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Stereoselective Intramolecular Enone-Olefin Photocycloadditions of 1,7-Dienes: Model Studies on the Synthesis of Lycopodium Alkaloids

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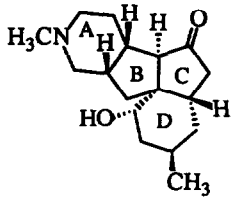
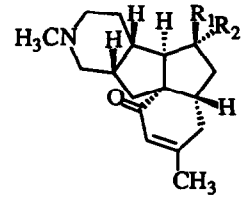
Key Words: Stereoselective photocycloadditions, lycopodium alkaloids, homoenolate.

Abstract: *The synthesis and stereoselective intramolecular [2+2] photocycloaddition reactions of enones 4a and 4s has been accomplished, yielding possible precursors for the development of a total synthesis of several lycopodium alkaloids.*

Paniculatine **1**, magnellanine **2**, and magnellaninone **3** are three structurally similar tetracyclic alkaloids isolated and characterized by Castillo in 1976.[2] Despite their unusual and interesting structures, there has been a paucity of effort directed toward the synthesis of this class of alkaloids.[3] We report here our studies on the synthesis and characterization of two tricyclic intermediates which could serve as models for further development of a synthetic approach to several of these alkaloids.



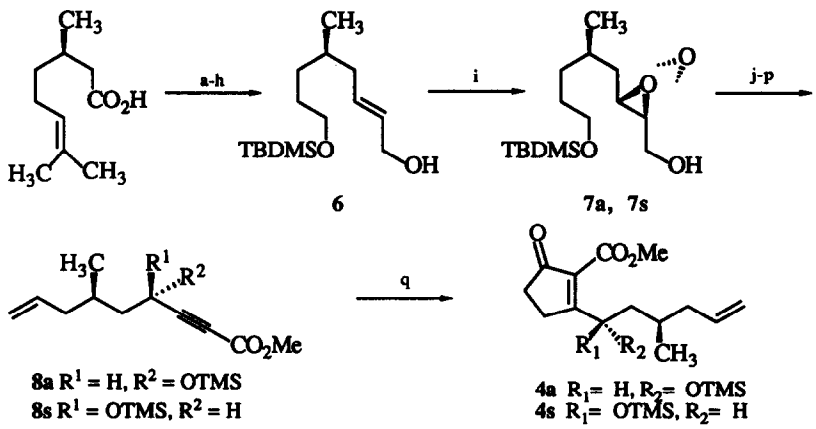
Paniculatine, **1**



Magnellanine: R_1= OH, R_2= H, **2**
Magnellaninone: R_1, R_2= O, **3**

Since several scenarios are available for the use of a paniculatine precursor for the preparation of magnellanine and magnellaninone, the initial strategy for entry into the BCD rings of these alkaloids was centered around an intramolecular [2+2] photocycloaddition[4] reaction of enone olefin **4a**. (Scheme 1). It was necessary to develop a preparation of **4a** (and eventually **4s**) that would allow control of the relative and preferably the absolute stereochemistry of the hydroxyl and methyl groups on the four carbon tether. The preparation of **4a** is shown in Scheme 1.[5] Allylic alcohol **6** can be prepared in multigram quantities from the readily available (R)-(+)-methyl citronellate using the seven step procedure shown. Epoxides **7a** or **7s** can then be synthesized using the Sharpless asymmetric epoxidation.[6] This epoxidation allows control of the diastereomeric relationship needed for the successful synthesis of either the syn or the anti photosubstrates **4a** or **4s**. Acetylenic esters **8** can then be obtained from epoxide **7** as illustrated in Scheme 1.[7] The synthesis of photosubstrates **4a** and **4s** is then completed by taking advantage of the zinc homoenolate addition-cyclization reaction developed previously in our laboratory.[8] This synthetic sequence allowed for the production of gram quantities of diastereomerically pure photosubstrates for further investigations.

Irradiation of enone **4a** in hexanes at >350 nm followed by hydrolysis of the silyl ether resulted in a 8.2:1.2:1 mixture of photoadducts (Scheme 2). The stereochemistry of the major photoadduct **9a** (68% overall isolated yield from **4a**) was initially assigned based on difference NOE data shown in the bottom of Scheme 2. An 8% NOE between protons H_2 and H_3 and an 8% NOE between protons H_4 and H_5 coupled with the compounds failure to lactonize under the appropriate conditions led to the assigned structure. This structural assignment was confirmed by a single crystal *x*-ray structure of the triol **10a** which was obtained by $LiAlH_4$ reduction of **9a** (Scheme 2).



