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Total Synthesis of (−)-8-Deoxyserratinine via an Efficient Helquist Annulation and Double N-Alkylation Reaction

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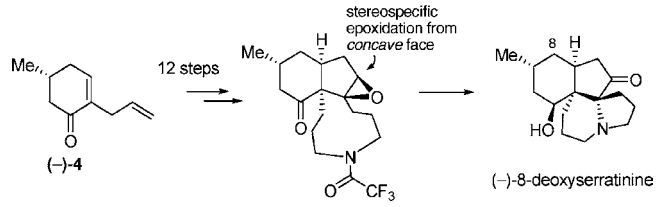
ABSTRACT



The first enantioselective total synthesis of (−)-8-deoxyserratinine has been achieved in 15 steps from enone 4 with 7% overall yield. The key features include a highly efficient Helquist annulation to furnish the cis-fused 6/5 bicycle, facile construction of the aza nine-membered ring system employing double N-alkylation strategy, as well as asymmetric Shi epoxidation, delivering the desired β-epoxide stereospecifically.

The *Lycopodium* alkaloids are a diverse group of structurally complex natural products.[1] Owing to both their appealing, synthetically challenging polycyclic systems with dense stereochemical array and wide-ranging biological activities, a wealth of total synthesis of *Lycopodium* alkaloids have been reported.[2] Among the known *Lycopodium* alkaloids, serratinine **2**[3] and 8-deoxyserratinine **1**[4] are noteworthy due to their unique tetracyclic structures containing two contiguous quaternary stereocenters and the interesting biogenetic connection with serratezomine A **3**[5] via fascinating rearrangements (Figure 1). The first, and to date only, total syntheses of serratinine **2** and 8-deoxyserratinine **1** were accomplished in racemic forms by the Inubushi group at 1974 and 1979.[6] Herein, we wish to report the first asymmetric total synthesis of (−)-8-deoxyserratinine **1** via a novel efficient route, in particular, hoping to address the issues of efficiency and selectivity of the synthesis.

In Inubushi's pioneering synthesis,[6f,g] as shown in Scheme 1, they recognized the possibility to control the stereochem-

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(1) For recent reviews of the *Lycopodium* alkaloids, see: (a) Hirasawa, Y.; Kobayashi, J.; Morita, H. *Heterocycles* **2009**, *77*, 679–729. (b) Ma, X.; Gang, D. R. *Nat. Prod. Rep.* **2004**, *21*, 752–772.

(2) For selected recent total syntheses of *Lycopodium* alkaloids, see: (a) Chandra, A.; Pigza, J. A.; Han, J.-S.; Mutnick, D.; Johnston, J. N. *J. Am. Chem. Soc.* **2009**, *131*, 3470–3471. (b) Nilsson, B. L.; Overman, L. E.; Alaniz, J. R.; Rohde, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 11297–11299. (c) Kozak, J. A.; Dake, G. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 4221–4223. (d) Bisai, A.; West, S. P.; Sarpong, R. *J. Am. Chem. Soc.* **2008**, *130*, 7222–7223.

(3) (a) Inubushi, Y.; Ishii, H.; Yasui, B.; Hashimoto, M.; Harayama, T. *Chem. Pharm. Bull.* **1968**, *16*, 82–91. (b) Inubushi, Y.; Ishii, H.; Yasui, B.; Hashimoto, M.; Harayama, T. *Chem. Pharm. Bull.* **1968**, *16*, 92–100.

(4) Inubushi, Y.; Ishii, H.; Yasui, B.; Harayama, T.; Hosokawa, M.; Nishino, R.; Nakahara, Y. *Yakugaku Zasshi* **1967**, *87*, 1394–1404.

(5) (a) Morita, H.; Arisaka, M.; Yoshida, N.; Kobayashi, J. *J. Org. Chem.* **2000**, *65*, 6241–6245. (b) Morita, H.; Kobayashi, J. *J. Org. Chem.* **2002**, *67*, 5378–5381.

