

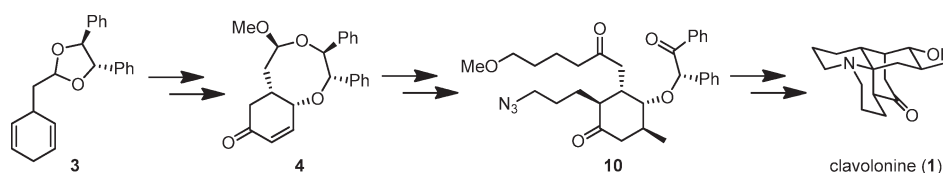
Asymmetric Total Synthesis of Clavolonine

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ABSTRACT



The asymmetric total synthesis of clavolonine (**1**) has been achieved based on chiral auxiliary multiple-use methodology. Our synthetic route features stereoselective transformations on the cyclohexane ring utilizing the steric environment of the chiral auxiliary and an intramolecular Mannich reaction to construct the fused ring system.

The *Lycopodium* alkaloids have received significant attention because of their architectural complexity and wide-ranging biological properties.¹ Recently, the asymmetric total synthesis of various structural types of *Lycopodium* alkaloids have been achieved by many research groups.² Clavolonine (**1**) was first isolated in 1960 from the club moss *Lycopodium clavatum* by Burnell and co-workers.³ This alkaloid is structurally categorized into the lycopodine (**2**)^{4,5} class.^{1a} Our

interest in the synthesis of **1** was stimulated by its intriguing structure, a tetracyclic framework with six contiguous stereogenic centers (Figure 1), as well as potential anticholinesterase activity.⁶ The development of a facile entry to **1** would set the stage for allowing a total synthesis of other structurally related alkaloids.⁷ To date, three total syntheses of **1** have been reported. One was in racemic form,⁸ the other two were in enantiomerically pure form.⁹

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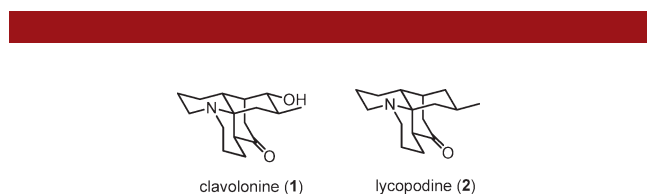


Figure 1. Structures of clavolonine (**1**) and lycopodine (**2**).

As a part of our ongoing study on the development of asymmetric reactions using C_2 -symmetric diols as chiral auxiliaries, we have described a diastereoselective

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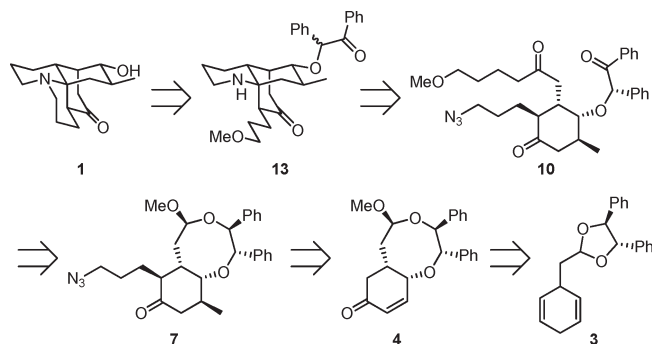
(7) A number of structurally related analogues have been isolated (see ref 1a). In fact, Breit et al. converted **1** into the two natural products (–)-deacetylclavocettine and (+)-acetylclavocettine (see, ref 9b).

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desymmetrization of symmetric dienes¹⁰ that leads to many stereogenic centers being installed in a one-pot reaction. This chemistry has been applied in natural product synthesis.¹¹ During our studies, we have recently developed a new strategy for the asymmetric synthesis of natural products, known as chiral auxiliary multiple-use methodology.¹² Usually, chiral auxiliaries work only during asymmetric reactions to induce asymmetric centers, and they are then removed from the substrates as stoichiometric waste or recyclable molecules. In contrast, we have utilized a single chiral auxiliary not only for asymmetric induction but also as a regio- or stereochemical directing group and a protective group for hydroxyl functions during further transformations, and achieved a concise synthesis of (+)-Sch 642305.¹² As an extension of this concept, we now report an expeditious asymmetric total synthesis of clavulonine.

