

Synthetic Study of Pyrrocidines: First Entry to the Decahydrofluorene Core of Pyrrocidines

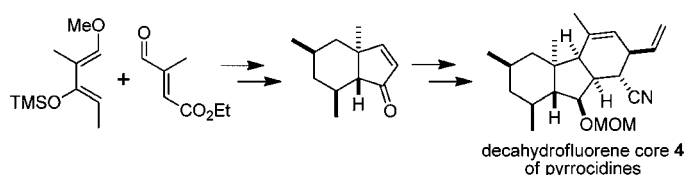
Ryo Tanaka, Kentaro Ohishi, Noriyuki Takanashi, Tomohiko Nagano, Hiroshi Suizu, Takahiro Suzuki, and Susumu Kobayashi*

Faculty of Pharmaceutical Sciences, Tokyo University of Science (RIKADAI),
2641 Yamazaki, Noda-shi, Chiba 278-8510, Japan

kobayash@rs.noda.tus.ac.jp

Received August 9, 2012

ABSTRACT



The first synthesis of decahydrofluorene core 4 of pyrrocidines was accomplished. The *cis,trans*-fused tricyclic ring system was stereoselectively constructed via Diels–Alder reaction using two Danishefsky dienes.

Pyrrocidine A (1) and B (2) were isolated from the fermentation broth of a fungus, LL-Cyan 426.¹ These compounds exhibit significant antibiotic activities against most Gram-positive bacteria, including drug-resistant strains, and have been recognized as promising lead antimicrobial agents.^{1,2} Recently, a dimeric pyrrocidine was also isolated by the Shiono group.³ Structural features of pyrrocidines include the following: (i) a *cis,trans*-fused tricyclic decahydrofluorene core (ABC-ring) and (ii) a 13-membered macrocycle containing a γ -hydroxy- γ -lactam ring and including a *para*-substituted aryl ether moiety. Nature also produces structurally related GKK1032s,⁴ hirsutellones,⁵ and pyrrospirones,⁶ which have a *trans,trans*-fused ABC-ring system. The complex molecular architecture of this family of compounds makes them very attractive target molecules from a synthetic point of view. Indeed, to date there have been numerous reports of

synthetic investigations involving a *trans,trans*-fused ABC-ring system (GKK1032s,⁷ hirsutellones⁸). By contrast, there have been no reports in the literature concerning synthesis of the fully elaborated tricyclic decahydrofluorene core of pyrrocidines.⁹ With the total synthesis of pyrrocidines in mind, we initially attempted to establish a stereoselective and scalable method for the synthesis of the *cis,trans*-fused 6–5–6 tricyclic system. Herein, we describe the first

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

(2) Wicklow, D. T.; Poling, S. M. *Phytopathology* **2009**, *99*, 109.

(3) Shiono, Y.; Kosukegawa, A.; Koseki, T.; Murayama, T.; Kwon, E.; Uesugi, S.; Kimura, K. *Phytochem. Lett.* **2012**, *5*, 91.

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

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

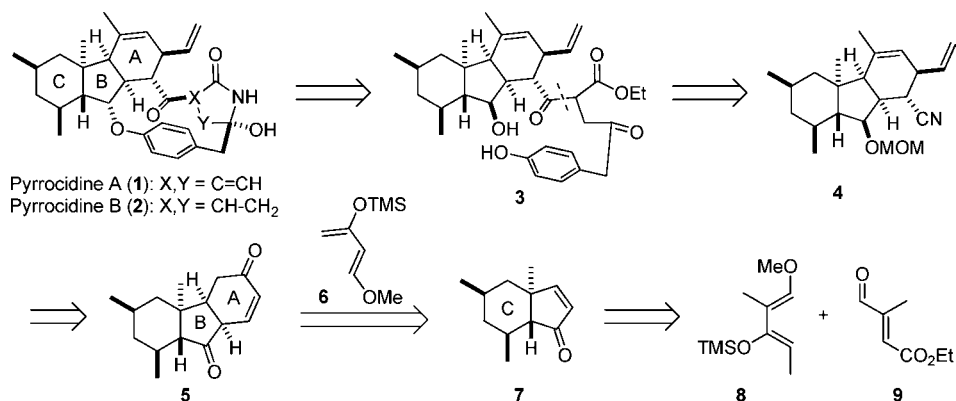
(6) Shiono, Y.; Shimanuki, K.; Hiramatsu, F.; Koseki, T.; Tetsuya, M.; Fujisawa, N.; Kimura, K. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6050.

