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Total Synthesis of Hirsutellone B via Ullmann-Type Direct 13-Membered Macrocyclization

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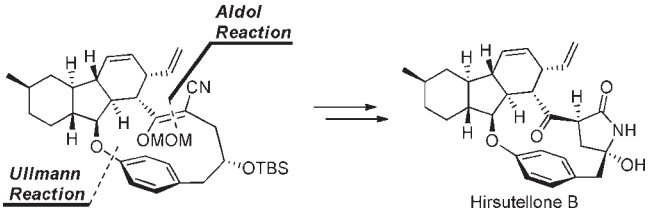
ABSTRACT



Total synthesis of Hirsutellone B has been achieved by a convergent synthetic strategy. This synthesis features direct construction of the highly strained 13-membered macrocycle of Hirsutellone B utilizing the Ullmann-type reaction. To the best of our knowledge, this is the first application of macrocyclization utilizing an intramolecular Ullmann-type reaction between an aliphatic alcohol and aryl halide.

Recently, several novel decahydrofluorene-class bioactive natural products such as hirsutellones,[1] GKK1032s,[2] and pyrrocidines[3] have been reported. These compounds have similar structural features including (i) a tricyclic decahydrofluorene skeleton and (ii) a highly strained 13-membered macrocycle including a γ-hydroxylactam (Figure 1). However, the reported biological activities of these compounds are different.[1−3] We therefore embarked on the total synthesis of this series of compounds to clarify their mode of action and their structure−activity relationships.

Hirsutellone B (**1**) was isolated from the insect pathogenic fungus *Hirsutella nivea* BCC 2594 by Isaka et al. in 2005 and exhibits antituberculosis activity against *Mycobacterium tuberculosis* $H_{37}Ra$, with a minimum inhibitory concentration (MIC) value of 0.78 μg/mL.[1] The structural novelty and intriguing biological activity of the hirsutellones have attracted much attention from synthetic chemists and pharmaceutical researchers.

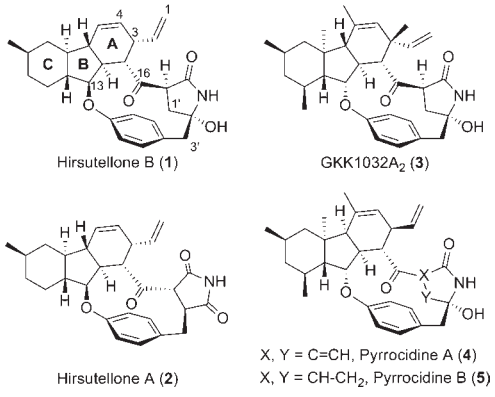


Figure 1. Structures of Hirsutellone B (**1**) and related compounds.

The most difficult and challenging task in the total synthesis of Hirsutellone B (**1**) is the construction of the highly strained 13-membered macrocycle which includes a bent benzene ring. Therefore, while several projects are currently underway to synthesize hirsutellones, only one asymmetric total synthesis has been achieved to date.[4] The Nicolaou group achieved the first total synthesis of

(1) Isaka, M.; Rugseree, N.; Maithip, P.; Kongsaeree, P.; Prabpai, S.; Thebtaranonth, Y. *Tetrahedron* **2005**, *61*, 5577. (b) Isaka, M.; Prathumpai, W.; Wongsa, P.; Tanticharoen, M. *Org. Lett.* **2006**, *8*, 2815.

(2) Koizumi, F.; Hasegawa, A.; Ando, K.; Ogawa, T.; Hara, M. Jpn. Kokai Tokkyo Koho, JP 2001247574 A2 20010911, 2001; *Chem. Abstr.* 2001, *135*, 209979.

(3) He, H.; Yang, H. Y.; Bigelis, R.; Solum, E. H.; Greenstein, M.; Carter, G. T. *Tetrahedron Lett.* **2002**, *43*, 1633.

