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# Total Synthesis of GKK1032A$_2$ *via* Direct 13-Membered Macrocyclization Utilizing Aromatic Nucleophilic Substitution of an $\eta^6$-Arene Chromium Complex

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**Abstract:** The first enantioselective total synthesis of GKK1032A$_2$ has been achieved. The key step is direct construction of the highly strained 13-membered macrocycle of GKK1032A$_2$ by an intramolecular aromatic substitution ($S_NAr$) reaction. To the best of our knowledge, this is the first successful example of construction of a macrocycle with an aryl ether linkage utilizing an intramolecular $S_NAr$ reaction of an $\eta^6$-arene chromium complex.

Recently, decahydrofluorene-class natural products such as GKK1032A$_2$ (**1**), Pyrrocidine A (**2**), Hirsutellone B (**3**), Embellicine A (**4**) have been discovered[1,2] (Figure 1). Over a decade and a half, many researchers have studied the synthesis of these natural products because of their fascinating biological activities and synthetically challenging chemical structures.[3] However, the total synthesis of Hirsutellones have only been achieved because construction of their highly strained 13-membered macrocycles with bent benzene rings is still a difficult problem. In 2009, Nicolaou *et al.* reported the first total synthesis of Hirsutellone B (**3**).[4] In this study, the construction of the 13-membered macrocycle was achieved by the Ramberg-Bäcklund reaction of a less strained 14-membered cyclic sulfone. On the contrary, we achieved the first direct macrocyclization utilizing intramolecular Ullmann C–O coupling reaction, and the second total synthesis of Hirsutellone B (**3**) was reported in 2011.[5] Thereafter, Sorensen *et al.* also achieved macrocycle construction together with formation of a decahydrofluorene skeleton by their original approach.[6]

Total synthesis of GKK1032A$_2$ (**1**) is a more difficult problem because the compound has two quaternary chiral centers at the C3 and C7 positions, and, in contrast to Hirsutellones, its ether linkage at the C13 position is on the sterically more hindered $\alpha$-side of the decahydrofluorene core. GKK1032A$_2$ (**1**) was discovered as the first decahydrofluorene class of natural products with antitumor activity from the culture broth of *Penicillium* sp. GKK1032 in 2001 by researchers of Kyowa Hakko Kogyo Co. Ltd.[1a] Its unique chemical structure has received much attention from researchers in the field of biosynthesis. In 2003, Oikawa proposed a biosynthetic pathway for GKK1032A$_2$ (**1**) based on detailed studies using isotopically labeled precursors.[7] Nay *et al.* also discussed several alternative biosynthetic pathways for the decahydrofluorene skeleton.[3] Synthetic studies of GKK1032A$_2$ (**1**) have been extensively reported by Kuwajima's, Katoh's, and Tadano's groups.[8-10] These three groups independently achieved the synthesis of the decahydrofluorene core. Recently, Tadano *et al.* has also been successful in the construction of the 13-membered macrocycle by means of conjugated addition of nitroalkane to an enone;[10b] however, total synthesis utilizing the partially functionalized macrocycle has not been reported to date The strategy for functional group manipulations after construction of the macrocycle is also crucial. In the meantime, we have also achieved synthesis of the decahydrofluorene core using a sequential retro Diels–Alder and intramolecular Diels–Alder (retro-DA-IMDA) reaction.[11] In this study, we report the first total synthesis of GKK1032A$_2$ (**1**) *via* direct construction of the 13-membered macrocycle by intramolecular nucleophilic aromatic substitution utilizing an $\eta^6$-arene chromium complex.

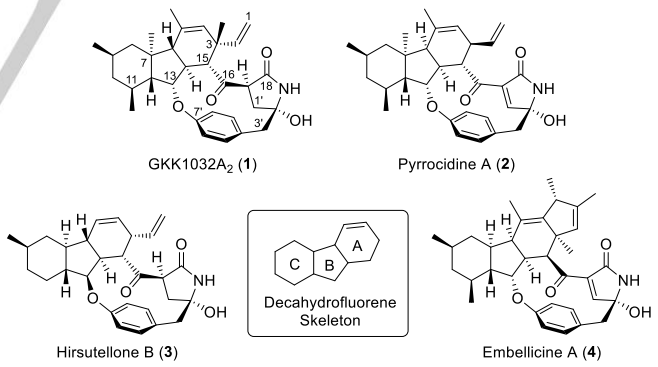


**Figure 1.** Decahydrofluorene-class natural products.

As described above, we have achieved synthesis of the decahydrofluorene core of GKK1032A$_2$ (**1**) in 2011.[11] We then expected that the 13-membered macrocycle could be constructed in a similar manner to our total synthesis of Hirsutellone B (**3**).[5] Actually, an intramolecular Ullmann C-O coupling reaction[12] of the preliminarily prepared precursor **5** was conducted as shown in Scheme 1.

