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**AN APPROACH TO CYCLIC α -AMINO ACIDS BY A NOVEL HETERO
DIELS-ALDER/INTRAMOLECULAR HYDANTOIN ENOLATE
ALKYLATION STRATEGY: AN APPROACH TO HALICHLORINE**

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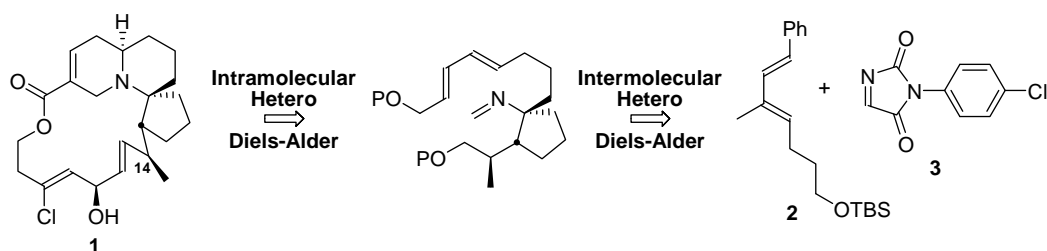
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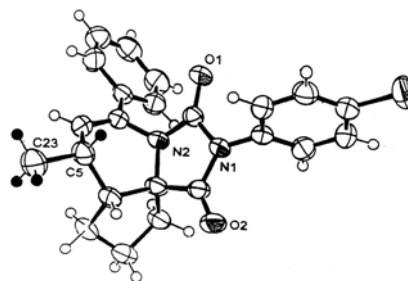
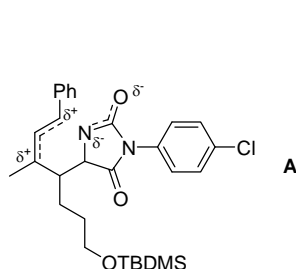
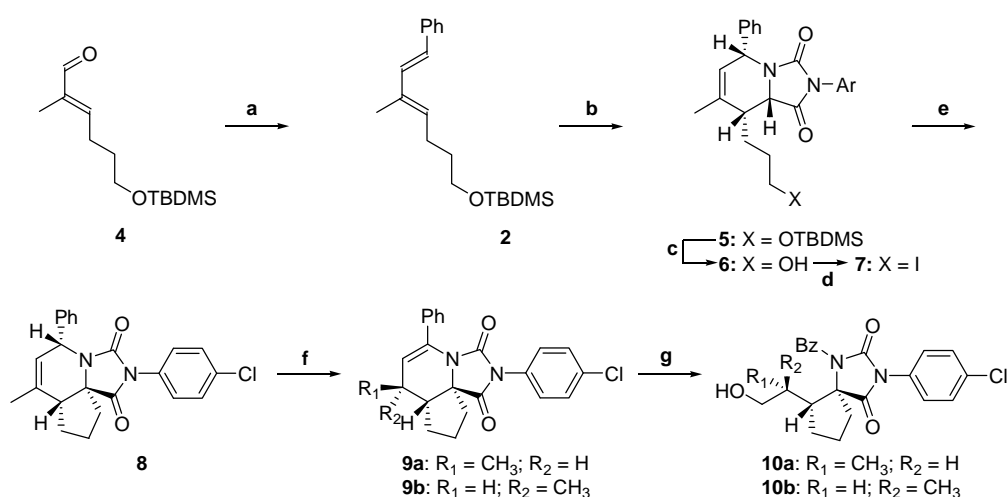
Abstract – An efficient, novel synthetic strategy has been developed for preparation of cyclic α -amino acid employing an intermolecular hetero Diels-Alder reaction and an intramolecular hydantoin enolate alkylation as key steps. Application of the present hetero Diels-Alder/intramolecular hydantoin alkylation methodology to synthesis of halichlorine was explored.

Halichlorine (**1**) was isolated by Uemura and co-workers from the Japanese sponge *Halichondria okadai* Kadota and shown to selectively inhibit the induction of vascular cell adhesion molecule-1 (VCAM-1).¹ Owing to its unique molecular architecture and potent biological activity, the marine natural product has attracted considerable attention from synthetic chemists, culminating in the first total synthesis by the Danishefsky group.² Intrigued by the notion that the azatricyclic core present in halichlorine might be constructed by a sequential inter- and intramolecular hetero Diels-Alder strategy as shown in Scheme 1, synthesis of this marine natural product was undertaken. In this communication we report an efficient synthetic strategy for construction of cyclic α,α -disubstituted α -amino acid derivatives³ such as spirobicycle (**10b**) based upon a highly regioselective hetero Diels-Alder reaction⁴ and an intramolecular hydantoin enolate alkylation as summarized in Scheme 2.