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hirsutellone B (**1**) in 2009[4c] by constructing a 13-membered macrocycle from a less strained 14-membered cyclic sulfone through a Ramberg–Bäcklund reaction. In contrast, our interest is to develop a direct 13-membered macrocyclization approach. In this paper, we report the total synthesis of Hirsutellone B (**1**) by using a copper-mediated Ullmann-type etherification as the key step.

Our retrosynthetic analysis is shown in Figure 2. Hirsutellone B (**1**) would be obtained by the formation of the γ-hydroxylactam moiety from ketoamide **6**, which is prepared from macrocycle **7** *via* several conversions. The 13-membered macrocycle of **7** would be constructed by intramolecular Ullmann-type etherification between the aryl iodide and the aliphatic secondary alcohol at the C13 position. Cyclization precursor **8** would be prepared by the oxidation of aldol adduct **9** and subsequent enol ether formation. We anticipated that the stereoselective formation of the *E*-form of the enol ether moiety would facilitate the desired intramolecular cyclization by limiting conformational flexibility. The aldol adduct would be obtained by a coupling reaction of decahydrofluorene skeleton **10** with an anion generated from a γ-siloxynitrile **11**.

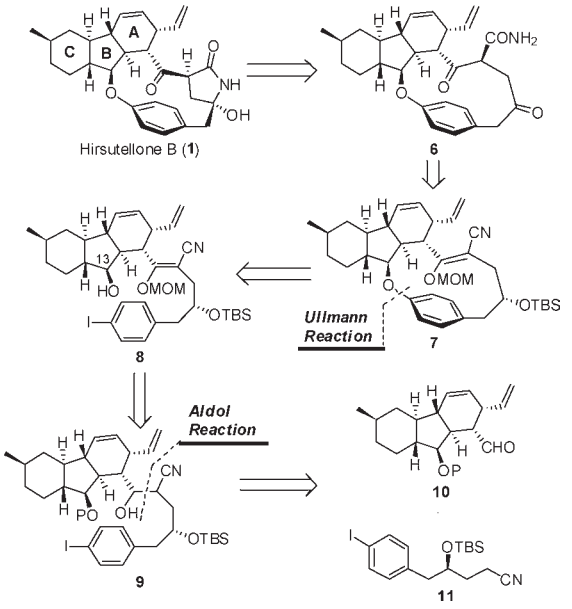
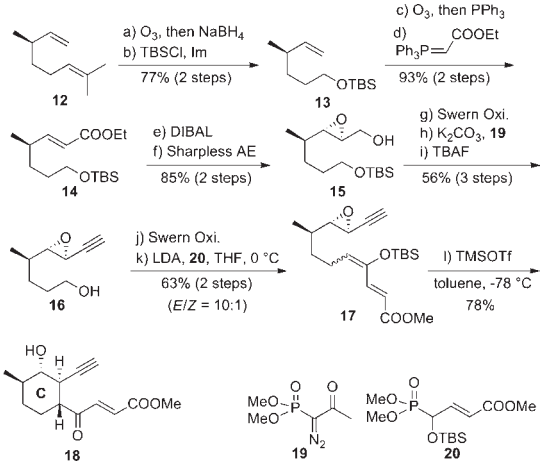


Figure 2. Retrosynthetic analysis of Hirsutellone B (**1**).

We are also studying the total synthesis of GKK1032s and previously reported the construction of its decahydrofluorene skeleton by utilizing a Lewis acid promoted intramolecular cyclization and a retro DA-IMDA reaction.[5] Therefore, we adopted a similar strategy for the construction of the decahydrofluorene skeleton **10**.