(7) Synthetic studies of GKK1032s: (a) Arai, N.; Ui, H.; Omura, S.; Kuwajima, I. *Synlett* **2005**, 1691. (b) Asano, M.; Inoue, M.; Katoh, T. *Synlett* **2005**, 1539. (c) Asano, M.; Inoue, M.; Katoh, T. *Synlett* **2005**, 2599. (d) Asano, M.; Inoue, M.; Watanabe, K.; Abe, H.; Katoh, T. *J. Org. Chem.* **2006**, *71*, 6942. (e) Uchiro, H.; Kato, R.; Sakuma, Y.; Takagi, Y.; Arai, Y.; Hasegawa, D. *Tetrahedron Lett.* **2011**, *52*, 6242. (f) Shiwaku, M.; Nagae, K.; Noyama, C.; Shinkawa, T.; Miyazaki, Y.; Kurosaka, J.; Munakata, R.; Takao, K.; Tadano, K. *Symposium Papers*, 48th Symposium on the Chemistry of Natural Products, Sendai, Japan, 2006; p 403. (g) Shimizu, Y.; Takao, K.; Tadano, K. *Symposium Papers*, 8th Symposium on Organic Chemistry – The Next Generation, Tokyo, Japan, 2010; 38. (h) Nagai, S.; Shimizu, Y.; Takao, K.; Tadano, K. *Symposium Papers*, 100th Symposium on Organic Synthesis, Japan, Tokyo, Japan, 2011; 64.

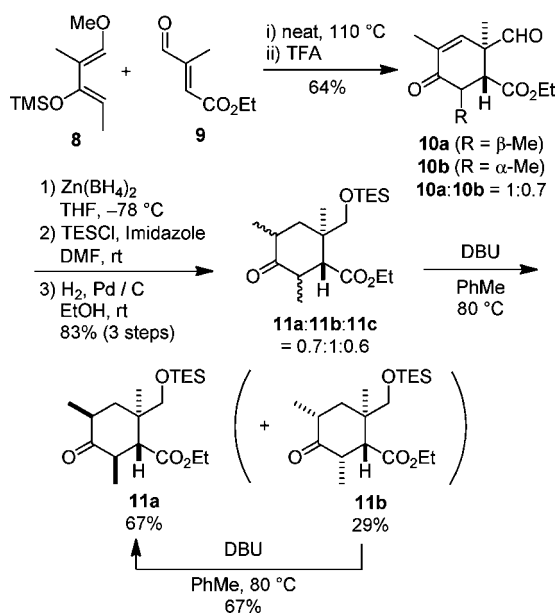
(8) Total synthesis of hirsutellone B: (a) Nicolaou, K. C.; Sarlah, D.; Wu, T. R.; Zhan, W. *Angew. Chem., Int. Ed.* **2009**, *48*, 6870. (b) Uchiro, H.; Kato, R.; Arai, Y.; Hasegawa, M.; Kobayakawa, Y. *Org. Lett.* **2011**, *13*, 6268. Synthetic studies of hirsutellones: (c) Tilley, S. D.; Reber, K. P.; Sorensen, E. J. *Org. Lett.* **2009**, *11*, 701. (d) Reber, K. P.; Tilley, S. D.; Sorensen, E. J. *Chem. Soc. Rev.* **2009**, *38*, 3022. (e) Huang, M.; Huang, C.; Liu, B. *Tetrahedron Lett.* **2009**, *50*, 2797. (f) Huang, M.; Song, L.; Liu, B. *Org. Lett.* **2010**, *12*, 2504. (g) Halvorsen, G. T.; Roush, W. R. *Tetrahedron Lett.* **2011**, *52*, 2072.

