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A Novel Synthesis of (−)-Huperzine A via Tandem Intramolecular Aza-Prins Cyclization−Cyclobutane Fragmentation

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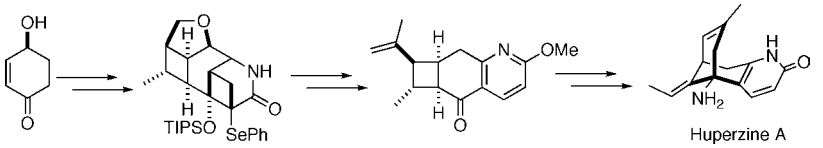
ABSTRACT



The acetylcholinesterase inhibitor (−)-huperzine A was synthesized from (*S*)-4-hydroxycyclohex-2-enone in 17 steps by a route that involved two cyclobutane fragmentations. The first of these employed a retro-aldol cleavage to generate the α-pyridone ring of huperzine A, and the second invoked a novel intramolecular aza-Prins reaction in tandem with stereocontrolled scission of a cyclobutylcarbinyl cation to create the aminobicyclo[3.3.1]nonene framework of the natural alkaloid.

Release of the 26−28 kcal/mol of ring strain in cyclobutanes through fragmentation is a well-known strategem for constructing new cyclic and acyclic systems.[1] The principle has been applied in natural product synthesis[2] where it is often the pivotal transformation,[3] but cyclobutane fragmentation in tandem with a second process that initiates ring cleavage is rare.[4]

We were intrigued by the possibility of choreographing fragmentation of a cyclobutylcarbinyl cation with an intramolecular acid-catalyzed aza-Prins reaction[5] in a cascade process that would lead to the aminobicyclo [3.3.1]nonene skeleton of the nootropic agent huperzine A (**1**).[6] The concept is diagrammed in Scheme 1 where C−C bond formation is initiated by attack of the endo isopropenyl group of **2** on an acyliminium ion to generate transiently a cyclobutylcarbinyl cation. Of the two cyclobutane bonds, *a* and *b*, susceptible to cleavage in **2**, the orbital alignment of external σ-bond *a* with the developing carbocation favors this mode of ring scission. The process is terminated by the stereoelectronically favored removal of a proton from the bicyclic ring fusion to form the exo ethylidene unit of **1**. We now report implementation of this concept in a synthesis of natural (−)-huperzine A (**1**).[7]

The starting point for our route to (−)-**1** was (*S*)-(−)-4-hydroxycyclohex-2-enone (**4**), obtained from (−)-quinic

(1) The concept of ring strain release as a synthetic tool has its roots in some of the earliest work in the synthesis literature; for example, see: Doering, W. von E.; Knox, L. H. *J. Am. Chem. Soc.* **1953**, *75*, 297.

(2) White, J. D.; Lee, N. C. Applications of Ring Strain in Natural Product Synthesis. In *Advances in Strain in Organic Chemistry*; Halton, B., Ed.; Jai Press: Hampton Hill, U.K., 1997; Vol. 6, pp 1−34.

(3) (a) White, J. D.; Dillon, M. P.; Butlin, R. J. *J. Am. Chem. Soc.* **1992**, *114*, 9673. (b) White, J. D.; Kim, J.; Drapela, N. E. *J. Am. Chem. Soc.* **2000**, *122*, 8665.

(4) Fragmentation/rearrangement of cyclobutane spiroepoxides is one of the few examples. See: (a) Tobe, Y.; Yamashita, S.; Kakiuchi, K.; Odaira, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 1259. (b) Pirrung, M. C.; Thomson, S. A. *J. Org. Chem.* **1988**, *53*, 227.

(5) Dobbs, A. P.; Guesne, S. J. J.; Parker, R. J.; Skidmore, J.; Stephenson, R. A.; Hursthouse, M. B. *Org. Biomol. Chem.* **2010**, *8*, 1064.

(6) The *Lycopodium* alkaloid huperzine A was first isolated by Wiesner (Yoshimura, H.; Valenta, Z.; Wiesner, K. *Tetrahedron Lett.* **1960**, *12*, 14) who misassigned its structure. Subsequent comparison of huperzine A with the known alkaloid selagine showed that they were identical and led to the correct assignment **1** (Ayer, W. A.; Browne, L. M.; Orszanska, H.; Valenta, Z.; Liu, J. S. *Can. J. Chem.* **1989**, *67*, 1538). For an early account of the history, chemistry, and pharmacology of huperzine A, see: Kozikowski, A. P.; Tuckmantel, W. *Acc. Chem. Res.* **1999**, *32*, 641 and references cited.

