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Total syntheses of (±)-musellarins A–C†

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The first, diastereoselective total syntheses of musellarins A–C were achieved concisely with 7.8–9.8% yields in 15–16 steps. The key synthetic features include (i) an Achmatowicz rearrangement, Kishi reduction, and Friedel–Crafts cyclization to construct the tricyclic framework and (ii) Heck coupling of aryldiazonium salts to introduce the aryl group into the dihydropyran in a 2,6-*trans* fashion in the final stage of synthesis.

Diarylheptanoid natural products are a family of secondary plant metabolites isolated from various sources, featuring the structural motif of a seven-carbon linkage of two aromatic rings.[1] Many diarylheptanoids displayed potent biological activities such as antioxidant, anticancer, antibacterial, antifungal, antiosteoporosis, antihepatotoxicity, and melanogenesis inhibition, and therefore have been increasingly recognized as potential therapeutic agents.[1] Among over 400 known diarylheptanoid natural products, musellarins A–E (Fig. 1) represent an unusual structural class for the presence of the rare bicyclic tetrahydropyran motif. Musellarin A was reported in 2002 by Kinghorn[2] and co-workers from hybrid plant fruits of *musa* × *paradisiaca* in Peru as the first example of diarylheptanoids containing such a bicyclic functionality, which had been established by extensive NMR studies and confirmed by single crystal X-ray diffraction analysis. In 2011, musellarin A was isolated again by Zhao[3] and coworkers from monotypic plant *Musella lasiocarpa* in Yunan, China, in 0.0006% yield (18 mg from 3 kg of dry plant materials). Zhao *et al.* also obtained several new congeners of musellarin A: musellarins B–E containing this rare bicyclic skeleton. Although the biological activities of musellarins C–E have not been reported, musellarin A significantly induced quinone reductase activity against Hepa1c1c7 cells,[2] and musellarin B has shown moderate cytotoxicity against several cancer cell lines including HL-60 (IC_{50} 21.3 μM), SMMC-7721 (IC_{50} 26.7 μM) and A-549 (IC_{50} 25.1 μM).[3] The potential bioactivity and unusual structures of musellarins within the family of diarylheptanoids prompted us to undertake their synthetic studies. Herein, we report the first total syntheses of musellarins A–C featuring a late stage stereoselective installation of the second aryl group *via* Heck coupling of aryl diazonium salts.

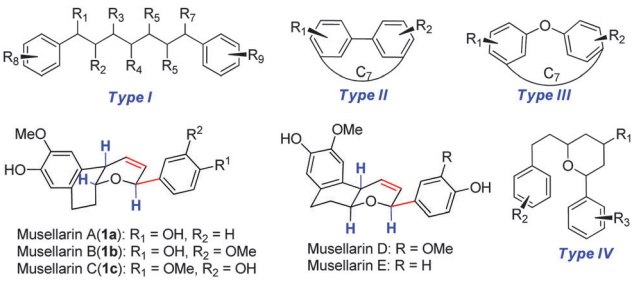

Fig. 1 Musellarins and other types of diarylheptanoids.

Retrosynthetically (Scheme 1), we planned to introduce the aryl group with different substituents *via* Heck coupling of enol ether **2** and aryl diazonium salts,[4] which was expected to simultaneously deliver the desired stereochemistry at C2 and an appropriate double bond at C3–C4. It was noted that the similar Heck couplings yielding the 2,6-*trans* disubstituted tetrahydropyran with excellent diastereoselectivity has been elegantly exploited by Schmidt in the total synthesis of centrolobine and various diarylheptanoid analogues (Type IV, Fig. 1).[5] The enol ether **2** could be prepared from ketone **3** *via* Pd-catalyzed reduction of its corresponding enol triflate. The ketone **3** was envisioned to be derived from intramolecular Friedel–Crafts cyclization[6] of γ-aryl enone **4**, which could be readily synthesized from furfuryl alcohol **6** through Achmatowicz rearrangement[7] and Kishi reduction.[8] Wittig olefination of **7** and **8** would deliver the requisite alcohol **6** after hydrogenation.