(9) There has been only one report concerning the construction of the *cis*-fused cyclohexene ring of pyrrocidines, see: Abdelkafi, H.; Evanno, L.; Deville, A.; Dubost, L.; Chiaroni, A.; Nay, B. *Eur. J. Org. Chem.* **2011**, *2011*, 2789.

Scheme 1. Retrosynthesis



Scheme 2. Synthesis of Ketone **11a**



stereoselective synthesis of decahydrofluorene **4**, which corresponds to the ABC-ring moiety of pyrrocidines.

Our retrosynthetic analysis is illustrated in Scheme 1. We envisioned that pyrrocidines might be synthesized from tricyclic hydroxyphenol **3** by formation of a 13-membered ring via a Mitsunobu reaction and generation of a γ -hydroxy- γ -lactam moiety. The cyclization precursor **3**, in turn, might be derived from key intermediate nitrile **4** via the aldehyde by an aldol-type homologation. The stereocontrolled access to *cis*,*trans*-fused decahydrofluorene **4** might be possible from tricyclic enone **5** by utilizing the stereochemical characteristics of the *cis*,*trans*-fused

ring system. The requisite *cis*-fused AB-ring moiety of **5** could be constructed by Diels–Alder reaction between Danishefsky–Kitahara diene **6**¹⁰ and bicyclo enone **7**.¹¹ The C-ring moiety in **7** could be synthesized by Diels–Alder reaction between dimethyl-substituted Danishefsky diene **8**¹² and the doubly activated dienophile **9**.¹³

Our synthesis commenced with the construction of the C-ring moiety (Scheme 2). Thus, Diels–Alder reaction between diene **8** and dienophile **9**, followed by acid treatment in one pot, afforded a fully substituted cyclohexenone **10a,b** in 64% total yield (**10a:10b** = 1:0.7).¹⁴ The aldehyde group of **10a,b** was chemoselectively reduced with $\text{Zn}(\text{BH}_4)_2$, and the resulting alcohol was then protected as a triethylsilyl ether. The conventional Pd-catalyzed hydrogenation of the mixture of two diastereomeric enones provided cyclohexanones **11a–c** in 83% overall yield for three steps.¹⁵ The obtained mixture of three diastereomers **11a–c** was subjected to DBU-promoted epimerization of methyl groups adjacent to the ketone moiety. Under thermodynamic control conditions, the desired ketone **11a** was obtained (67% yield) along with its stereoisomer **11b** (29% yield). Undesired ketone **11b** was easily removed and could be recycled to **11a** under the same equilibrium conditions. The stereochemistry of **11a** and **11b** was determined by NOE measurements.

Next, we turned our attention toward the transformation to bicyclic enone **7** (Scheme 3). The ketone **11a** was stereoselectively reduced with L-Selectride, and the resulting

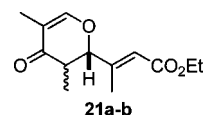
(10) Danishefsky, S.; Kitahara, T.; Schuda, P. F. *Org. Synth.* **1983**, *61*, 147.

(11) Several research groups achieved excellent stereoselective syntheses of the *trans*-fused AB-ring in GKK1032s by using an intramolecular Diels–Alder reaction approach. However, the secondary orbital interaction between the diene HOMO and dienophile LUMO prevents the construction of the *cis*-fused AB-ring in pyrrocidines. See ref 7d–7f.

(12) Danishefsky, S.; Yan., C.-F.; Singh, R. K.; Gammill, R. B.; McCurry, P. M., Jr.; Fritsch, N.; Clardy, J. *J. Am. Chem. Soc.* **1979**, *101*, 7001.