The first step was the construction of the C-ring (Scheme 1). Regioselective ozonolysis of (*R*)-(−)-citronellene **12** with reductive workup, followed by TBS protection, gave the corresponding silyl ether **13**. Further ozonolysis of **13** and a subsequent Wittig reaction afforded the α,β-unsaturated ester **14** as a single stereoisomer. DIBAL reduction of the ester group was carried out, and the resulting allylic alcohol was then converted to the chiral epoxide **15** by Sharpless asymmetric epoxidation[6] (L-(+)-DIPT, TBHP, $Ti(O\textit{i}\text{-}Pr)_4$, MS4A, CH_2Cl_2, −20 °C). After Swern oxidation[7] of the primary hydroxyl group of **15**, the obtained aldehyde was transformed to the acetylene by the Seyferth–Gilbert homologation reaction utilizing Ohira–Bestmann reagent **19**.[8] After deprotection of the TBS group, Swern oxidation was carried out to afford the corresponding aldehyde. The silyl enol ether moiety was constructed from the aldehyde by a vinylogous HWE reaction with α-siloxyphosphonate **20**[5] in 63% yield in two steps (*E*/*Z* = 10:1). With the cyclization precursor in hand, Lewis acid promoted C-ring formation was carried out. The desired intramolecular cyclization proceeded smoothly upon treatment with TMSOTf, and the cyclization product **18** was obtained in 78% yield and in optically pure form (> 99% *ee*).[9]

Scheme 1. Synthesis of Cyclization Product **18**



Next, the construction of the decahydrofluorene skeleton was investigated (Scheme 2). The highly reactive γ-keto-α,β-unsaturated ester moiety was protected prior to modifications of the acetylene moiety of **18**. The protection step

(4) (a) Tilley, S. D.; Reber, K. P.; Sorensen, E. J. *Org. Lett.* **2009**, *11*, 701. (b) Huang, M.; Huang, C.; Liu, B. *Tetrahedron Lett.* **2009**, *50*, 2797. (c) Nicolaou, K. C.; Sarlah, D.; Wu, T. R.; Zhan, W. *Angew. Chem., Int. Ed.* **2009**, *48*, 6870. (d) Reber, K. P.; Tilley, S. D.; Sorensen, E. J. *Chem. Soc. Rev.* **2009**, *38*, 3022. (e) Huang, M.; Song, L.; Liu, B. *Org. Lett.* **2010**, *12*, 2504. (f) Halvorsen, G. T.; Roush, W. R. *Tetrahedron Lett.* **2011**, *52*, 2072. (g) Nicolaou, K. C.; Sun, Y.; Sarlah, D.; Zhan, W.; Wu, T. R. *Org. Lett.* **2011**, *20*, 5708.

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(6) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

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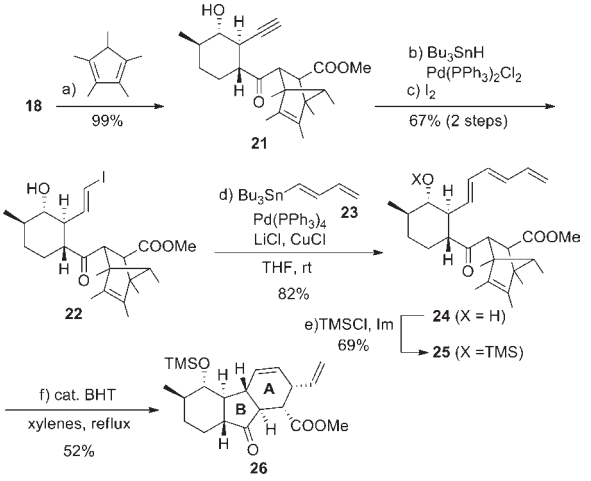
(8) (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561. (b) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, *6*, 521.

(9) An enantiomeric excess was determined by chiral HPLC analysis.

utilizing the intermolecular Diels–Alder reaction of **18** with 1,2,3,4,5-pentamethylcyclopentadiene afforded the corresponding norbornene-type compound **21** as a mixture of inseparable diastereomers. The acetylene moiety of **21** was then converted to the corresponding vinyl iodide **22** via hydrostannylation and subsequent iodination. A Stille coupling reaction between **22** and independently prepared dienyl stannane **23**[10] under Corey's conditions[11] afforded the corresponding triene moiety of **24**, and then the hydroxyl group was protected with a TMS group to give the cyclization precursor **25**. Refluxing of **25** in xylene resulted in the subsequent desired retro-DA-IMDA reactions, and the IMDA adduct **26** was obtained in 52% yield.