Our synthesis (Scheme 2) began with preparation of alcohol **10**, which was obtained in an excellent yield from commercially available isovanillin **9** by protection of the alcohol as triisopropylsilyl ether and reduction of the resulting aldehyde with $NaBH_4$. The alcohol **10** was

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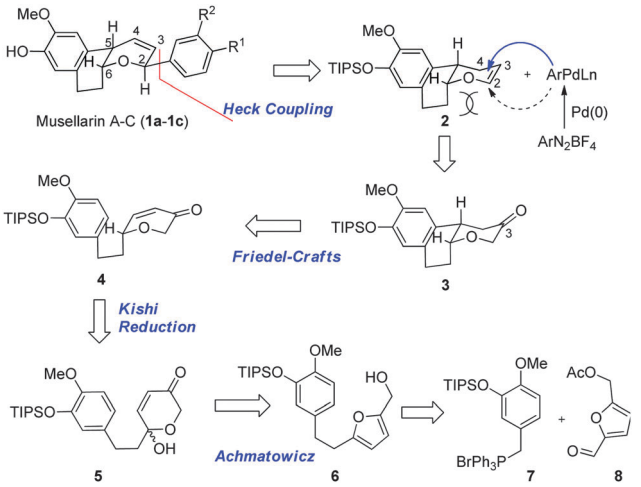
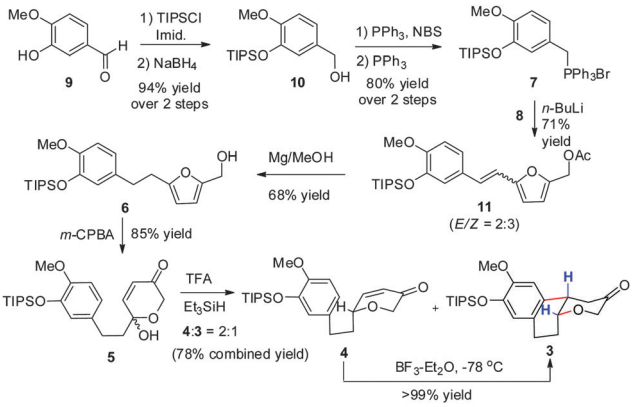


Scheme 1 Retrosynthetic analysis of musellarins A–C.



Scheme 2 Synthesis of the tricyclic compound **3**.

then converted into the phosphonium salt **7** in two straightforward steps. Wittig olefination of aldehyde **8** and phosphorus ylide generated *in situ* from **7** produced a 2 : 3 *E*/*Z* mixture of alkene **11** in 71% yield. The subsequent hydrogenation of **11** with Pd/C in methanol (or ethyl acetate), however, resulted in a rather complex mixture, partially due to over-reduction. Gratifyingly, we found that magnesium[9] (turnings) in methanol at room temperature could effectively saturate the double bond with concomitant deacetylation[10] to provide the furfuryl alcohol **6** in 68% yield. Achmatowicz rearrangement of **6** was smoothly promoted by *m*-CPBA at 0 °C to provide the dihydropyranone hemiacetal **5** in 85% yield. Kishi reduction of **5** using a classical combination of trifluoroacetic acid and triethylsilane generated a 2 : 1 mixture of dihydropyranone **4** and a surprising Friedel–Crafts cyclization adduct **3** in 78% combined yield.

As we had planned in our design stage, the intramolecular Friedel–Crafts cyclization of dihydropyranone **4** occurred in the presence of BF_3–Et_2O at −78 °C to provide the tricyclic compound **3** quantitatively, the structure of which was unambiguously confirmed using X-ray diffraction analysis (Fig. 2).

Encouraged by the unexpected result that Kishi reduction/Friedel–Crafts cyclization could occur in a one-pot manner, we

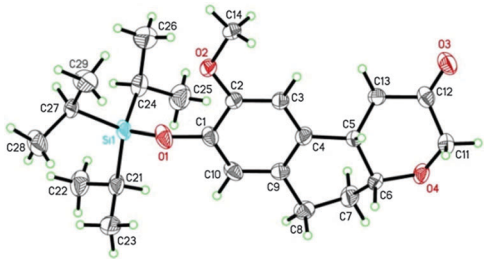


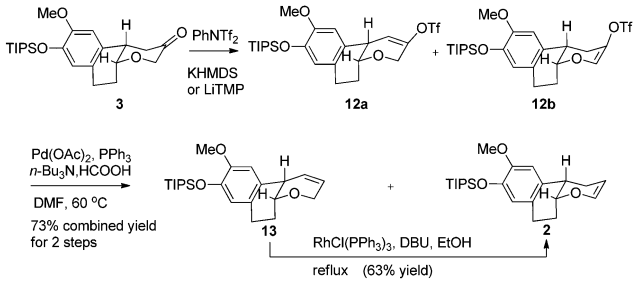
Fig. 2 ORTEP diagram of compound **3**.