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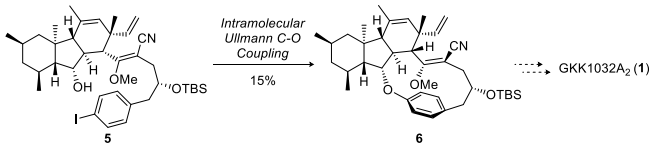



**Scheme 1.** Our preliminary study of construction of the 13-membered macrocycle of GKK1032A$_2$ (**1**) by use of an intramolecular Ullmann C-O coupling reaction.

However, the yield of the desired macrocycle (15%) is lower than that of our total synthesis of Hirsutellone B (**3**), likely due to the poor reactivity of the C13-hydroxyl group on the sterically hindered α-side of the decahydrofluorene core. On the contrary, through a synthetic study of an unnatural-type isomer of Hirsutellone B (**3**),[13] we are convinced that a π–π interaction on the precursor between the enol ether moiety and the benzene ring plays an important role in the 13-membered macrocyclization by stabilizing its transition state.[14] However, the energetic benefit may be reduced by the higher reaction temperature of the Ullmann C–O coupling reaction, leading to our interest in the intramolecular nucleophilic aromatic substitution by use of an $\eta^6$-arene chromium complex. These types of chromium complexes show higher reactivity for nucleophilic substitution *via* an addition/elimination ($S_NAr$) pathway under the mild condition of room temperature,[15,8] and their complexed aromatic rings easily create π–π interactions with other π–electron systems. The observed π–π interactions was also applied to an asymmetric reaction[16] and was proved successful *via* X-ray crystallographic analysis.[17] The interactive properies of $\eta^6$-arene chromium complexes are favorable for our desired 13-membered macrocyclization because its transition state would be largely stabilized by an enhanced π–π interaction between the enol ether moiety and the complexed aromatic ring (Figure 2).

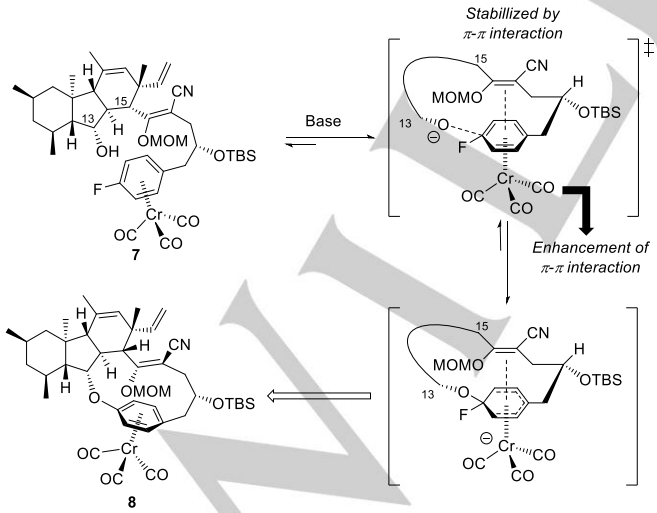



**Figure 2.** Our straTotal Synthesis of GKK1032A$_2$ via Direct 13-Membered Macrocyclization Utilizing Aromatic Nucleophilic Substitution of an η$^6$-Arene Chromium Complextegy for the direct construction of 13-membered macrocycle.

Our retrosynthetic analysis is shown in Figure 3. GKK1032A$_2$ (**1**) would be obtained by the formation of the γ-hydroxylactam moiety from ketoamide **9**, prepared from macrocycle **10** *via* several functional group transformations. The 13-membered macrocycle of **10** would be directly constructed by intramolecular nucleophilic aromatic substitution between the aliphatic secondary hydroxyl group at the C13 position and the $\eta^6$-arene complexed aryl fluoride moiety. On this cyclization, utilizing precursor **7** that has an *R*-configured chiral center at C19 position should be crucially important for stereoselective construction of the γ-hydroxylactam moiety. The point chirality at this position was revealed to be completely transferred to the point chirality of the γ-position on the lactam ring *via* the planar chirality of the enol ether moiety through the macrocyclization process of our total synthesis of Hirsutellone B (**3**), as shown in Figure 4.[5] The requisite cyclization precursor **7** would be prepared by Knoevenagel condensation of previously reported decahydrofluorene compound **12**[11] with a Cr(CO)$_3$-complexed α-siloxyaldehyde **13**.