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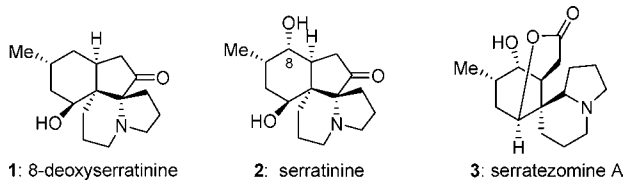
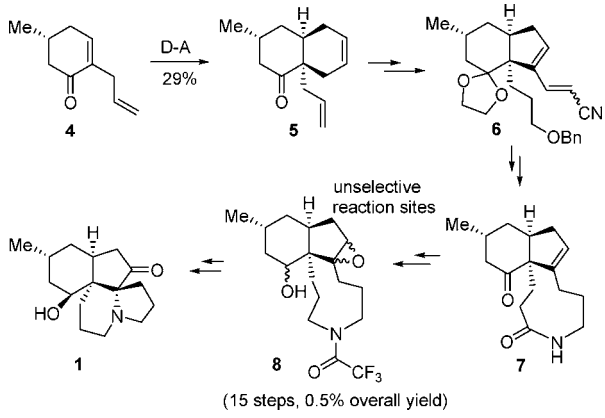


Figure 1. 8-Deoxyserratinine, serratinine, and serratezomine A.

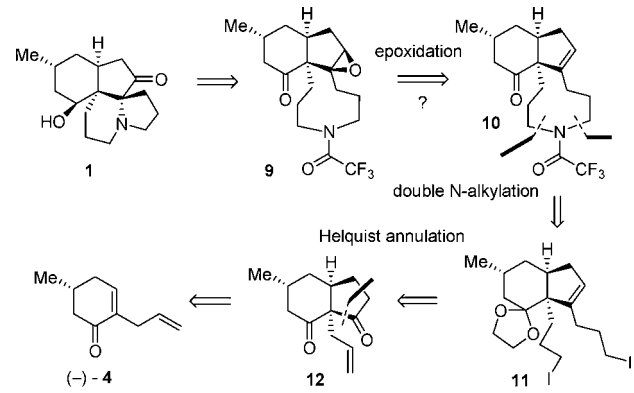
Scheme 1. Key Points of Inubushi's Pioneering Synthesis of 8-Deoxyserratinine (**1**)



istry of the challenging quaternary stereocenter of **5** by using a Diels−Alder addition between butadiene and racemic 2-allyl-5-methyl-cyclohex-2-en-1-one **4** (29% yield). Scission of the double bond of the newly formed six-membered ring of **5** followed by reclosure of the five-membered ring via aldol and Wadsworth−Emmons reaction afforded substituted 6/5 bicycle **6**, which was further elaborated to the tricyclic lactam **7**. Unfortunately, in the subsequent critical stage of setting the second quaternary stereocenter, i.e., stereoselective epoxidation of the double bond of the five-membered ring, a mixture of isomers were obtained, with the undesired α-epoxide predominating. The precursor of tetracyclic serratinine framework **8** was eventually synthesized in ca. 0.5% overall yield over 15 steps. At this point, a more efficient alternative route is still needed.

Our retrosynthetic analysis was outlined in Scheme 2. We proposed to install the second quaternary stereocenter and the tetracyclic system of 8-deoxyserratinine **1** at the late stage

Scheme 2. Retrosynthetic Analysis of 8-Deoxyserratinine (**1**)



via cascade removal of N-protective group and epoxide ring opening, a maneuver that had been utilized by Inubushi. Thus, the β-epoxide **9** became our subgoal of total synthesis of 8-deoxyserratinine **1**. First, the β-epoxide **9** could, in principle, be prepared from a selective epoxidation of the olefin **10**. However, as demonstrated in Inubushi's synthesis, this manipulation posed a problem as the standard *m*-CPBA procedure provided only minor amounts of β-epoxide **9** accompanied by its α-isomer as the predominant product (vide supra). This stereochemical outcome can be attributed to approach of the reagent from the convex face of the tricyclic system. Next, the key aza nine-membered ring of **10** was expected to be constructed by double N-alkylations of the bisiodide compound **11** with a nitrogen atom.[7] Finally, the cis-fused 6/5 bicyclic ring system **12** was envisioned to arise from Helquist annulation[8] of 2-allyl-5-methyl-cyclohex-2-en-1-one **4**. To our knowledge, Helquist annulation was still an underutilized approach for the synthesis of the polycyclic system,[9] and prior to us there had been no one who enlisted it to construct the framework of *Lycopodium* alkaloids.[10] Its uniqueness will be evident by virtue of the synthetic conciseness and efficiency in rapid construction of the key 6/5 bicycle, which stands in sharp contrast to those of Inubushi's Diels−Alder approach.