Table 1 Attempted conditions for one-pot Kishi reduction and intramolecular Friedel–Crafts cyclization[a]

Entry	Acid (equiv.)	R_3SiH (equiv.)	Temp. (°C)/time (h)	Ratio[b] (4 : 3)	Yield[c] (%)
1	TFA (10)	Et_3SiH	−40/1	2 : 1	78
2	TFA (10)	i-Pr_3SiH	−40/1	1 : 1	41
3	TFA (10)	Et_3SiH	−40/12	Complex	N/A
4	BF_3–Et_2O (2)	Et_3SiH	−78/1	14 : 1	74
5	BF_3–Et_2O (5)	Et_3SiH	−78/5	Complex	N/A
6	BF_3–Et_2O (0.5)	Et_3SiH	−78 → rt/24	5 : 1	45
7	TMSOTf (1)	Et_3SiH	−78/1	Complex	N/A
8	TESOTf (0.3)	Et_3SiH	−78/3	Complex	N/A
9	TBSOTf (0.3)	Et_3SiH	−78/3	Complex	N/A
10	$TiCl_4$ (1.2)	Et_3SiH	−78/1	0 : 1	30
11	$SnCl_4$ (1)	Et_3SiH	−78/1	Complex	N/A

[a] The reaction was run with 20 mg of compound **5**. [b] Ratio was determined by NMR analysis of the crude reaction mixture. [c] Combined yield after flash column chromatography on silica gel. Notes: TFA: trifluoroacetic acid. TMSOTf: trimethylsilyl trifluoromethanesulfonate. TESOTf: triethylsilyl trifluoromethanesulfonate. TBSOTf: *tert*-butyldimethylsilyl trifluoromethanesulfonate.

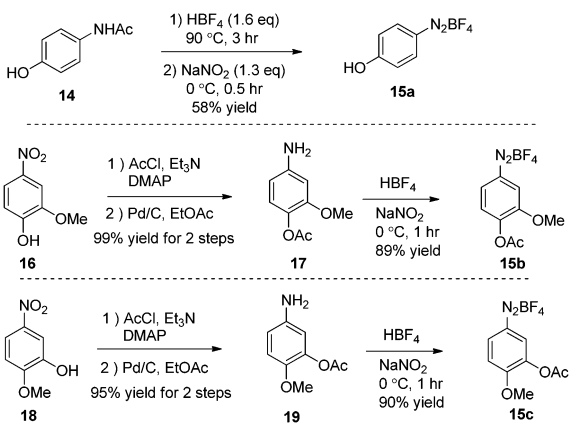
attempted to improve the yield of **3** in the one-pot process (Table 1). Under the classical Kishi reduction conditions reported previously (entries 1 and 4), TFA (or BF_3–Et_2O) and triethylsilane gave the dihydropyranone **4** as the major product in a good yield if the reaction was quenched within 1 h. Extending the reaction time (entry 3) or excess equivalent of BF_3–Et_2O (entry 5) did not lead to any further conversion of **4** to **3**. Instead, significant decomposition was observed. When the bulkier triisopropylsilane (entry 2) was used as the hydride donor, intramolecular Friedel–Crafts cyclization produced a 1 : 1 mixture of **4** and **3** in a low combined yield. Since other conditions employing triisopropylsilane and phenyldimethylsilane did not give a better yield of **3**, triethylsilane was used in further attempts. Reducing the equivalent of BF_3–Et_2O (entry 6) slowed the reduction and cyclization considerably, which required an elevated temperature and a longer reaction time for complete consumption of **5** but gave a lower yield as compared to entry 4. Other strong Lewis acids (entries 7–9, and 11) resulted in decomposition with a trace amount of desired compounds **3** or **4**. Interestingly, $TiCl_4$–Et_3SiH gave the tricyclic compound **3** exclusively in 30% yield. Unfortunately, the overall yield was synthetically too low and could not be improved under various conditions. It appeared to us that two-step operations would be the choice: Kishi reduction with TFA/Et_3SiH or BF_3–Et_2O/Et_3SiH (entries 1 and 4) and independent Friedel–Crafts cyclization with BF_3–Et_2O as shown in Scheme 2.