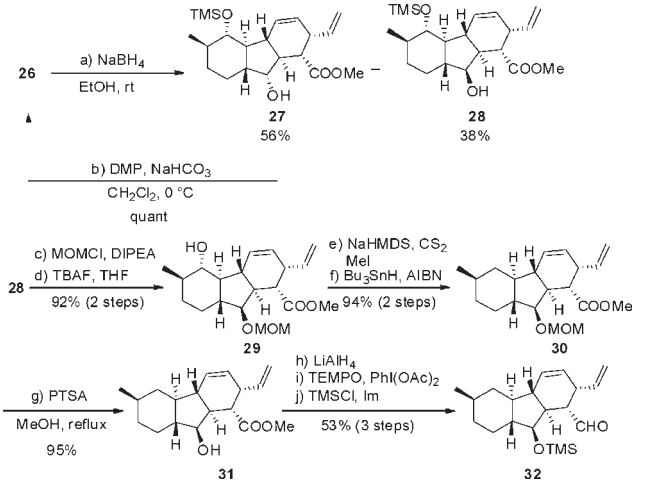
Scheme 2. Synthesis of Decahydrofluorene Skeleton **26**



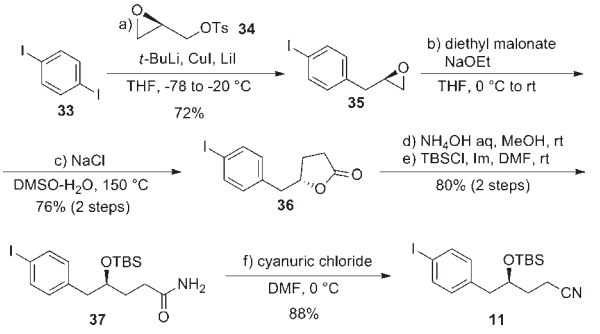
Further modifications of IMDA adduct **26** were conducted to complete the synthesis of the fully elaborated decahydrofluorene skeleton of hirsutellone (Scheme 3). Unfortunately, reduction of the C13 ketone group using $NaBH_4$ gave the desired alcohol **28** as a minor product (38% yield), along with its epimer **27** as the major product (56% yield). The undesired epimer **27** was converted to **26** quantitatively by Dess–Martin oxidation.[12] The obtained alcohol **28** was protected with the MOM group, followed by deprotection of the TMS group to give the alcohol **29**. The unnecessary hydroxyl group of **29** was then removed by the Barton–McCombie procedure[13] to give the deoxygenated compound **30**. MOM deprotection of **30** was conducted by treatment with PTSA. After the three-step modification of $LiAlH_4$ reduction, selective oxidation of the primary alcohol using a TEMPO catalyst,[14] and TMS protection of the secondary hydroxyl group, the desired decahydrofluorene skeleton **32** was successfully obtained.

As another fragment, the chiral γ-siloxynitrile **11** was prepared (Scheme 4). (*R*)-Glycidyl tosylate **34** was reacted with a cuprate prepared from 1,4-diiodobenzene **33**, to give the chiral epoxide **35**. Addition of diethyl malonate to epoxide **35** and subsequent decarboxylation afforded the lactone **36** with high optical purity (>99% *ee*).[9] The lactone moiety was then converted to the corresponding siloxyamide **37** by ammonolysis and subsequent TBS protection. The amide **37** was dehydrated by treatment with cyanuric chloride, and the desired γ-siloxynitrile **11** was obtained.