Our synthesis commenced with (−)-2-allyl-5-methyl-cyclohex-2-en-1-one **4**, which could be prepared in multigram quantities according to the Caine chiral pool strategy from *R*-pulegone.[11] With this enone in hand, we then tried

(6) For related research from the Inubushi group, see: (a) Inubushi, Y.; Yasui, H.; Yasui, B.; Hashimoto, M.; Harayama, T. *Tetrahedron Lett.* **1966**, *7*, 1537–1549. (b) Inubushi, Y.; Ishii, H.; Yasui, B.; Harayama, T. *Tetrahedron Lett.* **1966**, *7*, 1551–1559. (c) Ishii, H.; Yasui, B.; Harayama, T.; Inubushi, Y. *Tetrahedron Lett.* **1966**, *7*, 6215–6219. (d) Inubushi, Y.; Ishii, H.; Harayama, T.; Burnell, R. H.; Ayer, W. A.; Altenkirk, B. *Tetrahedron Lett.* **1967**, *8*, 1069–1072. (e) Harayama, T.; Ohtani, M.; Oki, M.; Inubushi, Y. *J. Chem. Soc., Chem. Commun.* **1974**, 827–828. (f) Harayama, T.; Takatani, M.; Inubushi, Y. *Tetrahedron Lett.* **1979**, *20*, 4307–4310. (g) Harayama, T.; Takatani, M.; Inubushi, Y. *Chem. Pharm. Bull.* **1980**, *28*, 2394–2402. For other synthetic efforts towards serratinine alkaloids, see: (h) Mehta, G.; Reddy, M. S.; Radhakrishnan, R.; Manjula, M. V.; Viswamitra, M. A. *Tetrahedron Lett.* **1991**, *32*, 6219–6222. (i) Cassayre, J.; Gagosz, F.; Zard, S. Z. *Angew. Chem., Int. Ed.* **2002**, *41*, 1783–1785.

(7) Fukuyama's chemistry about 2-nitrobenzenesulfonamide ($NsNH_2$) as an efficient nitrogen nucleophile for synthesis of medium- or large-sized cyclic amines is appreciated widely in this regard, see: (a) Kan, T.; Fujiwara, A.; Kobayashi, H.; Fukuyama, T. *Tetrahedron* **2002**, *58*, 6267–6276. (b) Fujiwara, A.; Kan, T.; Fukuyama, T. *Synlett* **2000**, *11*, 1667–1669. (c) Kan, T.; Kobayashi, H.; Fukuyama, T. *Synlett* **2002**, *5*, 697–699, and references therein. We thank one of the reviewers for bringing these references to our attention.

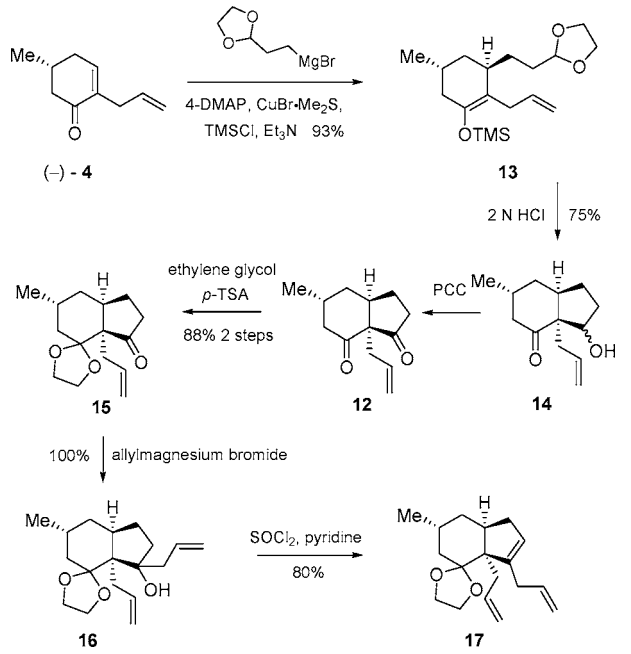
(8) Bal, S. A.; Marfat, A.; Helquist, P. *J. Org. Chem.* **1982**, *47*, 5045–5050.

