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# Vinyl Imidates in Cycloaddition Reactions: A Formal Synthesis of (±)-Reserpine

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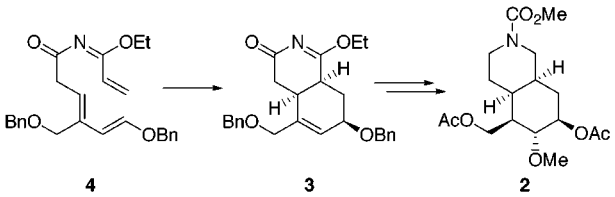
## ABSTRACT

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**The intramolecular Diels–Alder reaction of *N*-acylvinylimidates provides an efficient entry into *cis*-fused perhydroisoquinoline ring systems. This is demonstrated by the preparation of isoquinoline 2, an intermediate, which has been previously transformed to reserpine.**

The yohimbine alkaloids have attracted attention from chemists for both their medicinal properties and intriguing molecular structures.[1] Reserpine (**1**), the most complex member of the yohimbine family, contains five contiguous asymmetric centers embedded in a *cis*-fused perhydroisoquinoline ring system. The challenges associated with the construction of the stereochemically complex isoquinoline ring system present in reserpine have stimulated the development of a number of synthetic approaches which have culminated in both total and formal syntheses of reserpine.[2] In this manner, reserpine has served as a testing ground to evaluate the utility of synthetic methodology.

Our laboratory has been involved in the utilization of intramolecular Diels−Alder reactions for the preparation of perhydroisoquinoline ring systems. Employing vinyl imidates as the $2\pi$ electron component in intramolecular Diels−Alder reactions allows for the synthesis of isoquinoline ring systems with considerable potential for stereochemical control.[3] As a demonstration of this potential, we report the application of the intramolecular Diels−Alder reaction of *N*-3,5-hexadienoyl ethyl acrylimidates to the synthesis of perhydroisoquinoline **2**. This intermediate contains five of the six asymmetric centers in reserpine and constitutes its formal synthesis (Scheme 1).[4] Compound **2** was envisioned to result from elaboration of *N*-acylimidate **3**, which in turn arises from intramolecular cyclization of *N*-acylvinylimidate **4**. In this approach, all E-ring functionality is confined to the diene fragment **5**, which upon

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(2) For recent reviews, see: (a) Baxter, E. W.; Mariano, P. S. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Springer-Verlag: New York, 1992; Vol 8, pp 197−319. (b) Szántay, C.; Honty, K. In *Monoterpenoid Indole Alkaloids*; Saxton, J. E., Ed.; John Wiley & Sons: Chinchester, 1994; Chapter 4, pp 161−216. (c) Hanessian, S.; Pan, J.; Carnell, A.; Bouchard, H.; Lesage, L. *J. Org. Chem.* **1997**, *62*, 465.

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(4) (a) Wender, P. A.; Schaus, J. M.; White, A. W. *J. Am. Chem. Soc.* **1980**, *102*, 6157. (b) Wender, P. A.; Schaus, J. M.; White, A. W. *Heterocycles* **1987**, *25*, 263.

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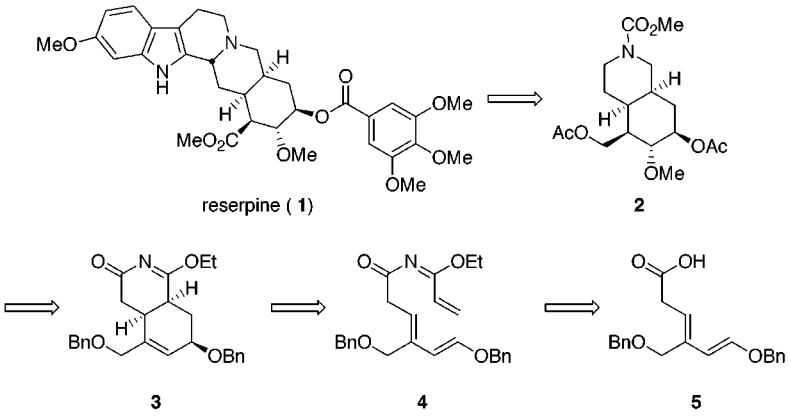
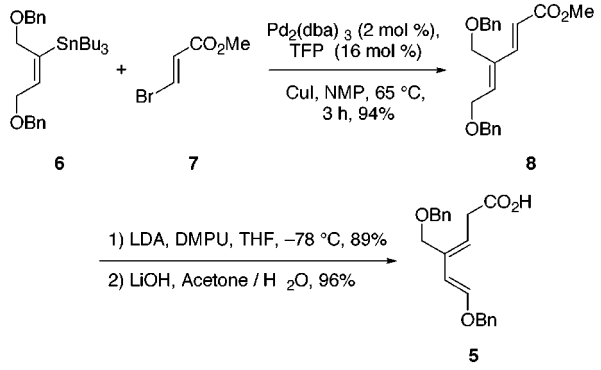
**Scheme 1.** Retrosynthetic Analysis Employing the Intramolecular Diels−Alder Reaction of *N*-3,5-Hexadienoyl Ethyl Acrylimidates




cyclization in the tether *endo* mode establishes three of the five asymmetric centers.