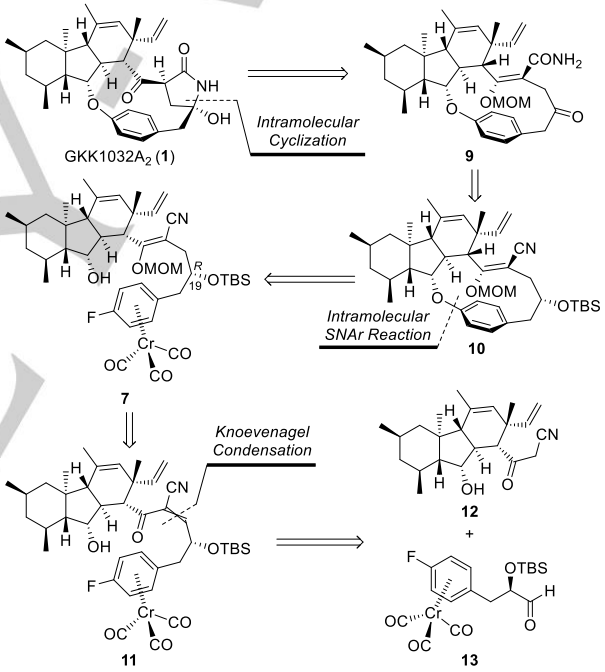



**Figure 3.** Retrosynthetic analysis of GKK1032A$_2$ (**1**).

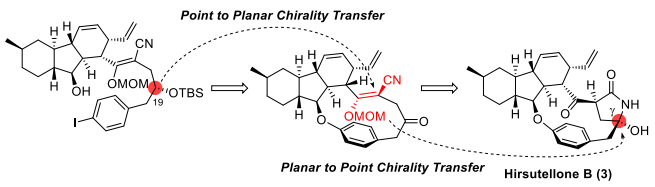
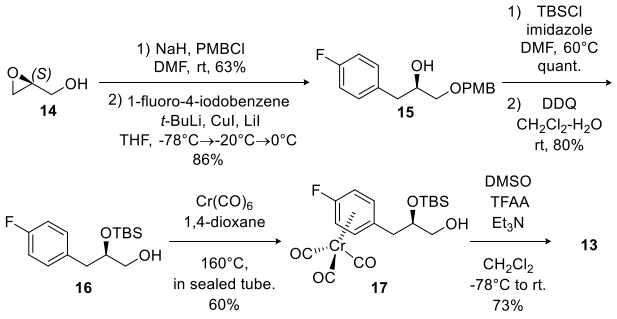


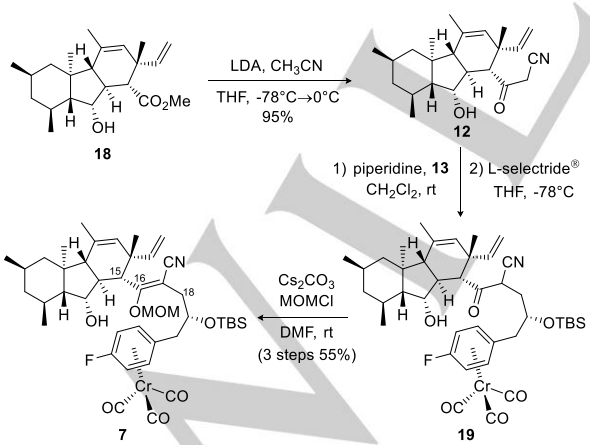

**Figure 4.** Our developed chirality-returning sequence on the total synthesis of Hirsutellone B (**3**)

First, we commenced the preparation of $Cr(CO)_3$-complexed α-siloxyaldehyde **13**[18] (Scheme 2). After *p*-methoxybenzyl (PMB) protection[19] of (*S*)-glycidol **14**, the obtained epoxide was subjected to addition with organocuprate prepared from 1-fluoro-4-iodobenzene to give alcohol **15**. The resulting secondary hydroxyl group was protected with a *tert*-butyldimethylsilyl (TBS) group and subsequent deprotection of the PMB group afforded primary alcohol **16**. Alcohol **16** was transformed into the corresponding $\eta^6$-arene complex **17** by a treatment with chromium hexacarbonyl ($Cr(CO)_6$)[20] in moderate yield, and subsequent oxidation under Swern conditions to afforded the desired $\eta^6$-arene complexed aldehyde **13**.