(9) For application of the Helquist annulation in natural product synthesis, see: (a) Johansson, M.; Sterner, O. *Org. Lett.* **2001**, *3*, 2843–2845. (b) Li, S.; Yamamura, S. *Tetrahedron* **1998**, *54*, 8691–8710.

(10) Yang, Y.-R.; Shen, L.; Wei, K.; Zhao, Q.-S. *J. Org. Chem.* **2010**, *75*, 1317–1320.

(11) Caine, D.; Procter, K.; Cassell, R. A. *J. Org. Chem.* **1984**, *49*, 2647–2648.

Scheme 3. Enantioselective Synthesis of Triene **17**

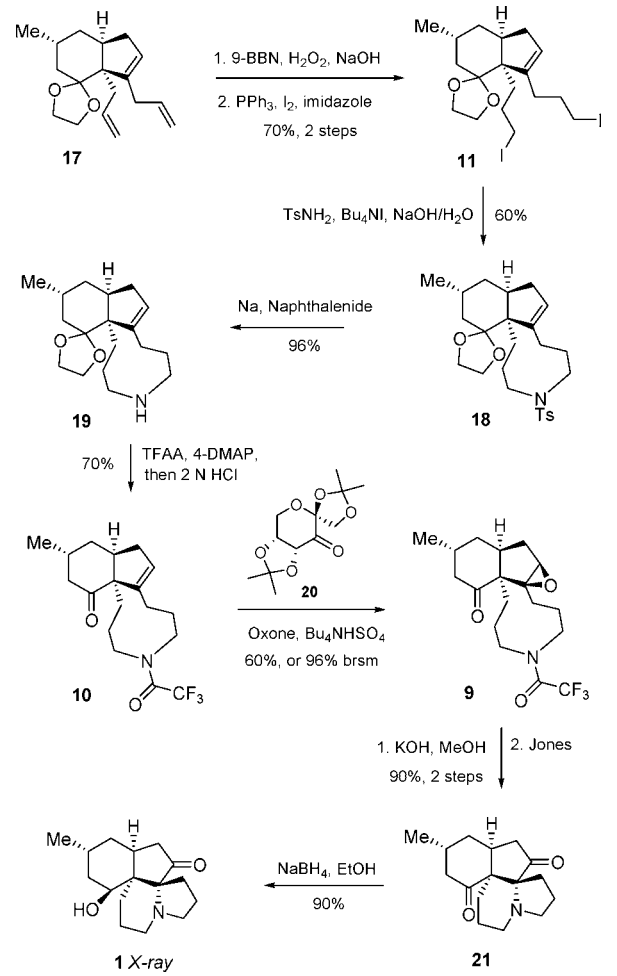


the Helquist annulation and were gratified to find it was very successful. Conjugate addition of the acetal-containing Grignard reagent derived from 2-(2-bromoethyl)-1,3-dioxolane to enone **4** performed well to provide *trans*-silyl enol ether **13** diastereoselectively (93%) (Scheme 3). This enol ether, upon treatment with warm 2 N HCl, successfully underwent cascade desilylation, acetal hydrolysis, and intramolecular aldol cyclization to give a separable 2.5:1 mixture of cis-fused 6/5 bicycle **14** (75%) having the correct configuration of the quaternary stereocenter. Oxidation of a mixture of the Helquist annulation products with PCC followed by brief treatment with ethylene glycol via azeotropic distillation afforded selectively protected cyclic acetal **15**, in which the carbonyl group within the cyclopentanone ring was untouched (88%, 2 steps).[12] The allyl bromide Grignard reagent attacked the cyclopentanone **15** providing the carbinol **16** quantitatively, which was subsequently exposed to thionyl chloride/pyridine conditions and was dehydrated readily with complete regioselectivity furnishing the endocyclic olefin **17** as the only product (80%). At this juncture, the full complement of 16 carbon atoms of 8-deoxyserratinine **1** have been installed in 49% yield over 6 steps.