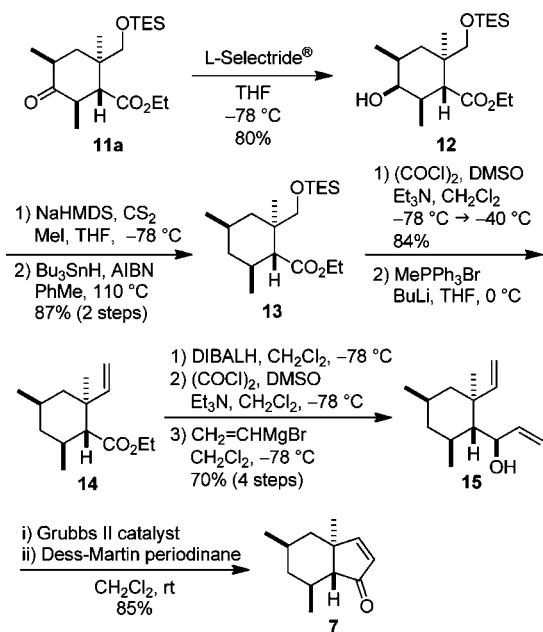
(13) Diene **8** was found to be less reactive with trisubstituted olefin because of the steric hindrance of its two methyl groups. Thus, electronically favored dienophile **9** was employed in the present study. See ref 7d.

(14) The moderate yield of **10a–b** was due to the competitive hetero-Diels–Alder reaction between the aldehyde function of **9** and diene **8** to afford a diastereomeric mixture of dihydropyranones **21a,b** (12%, dr = 1:1).



(15) The hydrogenation of one diastereomer stereoselectively afforded the ketone **11b**, while the other diastereomer afforded an almost equimolar mixture of **11a** and its epimer **11c**.

Scheme 3. Preparation of Bicyclic Enone 7



alcohol **12**¹⁶ was deoxygenated by the Barton–McCombie protocol¹⁷ to give **13**. In order to construct the cyclopentenone moiety of **7**, the triethylsilyl-protected hydroxymethyl moiety of **13** was directly oxidized under Swern conditions,¹⁸ and the resulting aldehyde was homologated by Wittig reaction to afford olefin **14**. The ester group of **14** was reduced to aldehyde through a reliable two-step transformation involving DIBALH reduction and Swern oxidation. Sequential Grignard reactions proceeded stereoselectively under Felkin–Anh control to give allylic alcohol **15** in 70% overall yield for four steps. The *trans*-fused bicyclic enone **7** was obtained by ring-closing metathesis using the Grubbs' second-generation catalyst and Dess–Martin oxidation in a one-pot reaction.¹⁹

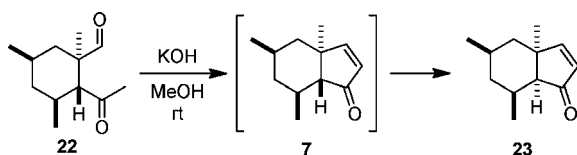
With bicyclic enone **7** in hand, we next attempted the key Diels–Alder cycloaddition (Scheme 4). Danishefsky–Kitahara diene **6** and cyclic dienophile **7** reacted at 110 °C without solvent to afford the *endo* product **16b** and the *exo*

(16) The resolution of (\pm)-**12** could be carried out by the formation of diastereomeric esters using (*R*)-*O*-acetyl mandelic acid. The detailed procedure of resolution and the determination of the absolute configuration of optically active **12** by the conversion to a known compound are provided in the Supporting Information. In the present study, racemic **12** was used for further transformation.

(17) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. I* **1975**, 1574.

(18) Rodríguez, A.; Nomen, M.; Spur, B. W.; Godfroid, J. J. *Tetrahedron Lett.* **1999**, *40*, 5161.

(19) The most straightforward intramolecular aldol reaction of keto aldehyde **22** afforded *cis*-fused compound **23** through the isomerization of the initially formed *trans*-fused bicyclic enone **7** under basic conditions.



product **16a** (**16a:16b** = 0.8:1). As expected, the angular methyl group served to block the α -face of the dienophile so that the diene approached from the β -face (Figure 1). Mild acidic treatment of obtained **16a,b** provided the tricyclic diketone **5** in 85% overall yield for the two steps. The stereochemistry of **5** was assigned by analysis of the NOE spectra.