This approach was reduced to practice in the following manner (Scheme 2). Diene **5** was prepared starting with the

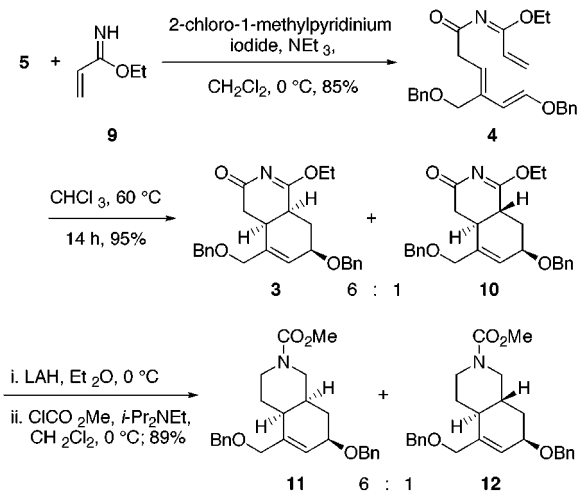
**Scheme 2**




Stille coupling[5] of vinylstannane **6**[6] with methyl (3*E*)-bromopropenoate (**7**)[7] in the presence of $Pd_2(dba)_3$ (2 mol %), tri-2-furylphosphine (TFP, 16 mol %), and copper(I) iodide in *N*-methylpyrrolidine to afford diene **8** in high yield. Kinetic deconjugation of 2,4-hexadienoic acid ester derivative **8** with LDA (1.2 equiv)/ DMPU/THF at −78 °C followed by an acidic quench (10% HCl, −78 °C) afforded a single product in 89% isolated yield.[8] Both $^1$H NMR and subsequent chemical studies established that the reaction gave exclusively the 3*E*,5*E* dienoic acid ester. Saponification provided diene **5** in high yield.

The Diels−Alder precursor was prepared by the coupling of diene **5** with 1-aza-2-ethoxy-1,3-butadiene (**9**)[3b] mediated by 2-chloro-1-methylpyridinium iodide[9] to afford *N*-acylvinylimidate **4** (85% isolated yield, Scheme 3).[10] Cycloaddition

**Scheme 3**




($CHCl_3$, 60 °C, 14 h) resulted in formation of two cycloadducts in a 6:1 ratio (95% yield).[11] The major cycloadduct, **3**, was assigned the *cis*-ring fusion on the basis of $^1$H NMR ($J_{H4a-H8a}$ = 5.5 Hz), corresponding to a tether-*endo* cycloaddition. The cycloaddition step sets three of the five stereocenters required for the preparation of the DE isoquinoline ring system in reserpine. *N*-Acylimidate reduction with lithium aluminum hydride was followed by treatment with methyl chloroformate to provide carbamates **11** and **12** (89% yield, two steps), which were chromatographically separated to afford *cis*-fused isoquinoline **11**.

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(6) Paterson, I.; Feβner, K.; Finlay, M. R. V.; Jacobs, M. F. *Tetrahedron Lett.* **1996**, *37*, 8803.
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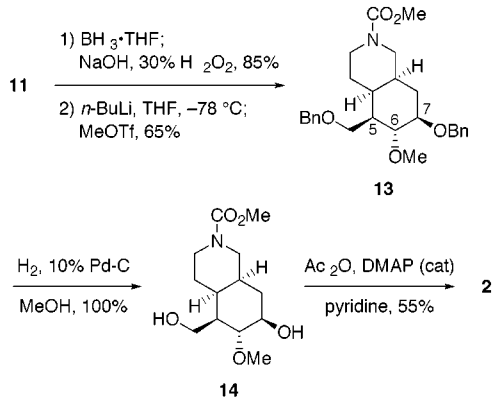
(9) Bald, E.; Saigo, Z.; Mukaiyama, T. *Chem. Lett.* **1975**, 1163.
(10) Under the coupling conditions, a minor amount (>5%) of cycloadduct was observed. The origin of cycloadduct may result from an intermediate *N*-acyliminium ion produced from the coupling reaction. This raises the possibility of protonic or Lewis acid catalysis of the cycloaddition step. This chemistry is currently being pursued.
(11) Cycloaddition in refluxing benzene provided a lower *endo*/*exo* ratio (4:1).

Completion of the DE isoquinoline ring system entailed installation of the C6 methyl ether and transposition of the benzyl groups for acetates (Scheme 4). This was accomplished by hydroboration of olefin **11** with $BH_3$·THF followed by oxidation (3 M NaOH, 30% $H_2O_2$) to afford a single alcohol (80%). The stereochemistry of the newly formed alcohol (C6) was secured by $^1$H NMR ($J_{H5-H6}$ = 9.7 Hz, $J_{H6-H7}$ = 9.7 Hz, see **13**). Methyl ether formation required forcing conditions[12] (*n*-BuLi/THF/−78 °C; MeOTf, 65%) due to steric hindrance about the secondary alcohol.

**Scheme 4**




Catalytic hydrogenolysis of the benzyl ethers ($H_2$, 10% Pd−C, 100%) proceeded smoothly to afford diol **14**. The stereochemistry of diol **14** was confirmed by spectroscopic comparison with an authentic sample derived from (−)-reserpine.[4] Completion of the formal synthesis was accomplished by acetylation ($Ac_2O$, DMAP, pyr, 55%) to furnish hydroisoquinoline **2**.

In summary, the synthesis of perhydroisoquinoline **2**, an intermediate previously transformed to reserpine (**1**), has been accomplished by employing the intramolecular Diels−Alder cycloaddition of *N*-3,5-hexadienoyl ethyl acrylimidate **4**. This approach demonstrates the utility of vinyl imidates in intramolecular cycloadditions for preparing stereochemically complex isoquinoline ring systems.

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**Supporting Information Available:** Experimental procedures and characterization data for compounds **2** and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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