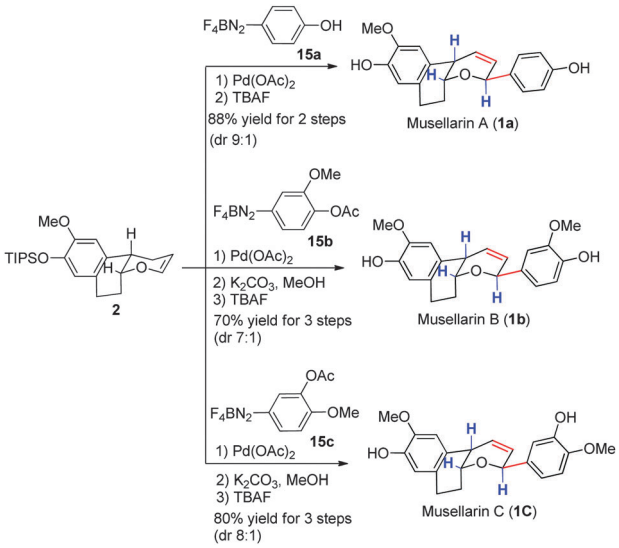
Scheme 3 Synthesis of the key intermediate enol ether **2**.

Next, we directed our attention to synthesize the tricyclic enol ether **2** *via* a two-step deoxygenation[11] of ketone **3** (Scheme 3). To this end, ketone **3** needed to be regioselectively deprotonated with a base to generate an enol anion, which would be triflated with $PhNTf_2$. However, treatment of ketone **3** with $PhNTf_2$ and a bulky base such as KHMDS or LDA at −78 °C led to exclusive formation of vinyl triflate **12a** in good yield.[12] When the more sterically demanding base LiTMP was used, a regiomeric mixture of **12a** and **12b** could be obtained in a lower yield (40–50%) with a 1 : 1 ratio of diastereomers, which could not be easily separated by column chromatography. In view of the difficulty in efficient preparation of the enol triflate **12b** using this straightforward method, we set out to explore the possibility of olefin isomerization[13] for the synthesis of enol ether **2** from **12a**. First, vinyl triflate **12a** was transformed into alkene **13** in an excellent yield by palladium-catalyzed reduction.[11] To our delight, the isomerization of **13** with the Wilkinson catalyst[14] in the presence of DBU proceeded smoothly upon refluxing to provide enol ether **2** in 63% yield, which served as the common key intermediate for the synthesis of musellarins A–C *via* Heck coupling with aryl diazonium salts.

Three aryl diazonium salts (**15a–c**), corresponding to musellarins A–C, were prepared (Scheme 4) by using similar protocols in the literature.[5] Specifically, acetaminophen (**14**), a widely used over-the-counter analgesic, could be successfully transformed into the aryl diazonium salt **15a**[5e] with 58% yield in two steps. The preparation of aryl diazonium salts **15b** and **15c** could be achieved in excellent yields from **16** and **18**, respectively, *via* a three-step sequence: acetylation, palladium-catalyzed reduction of nitro group to amine, and diazotization. It was noteworthy that acetyl protection of the phenol was essential to the success since 4-amino-phenols derived from direct reduction of nitrophenols (**16** and **18**) were unstable and could not be converted to the corresponding diazonium salts.



Scheme 4 Synthesis of the aryl diazonium salts.



Scheme 5 Completion of total syntheses of musellarins A–C.

With both coupling partners in hand, we then explored the Heck coupling using the conditions developed by Schmidt[5] (Scheme 5). Gratifyingly, the Heck reaction of the enol ether **2** with aryl diazonium salts **15a–c** using $Pd(OAc)_2$ as a precatalyst occurred smoothly to provide the corresponding coupling products, which were immediately subjected to desilylation with TBAF and/or deacetylation with K_2CO_3/MeOH to furnish musellarins A–C, respectively, in excellent yields with good diastereoselectivity (dr 7 : 1–9 : 1). Separation of the musellarins A–C from their minor diastereomers by preparative TLC (silica gel) led to analytically pure musellarins A–C. All spectroscopic data of our synthetic samples were identical to those reported for natural musellarins A–C.[15]

In summary, we have accomplished the first concise total syntheses of musellarins A–C in the longest linear sequence of 15–16 steps from commercially available materials. The synthetic strategy was enabled by (i) exploitation of the Achmatowicz rearrangement, Kishi reduction and Friedel–Crafts alkylation to construct the tricyclic framework **3** with a *cis* ring conjunction and (ii) high-yielding Heck coupling of aryl diazonium salts in good *trans*-diastereoselectivity in the final stage of synthesis. Importantly, the flexibility and convergence of the synthetic route developed here would permit an expedient entry into musellarins and their analogues for further biological studies.

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