Scheme 4. Construction of the Tricyclic Diketone 5

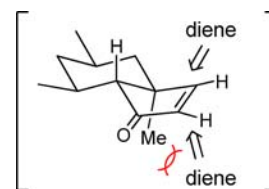
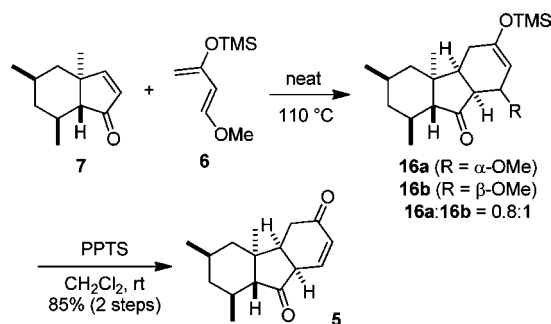
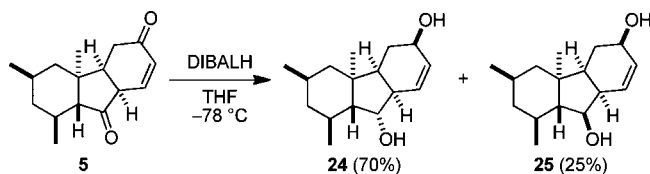


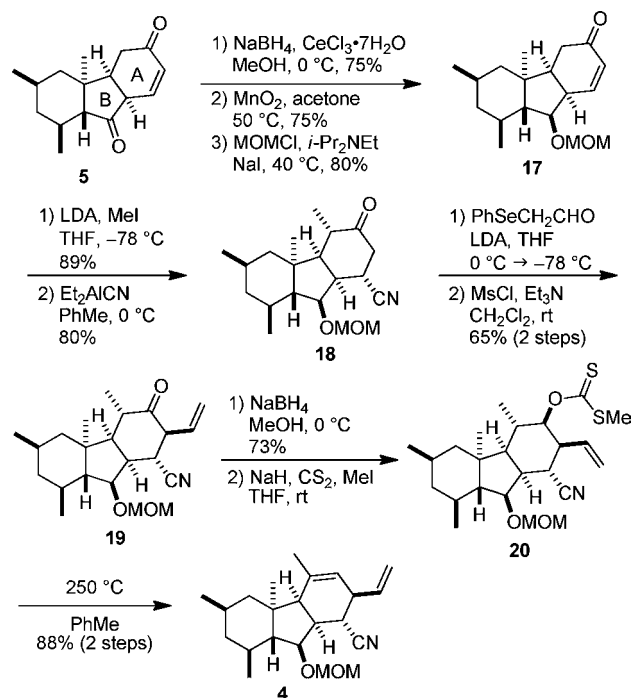
Figure 1. Proposed transition state for the Diels–Alder reaction.

Finally, the synthesis of decahydrofluorene **4** was accomplished (Scheme 5). The remaining task was to introduce the requisite substituents in a stereoselective manner to the A-ring moiety of **5**. Prior to the manipulation of the A-ring moiety, diketone **5** was stereoselectively reduced with NaBH₄ to afford the diol in 75% yield.²⁰ The resulting diol was then converted to enone **17** in two oxidation and protection steps. α -Methylation of ketone and conjugate addition of cyanide anion proceeded in a stereoselective manner to afford nitrile **18** in 71% overall yield for the two steps. The stereochemical course of the reaction can be well explained by considering the *cis*-fused AB ring. Installation of a vinyl group in the α -position of the ketone

(20) We also found that DIBALH reduction of diketone **5** afforded the diol **24** as a major isomer. In contrast to NaBH₄, the approach of bulky DIBALH from the convex face might be less favorable due to the presence of the angular methyl group. The present approach involves the Mitsunobu reaction for the formation of a 13-membered ring. The alternative Ullmann-type metal-catalyzed intramolecular arylation approach might also be possible using **24**.