(7) Two main lines of attack on the synthesis of huperzine A, both pioneered by Kozikowski and co-workers, have been developed and have been extended subsequently by others. One approach builds the bicyclo[3.3.1]nonene skeleton of **1** using a tandem Michael-aldol sequence; the other route employs a palladium-catalyzed annulation as the key step. For a recent summary of previous work in the field and the current state of play in huperzine A synthesis, see: (a) Koshiba, T.; Yokoshima, S.; Fukuyama, T. *Org. Lett.* **2009**, *11*, 5354. (b) Ding, R.; Sun, B.-F.; Lin, G.-Q. *Org. Lett.* **2012**, *14*, 4446.

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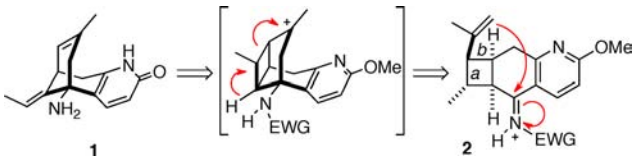
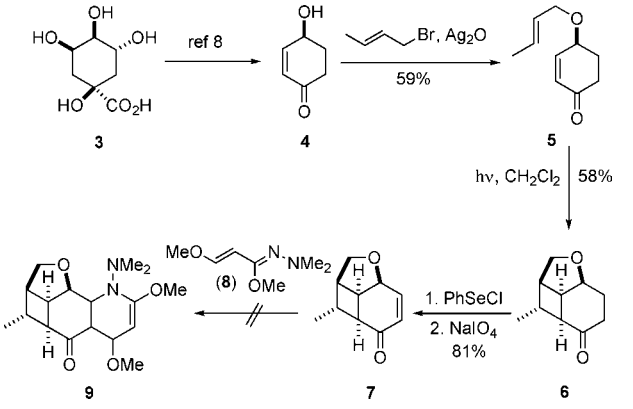
Scheme 1. Proposed Route to (−)-Huperzine A (**1**) via Intramolecular Aza-Prins Cyclization and Cyclobutane Fragmentation



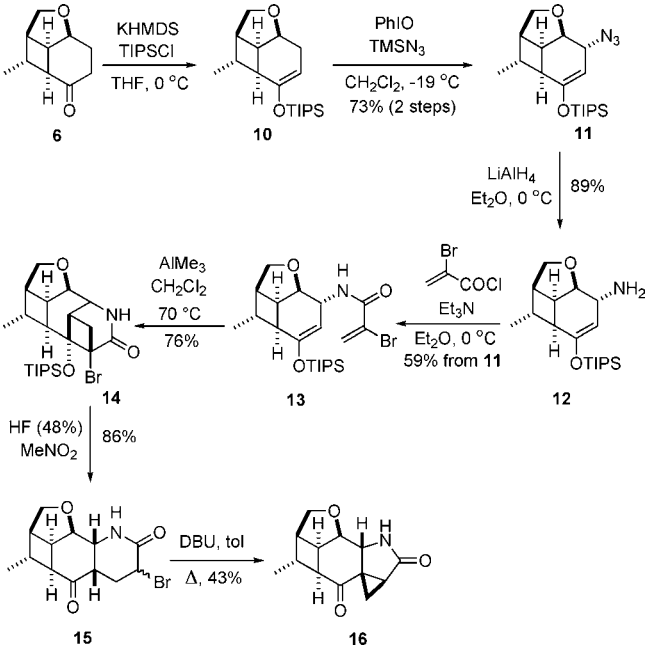
acid (**3**) by the method of Danishefsky.[8] Etherification of **4** with *trans*-crotyl bromide in the presence of silver(I) oxide[9] gave diene **5** which was irradiated in dichloromethane at 0 °C through Pyrex glass (Scheme 2). The resultant [2 + 2] photoadduct **6** was converted to enone **7** with the intention of using this dienophile in a Diels–Alder cycloaddition with azadiene **8**[10] to fabricate the α-pyridone ring of **1**, but this reaction failed to produce more than trace amounts of fused tetrahydropyridine **9**. Consequently, a revised plan was conceived for building a fused α-pyridone from **6** which first introduced a primary amine into the six-membered ring and then assembled the heterocycle in a stepwise sequence patterned after work by Magnus.[11]

Scheme 2. Synthesis of Tricyclic Ketone **6** from D-(−)-Quinic Acid (**3**)