Prior to closure of the critical aza nine-membered ring, the key intermediate bisiodide **11** was prepared through iodination of the two corresponding terminal hydroxyl groups, which were obtained via selective hydroboration of the triene **17** with 9-BBN (70%, 2 steps) (Scheme 4). By treatment of this bisiodide with $TsNH_2$ as the nucleophilic nitrogen source in the presence of Bu_4NI and NaOH in

(12) Compound **15** was more readily accessible by this selective ketalization of 1,3-diketone **12** than by what we previously reported in ref 10.

Scheme 4. Completion of the Total Synthesis of 8-Deoxyserratinine **1**



refluxing benzene, a smooth double N-alkylative ring closure was realized in a respectable 60% yield.[13] Removal of the tosyl group of **18** was effected by the use of sodium naphthalenide as reducing agent providing amine **19** nearly quantitatively.[14] Trifluoroacetylation of this amine and subsequent cleavage of the cyclic acetal could be carried out in one pot and afforded keto trifluoroacetyl amide **10** in 70% yield. With this keto trifluoroacetyl amide in hand, the stage was now set for the challenging selective epoxidation. After considerable efforts, it was found that this issue could be addressed satisfactorily through Shi asymmetric epoxidation with Shi D-fructose derived catalyst **20**.[15] A complete stereoselective epoxidation took place to provide the desired β-epoxide **9** as the sole product in 60% yield along with the recovered starting material **10** (96% yield, brsm). The

(13) Other nitrogen sources such as $BnNH_2$ and $PMBNH_2$ were also tried, but $TsNH_2$ was finally chosen not only because it can give the best yield but also because it can be readily deprotected into the free amine **19**, leaving the other functionalities of the substrate untouched.

(14) Similar conditions used by the Heathcock group in their fawcettimine total synthesis. Heathcock, C. H.; Blumenkopf, T. A.; Smith, K. M. *J. Org. Chem.* **1989**, *54*, 1548−1562.

(15) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224–11235.

β-epoxide **9** converted into tetracyclic diketone **21** via Inubushi's protocol, that is, tandem cleavage of trifluoroacetamide and intramolecular epoxide ring-opening reaction to furnish tetracyclic amino alcohol (not shown) in a refluxing methanolic KOH solution and subsequent Jones oxidation of the amino alcohol intermediate. At this stage, we were pleased to find our diketone **21** was identical with the literature compound which was obtained from the natural (−)-serratinine degradation (see Supporting Information).[16] Selective reduction of the carbonyl functionality of the six-membered ring through careful addition of 2 equiv of $NaBH_4$ at 0 °C was realized, providing 8-deoxyserratinine **1** nearly quantitatively. The synthetic **1** exhibited a rotation of −14.2 (*c* 0.38, EtOH), essentially identical to that of the natural substance,[17] and its structure was again secured by single-crystal X-ray analysis (see Supporting Information). Therefore, the absolute configuration of 8-deoxyserratinine **1** has been established as shown in Scheme 4.

In summary, the first enantioselective total synthesis of (−)-8-deoxyserratinine **1** has been achieved in 15 steps from enone **4** with 7% overall yield. The key features include a highly efficient Helquist annulation to furnish the cis-fused 6/5 bicycle, facile construction of the aza nine-membered ring system employing double N-alkylation strategy, as well as asymmetric Shi epoxidation, delivering the desired β-epoxide stereospecifically. The synthetic efficiency and selectivity control of this new approach have been significantly enhanced. This strategy is sufficiently general to allow the synthesis of many other complex members of the *Lycopodium* alkaloids. Studies in this regard are currently underway and will be reported in due course.

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Supporting Information Available: Experimental procedures, copies of all spectral data, and full characterization and CIF file for compound **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) The reported optical rotation for natural (−)-8-deoxyserratinine is $[\alpha]_D$−15.6 (*c* 1.0, EtOH). Ishii, H.; Yasui, B.; Nishino, R.; Harayama, T.; Inubushi, Y. *Chem. Pharm. Bull* **1970**, *18*, 1880–1888.