Scheme 1. Retrosynthetic Plan



To commence the synthesis, the requisite trisubstituted diene (**2**) was prepared as a 4:1 mixture of (*E*)- and (*Z*)-isomers in 88% yield from known (*E*)-enal (**4**)⁵ by treatment with benzyltriphenylphosphonium bromide⁶ and *t*-BuOK in THF, setting the stage for the crucial intermolecular hetero Diels-Alder cycloaddition.

Scheme 2. Synthesis of Spirobicyclic (**10b**)^aX-ray structure of **9b**

^aReagent and Conditions: a) Ph₃PCH₂PhBr, *t*-BuOK, THF, -5 °C to rt, 2 h, 88% (*E*:*Z* = 4/1); b) 3-(4-chlorophenyl)-5-methoxyhydantoin, xylene, reflux, 8 h, 96%; c) AcOH/THF/H₂O (3:1:1), rt, 3 d, 98%; d) I₂, imidazole, Ph₃P, Et₂O/CH₃CN (3:1), 0 °C to rt, 10 min, 95%; e) LiHMDS (2 eq), THF, -78 °C, 20 min, 95%; f) DBU, xylene, 140 °C, 2.5 h, 95% (**8**/**9b** = 3.5:1); g) O₃, EtOAc, -78 °C, 30 min, then Ph₃P, rt, overnight; h) NaBH₄, MeOH, -40 °C, 2 h, 88% (for 2 steps).

To our satisfaction, intermolecular hetero Diels-Alder reaction of diene (**2**) with known heterodienophile (**3**), generated *in situ* from 3-(4-chlorophenyl)-5-methoxyhydantoin,⁷ in refluxing xylene for 8 h furnished the desired Diels-Alder adduct (**5**) as a single diastereomer in excellent yield (96%), presumably through dipolar and nonsynchronous transition state A for the [4+2] cycloaddition reaction.⁸ It should be noted that the phenyl group in the diene moiety was chosen to both control the regioselectivity of the hetero Diels-Alder reaction and for subsequent isomerization of the cyclohexene double bond in tricycle (**8**) (*vide infra*).

With key hetero Diels-Alder adduct (**5**) secured, we then addressed the key intramolecular hydantoin enolate alkylation for stereoselective annulation of the cyclopentane moiety. Towards this end, intramolecular amide enolate alkylation substrate (**7**) was prepared from hetero Diels-Alder adduct (**5**) by desilylation under the conditions of Corey⁹ and iodination of the resulting primary alcohol (**6**) with I₂, imidazole, and Ph₃P in Et₂O/acetonitrile (3/1)¹⁰ in 93% overall yield for the 2 steps. We were pleased to find that treatment of iodide (**7**) with LiHMDS in THF at -78 °C for 20 min led to the desired *cis*-fused tricyclic hydantoin (**8**) in excellent yield (95%). Internal alkylation of the corresponding bromide with LiHMDS led to the formation of an *O*-alkylation product.

With the desired tricyclic hydantoin (**8**) in hand, we envisioned that isomerization of the cyclohexene double bond in (**8**) in conjugation with the strategically placed phenyl group would provide the desired conjugated olefin (**9a**) with the correct stereochemistry at C(14). Contrary to our expectation, treatment of internal alkylation product (**8**) with DBU in xylene at 140 °C furnished a 3.5 : 1 equilibrium mixture of starting tricycle (**8**) and conjugated olefin (**9b**), whose configuration at C(14) is opposite to that of halichlorine, in 95% total yield. The structure of tricycle (**9b**) was firmly established by X-ray crystallography. Finally, olefin (**9b**) was converted into spirobicycle (**10b**) by a reductive ozonolysis.¹¹

In conclusion, cyclic α -amino acid derivative (**10b**) was synthesized in a highly stereoselective fashion employing an intermolecular hetero Diels-Alder reaction and intramolecular hydantoin enolate alkylation as key steps. The present hetero Diels-Alder/intramolecular hydantoin alkylation methodology provides an alternative synthetic method for spirocyclic α -amino acids.

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Dedicated to Professor Steven M. Weinreb on the occasion of his 65th birthday.

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