The revised route began with exposure of ketone **6** to triisopropylsilyl chloride in the presence of a strong base to furnish silyl enol ether **10**, and this was reacted with iodosobenzene and trimethylsilyl azide to give azide **11** as a single epimer (Scheme 3).[12] The latter was reduced to amine **12** which was acylated with α-bromoacryloyl chloride to give amide **13**. Treatment of **13** with trimethylaluminum in

Scheme 3. Attempted Synthesis of the Fused α-Pyridone of Huperzine A from Tricyclic Ketone **6**



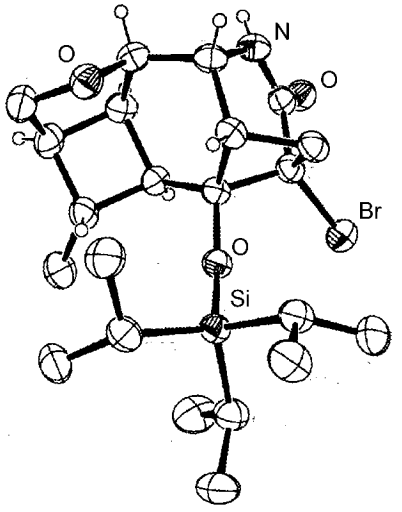


Figure 1. ORTEP representation of the X-ray crystal structure of **14**.

dichloroethane at 70 °C cleanly produced [2 + 2] cycloadduct **14** whose structure was secured by X-ray crystallographic analysis (Figure 1). Exposure of **14** to aqueous HF in nitromethane caused silyl ether cleavage[13] and subsequent retro-aldol fragmentation to give α-bromo lactam **15** as a 3:1 mixture of stereoisomers. Our expectation was that the pyridine ring of **2** could be fashioned from **15** by

(8) Audia, J. E.; Boisvert, L.; Patten, A. D.; Villalobos, A.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 3738.

(9) Martin, S. F.; Rueger, H.; Williamson, S. A.; Grzejszczak, S. *J. Am. Chem. Soc.* **1987**, *109*, 6124.

(10) (a) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869. (b) Serckx-Poncin, B.; Hesbain-Frisque, A.-M.; Ghosez, L. *Tetrahedron Lett.* **1982**, *23*, 3261.

(11) Magnus, P.; Rigollier, P.; Lacour, J.; Tobler, H. *J. Am. Chem. Soc.* **1993**, *115*, 12629.

(12) Magnus, P.; Lacour, J. *J. Am. Chem. Soc.* **1992**, *114*, 767.

(13) The use of nitromethane as solvent in this reaction is critical to its success. See: White. J. D.; Carter, R. G. Silyl Ethers. *Science of Synthesis*; Thieme: Stuttgart, Germany, 2002; Vol. 4, pp 371–412.

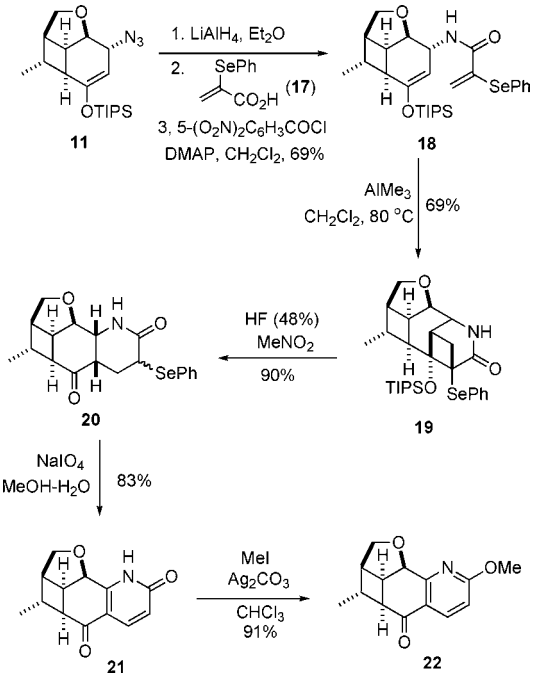
dehydrobromination to an α,β-unsaturated lactam which could then undergo further oxidation to a pyridone. However, treatment of **15** with a variety of bases led exclusively to fused cyclopropane **16** resulting from intramolecular alkylation rather than the desired 1,2-elimination.