Scheme 1

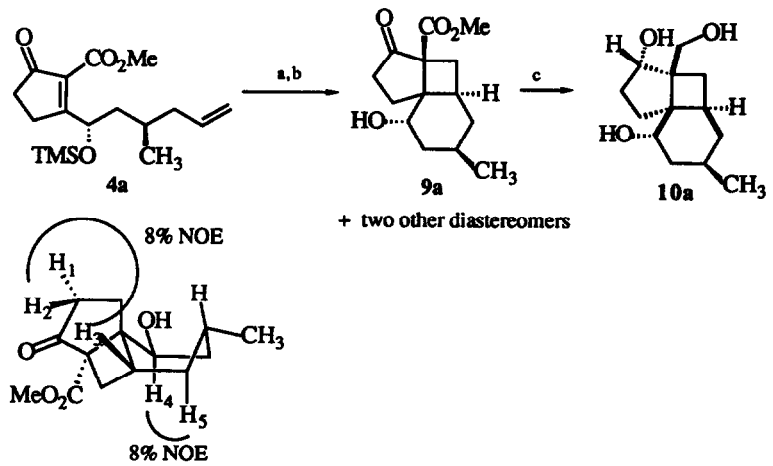
(a) MeOH, HCl, reflux. (b) O_3, CH_2Cl_2, -78°C, then Me_2S. (c) $NaBH_4$, MeOH, 0°C. (d) TBDMSCl, imidazole, DMAP, CH_2Cl_2. (e) LAH, Et_2O, 0°C. (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2. (g) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2. (h) DIBAL-H, THF, -78°C, 30% 8 steps. (i) $Ti[OCH(CH_3)_2]_4$, (+) or (-)-$[CH(OH)CO_2Et]_2$, *t*-BuOOH, CH_2Cl_2, 4Å sieves, -20°C, 87%. (j) CCl_4, Ph_3P, reflux, 90%. (k) TBAF, THF, 100%. (l) Bu_3P, o-$NO_2C_6H_4SeCN$, CH_2Cl_2, 90%. (m) H_2O_2, CH_2Cl_2, 79%. (n) LDA, THF, -78°C. (o) TMSCl, Et_3N, DMAP, CH_2Cl_2, 87% 2 steps. (p) *n*-BuLi, $ClCO_2Me$, THF, -40°C, 85%. (q) $ZnCl_2$, [(1-ethoxycyclopropyl)oxy]-trimethyl silane, Et_2O, sonication, then CuBr-Me_2S, HMPA, THF, 0°C-20°C, 69%.

Irradiation of the syn diastereomer **4s** at >350nm in hexanes yielded 66% of a 93:7 mixture of photoadducts consisting mainly of **9s** (Scheme 3). Isolation and deprotection of **9s** resulted in 43% overall yield of compound **10s**. The stereochemistry of **10s** was assigned using difference NOE data (Scheme 3). A 12% NOE between H_4 and H_5 and no NOE between H_2 and H_3 along with the fact that **10s** does not lactonize under appropriate conditions led to the assigned structure. The lack of an NOE between H_2 and H_3 for **10s** coupled with the significant NOE between H_2 and H_3 in **9a** indicates a trans 6-4 ring fusion for **10s**.[9]

The intramolecular [2+2] photocycloaddition reaction of **4a** and **4s** to our knowledge are the first examples demonstrating significant asymmetric induction directed by a stereogenic center on a four carbon tether.[10] The excellent diastereoselectivity observed in these reactions can be rationalized by the transition states **11a** and **11s** proposed in Scheme 4. There are 16 distinct conformations (8 chair and 8 boat) through which each of the photosubstrates can react. The anti photosubstrate reacts predominantly through a boat conformation placing the protected hydroxyl and methyl groups in the energetically more favorable equatorial positions of the forming six-membered ring. In contrast the syn photosubstrate reacts through a chair conformation again allowing the protected hydroxyl and methyl groups to occupy equatorial positions on the six-membered ring.

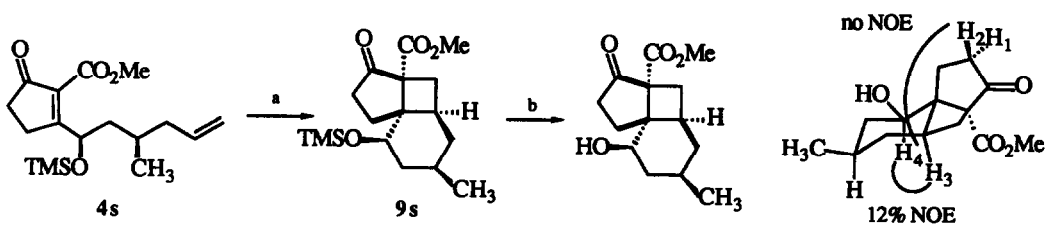
The stabilities of these two conformations relative to the other possible conformations is supported by molecular mechanics calculations. Deprotection of the hydroxyl group prior to the photoreaction has no effect on the selectivity of these reactions. The reversal of the ring juncture stereochemistry based on the stereochemistry of the tether is worthy of note. In both major photoadducts the methyl group is trans to the ring juncture methine proton.