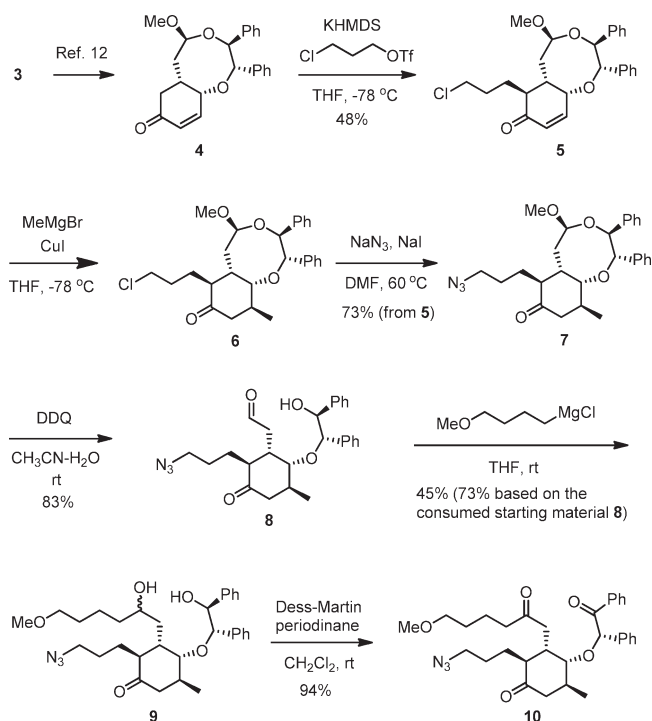
Scheme 1. Retrosynthetic Analysis



Our retrosynthetic analysis is outlined in Scheme 1. In principle, construction of the tetracyclic structure in **1** could be achieved from **13**, which could be formed through a Staudinger/aza-Wittig reaction, an isomerization at the α -position of the ketone, and an intramolecular Mannich reaction on **10**. The synthesis of the cyclization precursor **10** was envisioned to come from the acetal **7**, which could be obtained from **4** by stereoselective introduction of alkyl units on the cyclohexane ring utilizing the steric environment of the eight-membered acetal. The cyclohexenone **4** has already been synthesized through stereoselective bromoetherification of the C_2 -symmetric diene acetal **3** in our laboratory.^{11a,12}

Our synthesis commenced with the enone **4**, which is readily prepared in multigram quantities from the

Scheme 2. Synthesis of 10



cyclohexadiene acetal **3** by sequential bromoetherification and hydroboration/oxidation using (*S,S*)-hydrobenzoin as a chiral auxiliary (Scheme 2).¹² The bulky eight-membered acetal moiety of **4** shields the α -face of the cyclohexane ring to prevent ring inversion, since the two phenyl groups prefer to occupy an equatorial position which restricts the conformational flexibility. We assumed that stereoselective introduction of the alkyl chains on the cyclohexane in **4** could then occur. The coupling of the lithium enolate of **4** with 3-chloropropyl triflate¹³ gave poor results due to the low reactivity of the resulting conjugated enolate. After extensive experimentation, we chose KHMDS as the base to afford **5** in a moderate yield (48%), along with a competitive *O*-alkylative product. A Michael addition to **5** with MeMgBr in the presence of CuI gave **6**. It was followed by azidation (NaN₃, NaI) to provide **7** in 73% in two steps. The azide **7** was obtained as a single diastereomer, suggesting that the alkylations (**4**→**5**, **5**→**6**) proceeded with a facial selectivity from the sterically less-hindered side (the upper side of the cyclohexane ring). Hydrolysis of the acetal in **7** with DDQ¹⁴ afforded the corresponding aldehyde **8** in 83% yield. A chemoselective Grignard reaction was accomplished with 4-methoxybutanemagnesium chloride¹⁵ to provide the diol **9** in 45% yield (73% yield based on the consumed starting material **8**) (dr = ca. 5:1). Finally, treatment of **9** with

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Dess–Martin periodinane gave the cyclization precursor **10** in 94% yield.