Recourse to α-phenylselenylacrylic acid (**17**)[14] circumvented the problem that produced **16**. By converting azide **11** via amine **12** to amide **18** with **17** in the presence of 3,5-dinitrobenzoyl chloride and then reacting **18** with trimethylaluminum, [2 + 2] cycloadduct **19** was obtained in a consistent yield of 65−70% (Scheme 4). As expected, **19** underwent silyl ether cleavage and retro-aldol fragmentation with aqueous fluoride to furnish a separable mixture of stereoisomeric α-selenyl δ-lactams **20**.[15] Oxidation of this mixture with sodium periodate then led directly to α-pyridone **21** in good yield.[16] Methylation of **21** with methyl iodide in the presence of silver carbonate furnished methoxypyridine **22**.

Our next task, reductive cleavage of the pyridylic ether **22**, proved more troublesome than expected. Although the C−O bond in **22** is activated by the adjacent methoxypyridine, attempted hydrogenolysis of this ether led mainly to reduction of the ketone with no evidence of C−O scission. Samarium diiodide and other electron transfer reductants gave similar results. However, when **22** was exposed to activated zinc dust[17] in methanol containing 0.2 M sodium hydroxide, alcohol **23** was formed in excellent yield (Scheme 5). Hydroxy ketone **23** was oxidized with Dess-Martin periodinane[18] to keto aldehyde **24** which underwent a selective Grignard reaction with methylmagnesium iodide at the aldehyde carbonyl to yield hydroxy ketone **25** as a 1:1 mixture of diastereomers. Oxidation of this mixture of alcohols gave a single diketone **26**.

At this point, our blueprint specified methylenation of the methyl ketone of diketone **26**. This process was expected to be selective since the cyclic ketone in **26** was presumed to be less reactive due its conjugation through the pyridine to the remote methoxy substituent and therefore formally equivalent to the carbonyl in a vinylogous ester. However, we had failed to anticipate the severe steric hindrance to attack at the carbonyl of the methyl ketone of **26** by virtue of its endo placement on the cis fused cyclobutane in this congested structure. In the event, olefination of **26** under Wittig conditions[19] gave mixtures in which **28** was formed in only 27% yield; under forcing conditions, **28** was accompanied by the diene from double ketone methylenation as well as the alkene from sole methylenation at the cyclohexanone carbonyl. On the other hand, it was recognized that enolization of

Scheme 4. Synthesis of Fused Methoxypyridine **22** from Azide **11**



diketone **26** was more likely to occur at the methyl ketone than at the cyclohexanone carbonyl, where an endo double bond at the ring fusion in this bicyclo[4.2.0]octane would impose significant strain. In accord with this proposition, treatment of **26** with Comins reagent[20] and a sterically demanding base gave enol triflate **27** in good yield. A Stille reaction of the triflate with tetrakistriphenylphosphinepalladium and hexamethyldistannane[21] produced **28** for which X-ray crystallographic analysis confirmed that no epimerization had taken place at the cyclobutane during its derivation from diketone **26** (Figure 2).

Ketone **28** readily formed an oxime as well as imine derivatives with substituted benzylamines, but these substrates were uncooperative in the skeletal rearrangement programmed in Scheme 1. Generally, imine derivatives of **28** underwent hydrolysis back to the parent ketone or were decomposed in the presence of Lewis acids such as titanium tetrachloride.

Finally, when **28** was treated with methyl carbamate and *anhydrous p*-toluenesulfonic acid in hot benzene an immediate reaction took place that passed transiently through imine **29** and ended after rearrangement at **30**. The latter is the penultimate substance in Kozikowski's synthesis of huperzine A,[22] and a sample of **30** was prepared from natural huperzine A to confirm the identity

(14) Reich, H. J.; Willis, W. W.; Clark, P. D. *J. Org. Chem.* **1981**, *46*, 2775.

(15) The initial mixture of selenyl lactams was found to equilibrate in the presence of excess HF to a 10:1 mixture favoring the β (3*S*) stereoisomer.

(16) It is assumed that selenoxide elimination to an α,β-unsaturated lactam is the first step and that this is followed by allylic oxidation with excess periodate at the activated ring fusion to give **21**.

(17) Newman, M. S.; Arens, F. J. *J. Am. Chem. Soc.* **1955**, *77*, 946.

(18) Boeckman, R. K., Jr.; Shao, P.; Mullins, J. J. *Org. Synth.* **2000**, *77*, 141.