Current efforts are directed toward applying this strategy to the asymmetric total synthesis of magnellanine and magnellaninone through the photocycloaddition of intermediates similar to **4a**. It is important to note that the relative stereochemistry of the methyl group and the cyclobutyl methine proton (H_3, Scheme 2) in photoadduct **9a** is opposite of that required for developing a total synthesis of the more stereochemically challenging paniculatine. The trans 6-4 ring fusion present in photoadduct **10s** (Scheme 3) also renders this system inadequate for a strategy toward paniculatine. Strategies to influence these stereochemical trends in the photocycloaddition reaction are currently being studied.



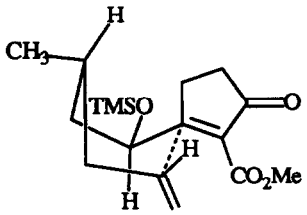
Scheme 2

(a) >350nm *hv*, hexanes. (b) PTSA, THF, H_2O, 68%. (c) LAH, Et_2O, 0°C, 80%.

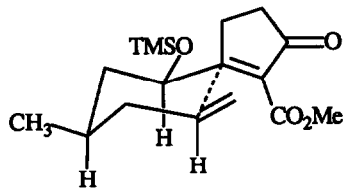


Scheme 3

(a) >350nm *hv*, hexanes, 66%. (b) PTSA, THF, H_2O, 76%.



11a



11s

Scheme 4

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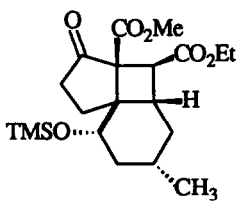
References and Notes

1. Department of Education Fellow, 1991-93.
2. (a) Castillo, M.; Loyola, L.A.; Morales, G. *Can. J. Chem.* **1976**, 2893-2899. (b) Castillo, M.; Morales, G.; Loyola, L.A. *Ibid* **1976**, 2900-2908. (c) Loyola, L.A.; Morales, G.; Castillo, M. *Phytochemistry* **1979**, *18*, 1721.
3. (a) Hirst, G.C.; Howard, P.N.; Overman, L.E. *J. Am. Chem. Soc.* **1989**, *111*, 1514-1515. (b) Mehta, G.; Reddy, M.S. *Tetrahedron Lett.* **1990**, *31*, 2039-2042. (c) St. Laurent, D.R.; Paquette, L.A. *J. Org. Chem.* **1986**, *51*, 3861-3864.
4. For recent reviews see Crimmins,M.T.; Reinhold, T.L. *Org. Reactions*, in press. Crimmins, M.T. *Chem. Reviews*, **1988**, *88*, 1453 and references therein.
5. All new compounds gave consistent ^{1}H and ^{13}C and IR spectra as well as satisfactory C,H combustion analyses or HRMS. All yields are for chromatographically pure material accept where indicated.
6. (a) Sharpless, K.B.; Katsuki, T. *J. Am. Chem. Soc.* **1980**, *102*, 5976. (b) Sharpless, K.B.; Gao, Y.; Hanson, R.M.; Klunden, J.M.; Ko, S.Y.; Masamune, H. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
7. Yadav, J.S.; Deshpande, P.K.; Sharma, G.V.M. *Tetrahedron* **1990**, *46*, 7033-7046.
8. Crimmins, M.T.; Nantermet, P.G. *J. Org. Chem.* **1990**, *55*, 4235-4237.
9. This structural assignment is further supported by a single crystal *x*-ray of the derivative below which is the major photoadduct from irradiation of the corresponding enone-olefin.



10. There have been two similar examples reported using four atom tethers, the first contained in a vinylogous amide and the second in an enone acetal. See: (a) Winkler, J.D.; Hershberger, P. M.; Springer, J.P. *Tetrahedron Lett.* **1986**, *27*, 5177-5180. (b) Pirrung, M.C.; Thomson, S.A. *Tetrahedron Lett.* **1986**, *27*, 2703-2706. Diastereoselectivity was reported only in the case of the vinylogous amide photoreaction (see 10a).

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