**Scheme 2.** Synthesis of $Cr(CO)_3$-complexed γ-siloxyaldehyde **13**. PMBCl = *p*-methoxybenzyl chloride. TBSCl = *tert*-butyldimethylsilyl chloride. DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone. TFAA = trifluoroacetic anhydride.

Next, synthesis of cyclization precursor **7** was investigated (Scheme 3). Previously reported hydroxylester **18**[11] was subjected to condensation with acetonitrile under basic conditions to afford ketonitrile **12**. After Knoevenagel condensation of ketonitrile **12** with aldehyde **13**, the resulting unsaturated bond was selectively reduced by L-selectride®. The following enol ether formation under basic conditions gave the desired cyclization precursor **7** as the *E*-isomer only. [21]




**Scheme 3.** Synthesis of cyclization precursor **7**. LDA = Lithium diisopropyl amide. MOMCl = Chloromethyl methyl ether.

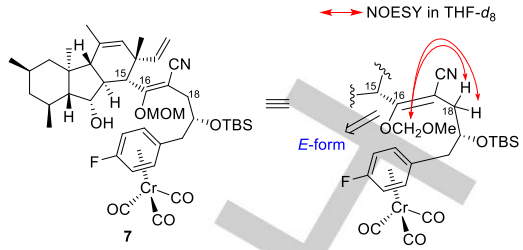



**Figure 5.** NOESY spectrums of cyclization precursor **7**.

With desired precursor **7** in hand, 13-membered macrocyclization using aromatic nucleophilic substitution between the C19-hydroxyl group and $Cr(CO)_3$-complexed aryl fluoride moiety was attempted. We first examined the reaction under general conditions similar to aromatic substitution of $\eta^6$-arene chromium complexes, that is, sodium hydride was used as a base in THF (Table 1, Entry 1);[15a] however, the desired macrocyclization did not proceed. We next employed *N*,*N*-dimethylformamide as a more polar solvent (Entry 2), but decomplexation of the aryl fluoride moiety was exclusively observed, likely due to instability of the $Cr(CO)_3$ complex in such a highly coordinating solvent. Therefore, 18-crown-6 was used with sodium hydride to generate a more nucleophilic naked anion.[22] As a result, macrocyclization proceeded at high temperature but the yield of the desired macrocycle **10** was miserably poor (10%, including the next decomplexation step). In contrast, use of potassium hydride as a substitute base resulted in the reaction proceeding smoothly at lower temperature and the yield of desired macrocycle **10** was greatly improved, up to 91% (in 2 steps). Although the precise cause of the observed remarkable improvement has not yet been revealed, a computational conformation study of the non-complexed cyclization precursor suggested the existence of a hydrogen bond between the C13 hydroxyl group and one of the oxygen atoms of the MOM enol ether moiety. As a result of this strong hydrogen bonding, undesirable lowering of the acidity of the C13 hydroxyl group occurred and a stronger base would be required for deprotonation.[23]

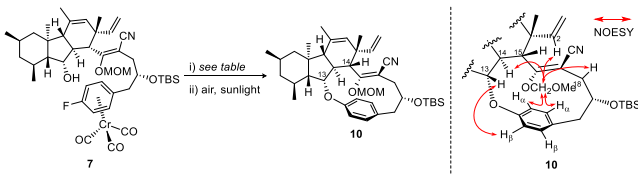


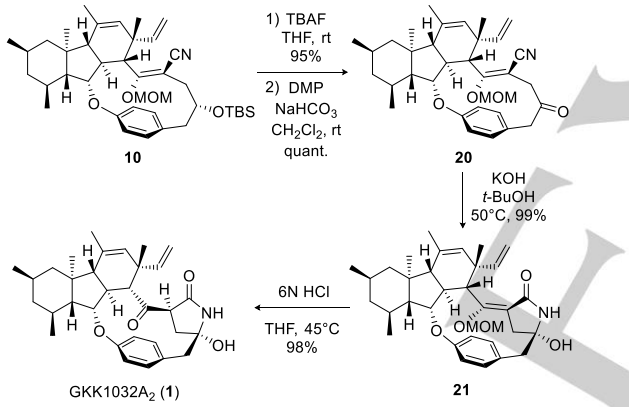

**Table 1.** Conditions for the intramolecular $S_NAr$ reaction.

| Entry | Condition[a] | Result |
|---|---|---|
| 1 | NaH, THF, reflux | NR |
| 2 | NaH, DMF, 60°C | decomplexation |
| 3 | NaH, 18-crown-6, THF, reflux | 10% (2 steps) |
| 4 | KH, THF, rt | 91% (2 steps) |

[a] Reactions were conducted in 0.006[M].