Scheme 3. Further Modifications of IMDA Adduct **26**



Scheme 4. Synthesis of γ-Siloxynitrile **11**



Thus prepared γ-siloxynitrile **11** was coupled with the siloxyaldehyde **32** by an aldol reaction. The resulting hydroxyl group was oxidized by use of DMP to the corresponding ketonitrile **38**. Ketonitrile **38** was converted to the MOM enol ether by treatment with Cs_2CO_3 and MOMCl, and the TMS group was removed in a one-pot reaction by the addition of methanol. Then, with the desired cyclization precursor **8** in hand as a single *E*-isomer, we tried an intramolecular Ullmann-type reaction to construct the

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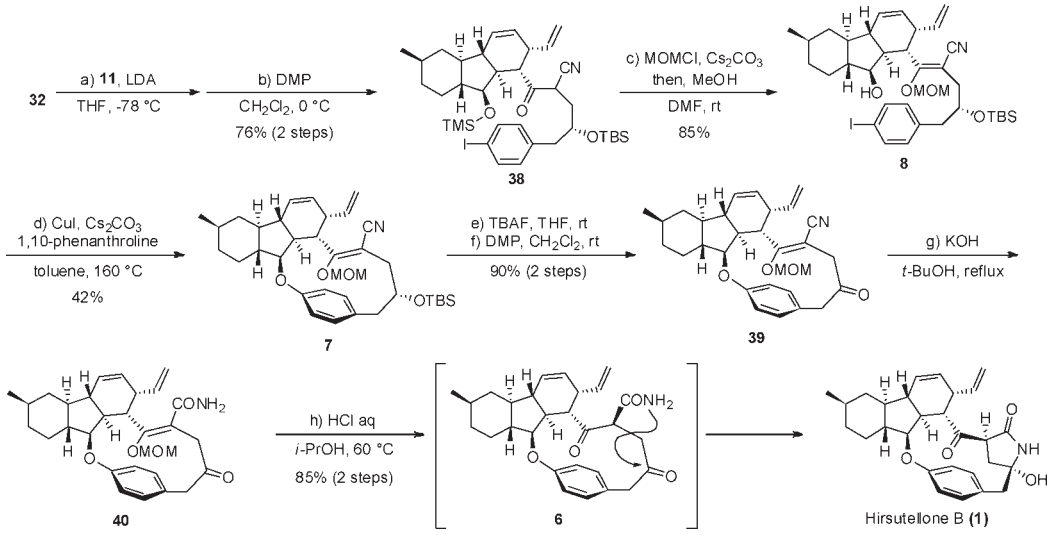
(11) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600.
(12) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
(13) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, *16*, 1574.
(14) de Nooy, A. E. J.; Besemer, A. C.; van Bekkum, H. *Synthesis* **1996**, *1996*, 1153.

Scheme 5. Total Synthesis of Hirsutellone B (**1**)



highly strained 13-membered macrocycle. Although standard Buchwald conditions[15] were not effective for this reaction, the desired cyclization product was obtained in 42% yield by increasing the reaction temperature to 160 °C. To date, several macrocyclization reactions based on the construction of a biaryl ether linkage utilizing the intramolecular Ullmann-type reaction have been reported.[16] However, to the best of our knowledge, this is the first successful example of a macrocyclization between an aliphatic alcohol and an aryl halide.[17]

Several steps remained to complete the total synthesis. The TBS group of **7** was deprotected, and successive Dess–Martin oxidations of the resulting hydroxyl group afforded the ketone **39**. The nitrile moiety of **39** was hydrolyzed to the corresponding amide under basic conditions (refluxed with KOH in *t*-BuOH). Finally, the MOM group of **40** was removed by treatment with 1 N HCl aq at 60 °C. Under these reaction conditions, it is noteworthy that the desired γ-hydroxylactam formation of the resulting ketoamide **6** also proceeded in a stereoselective manner. Thus, the total synthesis of Hirsutellone B (**1**) was successfully accomplished (Scheme 5).

In conclusion, we have achieved the total synthesis of Hirsutellone B (**1**) *via* direct construction of the highly strained 13-membered macrocycle utilizing Ullmann-type etherification. It is strongly expected that the developed synthetic strategy will be useful for the synthesis of related decahydrofluorene-class natural products (i.e., GKK-1032s and pyrrocidines), aiding structure–activity relationship studies of these compounds. Further investigations into the total synthesis of this series of compounds are now in progress and will be described in the near future.

Supporting Information Available. Experimental pocedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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