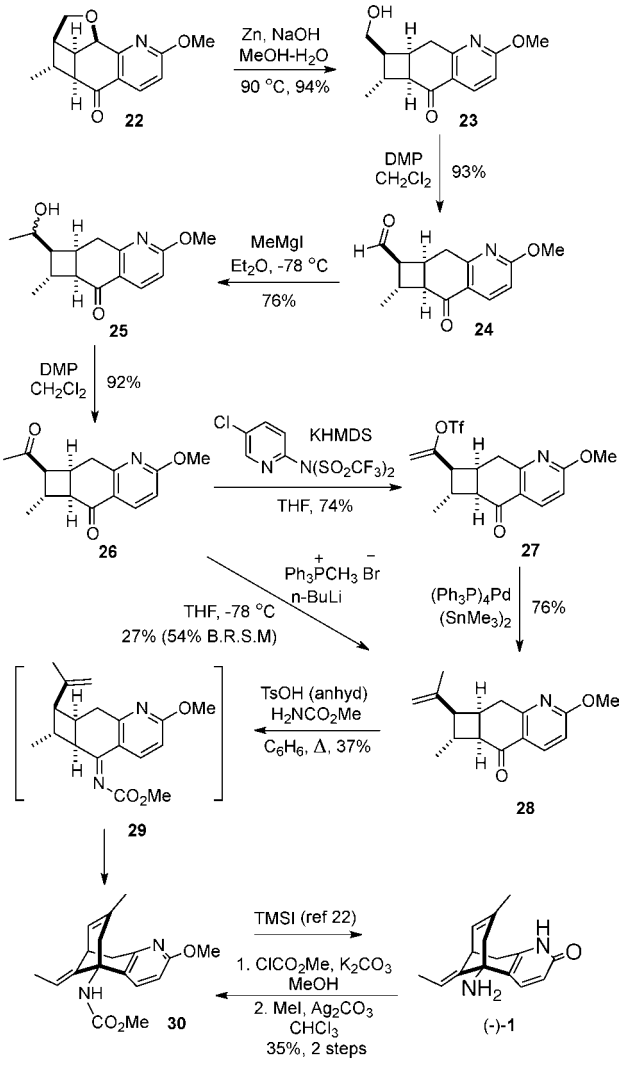
(19) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

(20) Comins, D. L.; Dehgani, A. *Tetrahedron Lett.* **1992**, *32*, 6299.

(21) Eschavarran, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478.

(22) Xia, Y.; Kozikowski, A. P. *J. Am, Chem. Soc.* **1989**, *111*, 4116. It was shown in this work that the *E* and *Z* exocyclic ethylidene substituents attached to the bicyclo[3.3.1]nonene frame equilibrate under relatively mild conditions and that the *E* isomer is thermodynamically more stable.

Scheme 5. Completion of the Synthesis of (−)-Huperzine A (**1**) from Methoxypyridine **22**



of our synthetic material. Thus, exposure of (−)-**1** to methyl chloroformate and potassium carbonate followed by methyl iodide in the presence of silver(I) carbonate produced material identical with the compound obtained from **28**. Treatment of **30** with trimethylsilyl iodide as described by Kozikowski[22] completed our route to (−)-**1**.

In summary, a synthesis of the acetylcholinesterase inhibitor huperzine A (**1**) is demonstrated in which

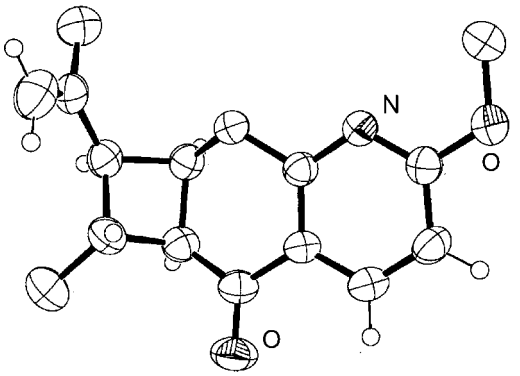


Figure 2. ORTEP representation of the X-ray crystal structure of **28**.

(a) the bicyclo[3.3.1]nonene portion of the natural product is created using an intramolecular aza-Prins reaction of an isopropenyl substituted cyclobutane in conjunction with stereoelectronically directed fragmentation of an intervening cyclobutylcarbinyl cation and (b) the α-pyridone is orchestrated via pentacycle **19** in a novel extrapolation of Magnus' chemistry.[11] Although shorter and more efficient routes to **1** exist, a useful paradigm suggested by this work is that incorporation of ring strain in a synthesis design in the form of a cyclobutane, along with appropriately placed substituents, can provide access to structures of substantial complexity.

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Supporting Information Available. X-ray diffraction data for **14** and **28**; full characterization data and copies of ^1H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.