Several remaining functional group transformations were conducted to achieve the total synthesis of GKK1032$A_2$ (**1**) (Scheme 4). Deprotection of the TBS group at the C19 position

and following oxidation of the resulting alcohol using Dess–Martin periodinane afforded the corresponding ketone **20**, quantitatively. The nitrile group of **20** was then converted to the amide group by treatment with an excess amount of potassium hydroxide in *tert*-butanol. In our reaction conditions, an intramolecular attack of the resulting amide group to the C13-ketone group afforded the corresponding γ-hydroxylactam **21**. Importantly, the cyclization process proceeded in a completely stereoselective manner, similar to our total syntheses of Hirsutellone B (**3**) and its unnatural-type isomer[5,13]. Finally, deprotection of the MOM enol ether moiety was conducted under acidic conditions and the desired final product was obtained in high yield. All of the obtained spectroscopic data ($^1$H-NMR, $^{13}$C-NMR, HRMS, IR, and $[\alpha]_D$) of the final product were in full agreement with those reported for the naturally occurring substance.[24] In addition, the positive $[\alpha]_D$ value of our synthetic sample established the absolute configuration of the natural product to be as depicted. Thus, the first total synthesis of GKK1032A$_2$ (**1**) was successfully accomplished. To the best of our knowledge, this work is the first successful example of the construction of a macrocyclic with an aryl ether linkage using nucleophilic aromatic substitution of an $\eta^6$-arene-type chromium complex.




**Scheme 4.** End game of total synthesis of GKK1032A$_2$ (**1**). TBAF = tetrabutylammonium fluoride. DMP = Dess–Martin periodinane.

In conclusion, we developed a new effective method for direct construction of the highly-strained 13-membered macrocycle of a decahydrofluorene-class of natural products. The method is based on the nucleophilic aromatic substitution utilizing an $\eta^6$-arene chromium complex, a process not previously used for macrocyclization of an aryl ether linkage. We believed that the above described remarkable improvement of the 13-membered macrocyclization is depend on the enhancement of intramolecular π–π interaction between chromium complexed aromatic ring and enol ether moiety of the cyclization precursor. Therefore, we would like to prove the existence of the interaction by further crystallographic or computational investigations. The developed macrocyclization is strongly thought to be useful for synthesis of other more complicated decahydrofluorene-class natural products that have fascinating biologically activities such as Pyrrocidine A (**2**) and Embellicine A (**4**). These challenging total synthesis are now in progress and will be reported in the near future.

## Experimental Section

The synthetic procedures and characterization of the compounds studied herein can be found in the Supporting Information.

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**Keywords:** gkk1032A$_2$ • total synthesis • direct 13-membered macrocyclization • Cr(CO)$_3$-arene complex • π–π interaction

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[21] The geometry of the enol ether moiety of cyclization precursor **7** was determined by noesy spectrum as shown in Scheme 3.

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[24] $^{1}$H and $^{13}$C-NMR spectrum of GKK1032A$_2$ (**1**) were taken by Kyowa Hakko Kogyo Co. Ltd. through the courtesy of Professor Hideaki Oikawa, Hokkaido University.

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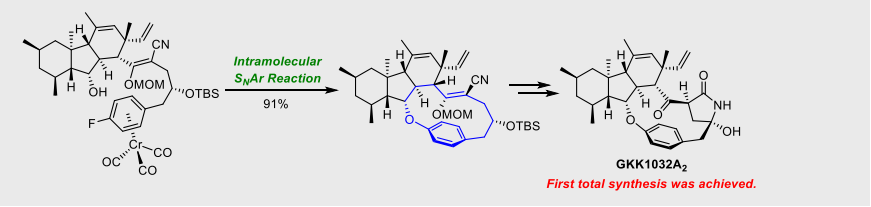
Layout 2:

# COMMUNICATION

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