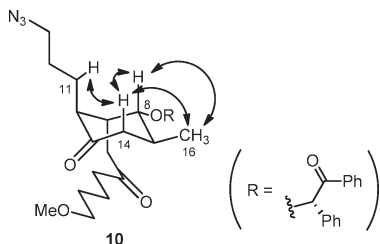


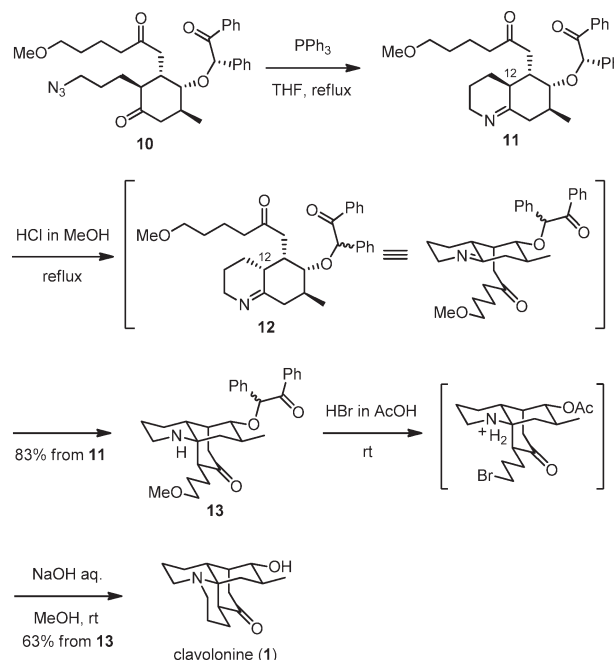
Figure 2. NOE experiment of **10**.

The stereochemistry of **10** was assigned based on an NOE experiment. NOEs between 11-H and 14-βH, 14-βH and 16-CH₃, 14-βH and 8-H, and 16-CH₃ and 8-H were observed as shown in Figure 2. This supported the stereochemical outcome in Figure 2, with 14-βH, 8-H, 11-H, and 16-CH₃, all situated on the same face of the cyclohexane ring in **10**.

For completion of the total synthesis of **1**, we envisioned that the intramolecular Mannich reaction would construct the tricyclic ring system, inspired by Heathcock's pioneering work (Scheme 3).¹⁶ The Staudinger/aza-Wittig reaction of **10** with PPh₃ quantitatively led to the imine **11**.^{9b} Direct exposure of the crude product **11** to methanolic HCl afforded the tricyclic amine **13** (dr = ca. 4:1) in an 83% overall yield from **11**. We speculated that this reaction would proceed via the intermediate **12**, which is the 12-C epimerization compound of **11**. The Mannich reaction of **11** would not be expected to proceed through the kinetically disfavored boat-like transition state, whereas the chairlike transition state from **12** would be predicted to smoothly produce **13**.¹⁷ Surprisingly, treatment of **13** with HBr in AcOH effected conversion of the methoxy group to the bromide with concomitant cleavage of the auxiliary unit and protection as an acetate. Intramolecular nucleophilic substitution and saponification under basic conditions (aqueous NaOH in MeOH) thereafter afforded clavulonine (**1**) in 63% yield. The spectroscopic data and optical rotation [[α]_D^{28.3} +22.8 (*c* 0.36, EtOH), lit.^{9a} [α]_D +21.3 (*c* 0.5, EtOH), lit.^{9b} [α]_D²⁰ +28.3 (*c* 0.50, EtOH)] were identical with the reported data.⁹

In conclusion, we have described a concise asymmetric total synthesis of clavulonine with a longest linear sequence of 10 steps from the enone **4** (10.4% overall

Scheme 3. Completion of the Total Synthesis of **1**



yield). Our synthetic route requires fewer steps for achieving the total synthesis than previous reports.⁹ The key feature is that a chiral auxiliary subunit in the molecules plays an important role in the construction of the asymmetric centers on the cyclohexane ring and it also serves as a protective group for the hydroxyl functions. The tetracyclic structure was assembled through the Staudinger/aza-Wittig reaction and subsequent intramolecular Mannich reaction. Our synthetic approach also provides potential access to related *Lycopodium* alkaloids and various designed analogues for biological studies. Further synthetic work is currently underway in our laboratory.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research (A) and (B), Grant-in-Aid for Scientific Research for Exploratory Research from Japan Society for the Promotion of Science, and Grant-in-Aid for Scientific Research on Priority Areas (17035047) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

Supporting Information Available. Experimental details and detailed spectroscopic data of all new compounds and synthetic clavulonine. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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