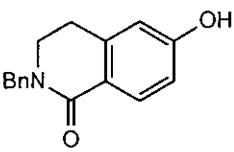

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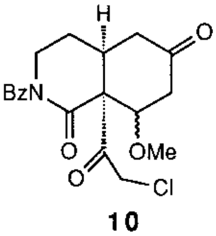

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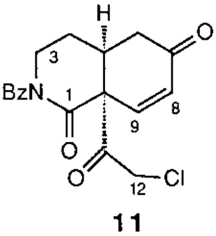

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was treated with **6** in refluxing *p*-cymene (2.5 h), the reaction proceeded more rapidly to give tetrahydroisoquinoline (**9**) (61%), after treatment with silica gel. The result may be visualized as involving the pyrolysis of the sulfinyl group of the primary adduct followed by elimination of methanol to afford the observed product. The most dramatic increase in reactivity came when electron-withdrawing groups were introduced both at the N and at the C-3 positions. Thus, in a similar way, the pyridinone (**4**) reacted with diene (**6**) at room temperature in CH_2Cl_2 (4 h, 33%) or refluxing benzene (1 h, 40%) to provide isoquinoline (**10**) as a 1:1 mixture of two diastereoisomers after treatment with oxalic acid.[9] In addition, treatment with KF instead of oxalic acid was accompanied by the elimination of MeOH to give **11**,[10] though chemical yield was lower (18%). When $Eu(FOD)_3$ was utilized as a catalyst, the reaction proceeded even at - 78°C (**10**, 20%).[11]

The observed *endo* selectivity in the reaction of **2** with **6** can be rationalized by the secondary orbital pertubation which lowers the energy of the *endo* reaction path, whereas the reaction of **4** with **6** gave a mixture of the *exo* and *endo* adducts.[12]

As a conclusion, 5,6-dihydro-2-pyridinone has shown to be a useful synthon for the synthesis of hydroisoquinoline derivatives that can be elaborated not only to manzamines but also to various isoquinoline alkaloids. Further extension of these reactions for the synthesis of manzamine A is currently under way.

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8. Physical data for **8**: mp 170.0-171.5°C; ir υ_{max}(KBr) 2950, 1700, 1690,1680, 1520 cm^{-1}; ^1H-nmr(500 MHz, $CDCl_3$) δ 1.91(1H, m, 4-H), 2.31(1H, m, 4-H), 2.50(1H, m, 8-H), 2.54(1H, m, 6-H), 2.67(1H, dd, J=15.4, 3.3 Hz, 6-H), 2.71(1H, m, 5-H), 2.94 (1H, m, 8-H), 3.01(1H, dd, J=7.1, 3.8 Hz, 10-H), 3.41(3H, s, OMe), 3.72(1H, m, 3-H), 4.00(1H, m, 3-H), 4.32(1H, m, 9-H), 7.71(2H, d, J=8.5 Hz, aromatic H), 8.24(2 H, d, J=8.3 Hz, aromatic H); ^{13}C-nmr(100 MHz, $CDCl_3$) δ 27.3, 33.8, 42.2, 44.0, 44.9, 47.4, 56.8, 81.5, 123.4, 128.4; m/z (%) 346 (16, M^+), 331(15, M^+-Me), 150(100); Anal. Calcd for $C_{17}H_{17}N_2O_6$: C, 58.95; H, 5.24; N, 8.09. Found: C, 58.94; H, 5.23; N, 7.94; The stereochemistry was established by NOESY on the fact that the nuclear Overhauser enhancement was only observed on 8-H when MeO was irradiated.
9. The ratio was determined from the ^1H-nmr spectrum in which 9-H signal assigned by COSY showed two triplet signals with same intensity at 4.38 and 4.37 ppm.
10. Physical data for **11**: Ir υ_{max}(KBr) 2950, 1700, 1660, 1640 cm^{-1}; ^1H-nmr (500 MHz, $CDCl_3$) δ 1.95(1H, m, 4-H), 2.33(1H, m, 4-H), 2.71(1H, m, 6-H), 2.86(1H, m, 6-H), 3.15(1H, m, 5-H), 3.56(1H, m, 3-H), 4.25(1H, m, 3-H), 4.74(1H, d, J=17.5 Hz, 12-H), 4.63(1H, d, J=17.5 Hz, 12-H), 7.39-7.55(7H, m, 8,9, and aromatic H).
11. The yield of **10** was not satisfactory probably due to the instability of **6** towards Lewis acids.
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