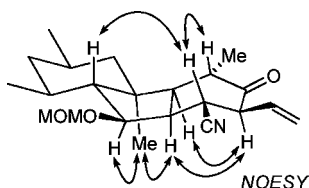
Scheme 5. Synthesis of Decahydrofluorene **4**



18 was best achieved by following the two-step procedure described by Clive and Russel.²¹ The aldol reaction of **18** with phenylselenoacetaldehyde gave the β -hydroxy ketone, which was converted to the β,γ -unsaturated ketone **19** upon treatment with methanesulfonyl chloride and triethylamine (65% yield from **18**). It was gratifying to find that the stereochemistry of the vinyl group was the same as that of pyrrocidines.²² This result indicates that phenylselenoacetaldehyde approached from the concave face of lithium enolate derived from **18**. We reasoned that the cyano group occupies a pseudoaxial orientation to avoid the 1,2-allylic strain and shields the convex face of

(21) Clive, D. L. J.; Russell, C. G. *J. Chem. Soc., Chem. Commun.* **1981**, 434.

(22) The relative stereochemistry of **19** was elucidated by measurement of NOESY correlations.



(23) Our explanation was supported by the conformational analysis of trimethylsilyl enolate derived from **18**. The strong NOE interaction between H-1 and H-2 was observed.

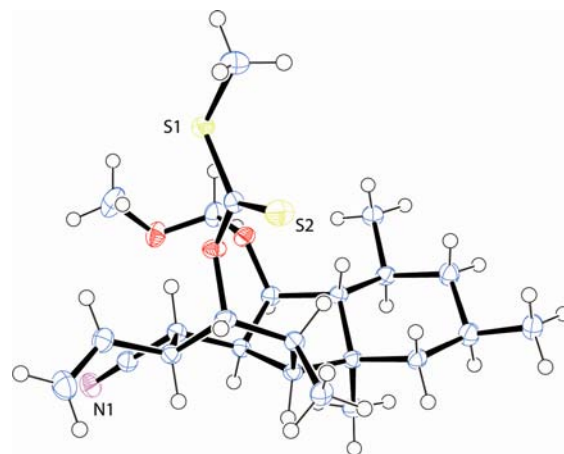
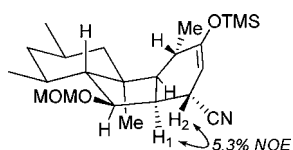


Figure 2. X-ray crystallography of xanthate **20**.

the enolate.²³ The β,γ -unsaturated ketone moiety was converted to the pyrrocidine-type unconjugated diene as follows. The ketone was reduced by sodium borohydride, and the resulting β -alcohol was regioselectively dehydrated by the Chugaev method²⁴ to furnish the decahydrofluorene **4** (64% yield from **19**). The relative configuration of the intermediate xanthate **20** was unambiguously determined through its X-ray crystallographic analysis (Figure 2).²⁵

In conclusion, we have accomplished the synthesis of the fully elaborated tricyclic decahydrofluorene core (ABC-ring system) of pyrrocidines. Our results are significant for the following reasons: (i) the present synthesis provides the first entry to an ABC-ring moiety of pyrrocidines, and (ii) Diels–Alder reaction using two Danishefsky dienes was employed to build the 6–5–6 tricyclic carbon skeleton. On the basis of the present results, further investigation toward the total synthesis of pyrrocidines is currently underway.

Acknowledgment. This research was supported in part by a Grant-in-Aid for Scientific Research (B) (KAKENHI No.22390004) from the Japan Society for the Promotion of Science.

Supporting Information Available. Experimental details, ¹H and ¹³C NMR spectra for all new compounds, and X-ray data for the xanthate (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

(24) (a) Chugaev, L. (Tschugaeff). *Chem. Ber.* **1899**, 32, 3332. (b) Depuy, C. H.; King, R. W. *Chem. Rev.* **1960**, 60, 431. (c) Nace, H. R. *Org. React* **1962**, 12, 57.

(25) CCDC 894936 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

The authors declare no competing financial interest.