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Syntheses of (−)-Tatarinoid A, (±)-Tatarinoid B, and (−)-Tatarinoid C

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ABSTRACT

The syntheses of (−)-Tatarinoid A, (±)-Tatarinoid B, and (−)-Tatarinoid C in one to three steps are described herein. (−)-Tatarinoid A and (−)-Tatarinoid C are both constructed in three steps from 1-bromo-2,4,5-trimethoxybenzene in overall yields of 63% and 74%, respectively. The addition of (1-methoxyethyl)triphenylphosphonium ylide to 2,4,5-trimethoxybenzaldehyde provides (±)-Tatarinoid B in one step in 97% yield.

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(−)-Tatarinoids A, B, and C are 3 of 19 compounds that have been isolated from the rhizome of the plant *Acorus tatarinowii*.[1] Used in Chinese medicine, *Acorus tatarinowii* possesses pharmacological effects on the central nervous system by regulating cyclic adenosine monophosphate (cAMP) activity. For example, it is commonly prescribed for the improvement of learning and memory.[2] The major constituents of *Acorus tatarinowii*, sesquiterpenoids and phenylpropanoids, have been found to possess antiepileptic properties[2] as well as anticonvulsive,[3] spasmolytic,[4] and neuroprotective effects.[5] Although (−)-Tatarinoids B and C have shown weak efficacy and (−)-Tatarinoid A has not yet been evaluated for its activity we continued our efforts toward the syntheses of these natural products since currently there are no reported syntheses of (−)-Tatarinoids A, C, and (±)-Tatarinoid B. Herein we report expeditious routes toward these natural products.

As illustrated in Scheme 1, (−)-Tatarinoid A, and Tatarinoid C can be accessed from 1-bromo-2,4,5-trimethoxybenzene (**2a**). The required organolithium **2b** would be accessed through a metal halogen exchange between the aryl bromide (**2a**) and *n*-butyllithium.

In the case of (−)-Tatarinoid A it would be necessary to convert the TBS protected methyl (*R*)-lactate (**1a**) into the Weinreb amide (**1b**) in order to avoid the over addition of the aryllithium (**2b**) to the carbonyl and yield only the necessary ketone, a precursor to the natural product.[6]

Alternatively, the desired (−)-Tatarinoid C would employ the TBS protected methyl (*R*)-lactate (**1a**),[7] in order to allow for the over addition of the aryllithium (**2b**) and result in the formation of the tertiary alcohol precursor.

The synthesis of (−)-Tatarinoid A was shown to proceed in three steps from Weinreb amide **1b**[8,9] and aryl bromide **2a** (Scheme 2).[10] Formation of the aryllithium (**2b**) proceeded from the treatment of the aryl bromide (**2a**) with *n*-BuLi at −78 °C for 1 h. Initial investigations toward the total synthesis of (−)-Tatarinoid A included the addition of aryllithium to the TBS protected ester **1a**. The mono addition product, ketone **3**, was observed as a minor product. As expected, the over addition of the aryllithium yielded the tertiary alcohol (**4**) as the major product; the precursor to (−)-Tatarinoid C (Scheme 3).

To avoid the formation of the tertiary alcohol, we turned our attention toward the derivatization of the TBS protected ester **1a** to the Weinreb amide **1b**, synthesized from the treatment of ester **1a** with *N*,*O*-dimethylhydroxylamine hydrochloride salt and *i*-PrMgCl in THF. The reaction proceeded smoothly in 99% yield without purification. As predicted, the mono addition of the aryllithium to the amide resulted in the desired ketone, **3**, in an 81% yield, without any of the overaddition product observed. Finally, removal of the TBS protecting group with TBAF (tetrabutylammonium fluoride)[11] in THF, at 0 °C for 2 h, afforded (−)-Tatarinoid A in 78% yield. Assembly of the natural product was accomplished in three steps and with an overall yield of 63%.

The synthesis of (−)-Tatarinoid C employed a similar strategy to that of (−)-Tatarinoid A. In this case, the over addition of the aryllithium (**2b**) to the TBS protected ester (**2a**) was crucial to provide the desired tertiary alcohol **4** (Scheme 3). The reaction was accomplished using 3 equiv of both aryl bromide and *n*-BuLi to yield **4** in 88% yield. Treatment of the tertiary alcohol with $BF_3{\cdot}OEt_2$ and

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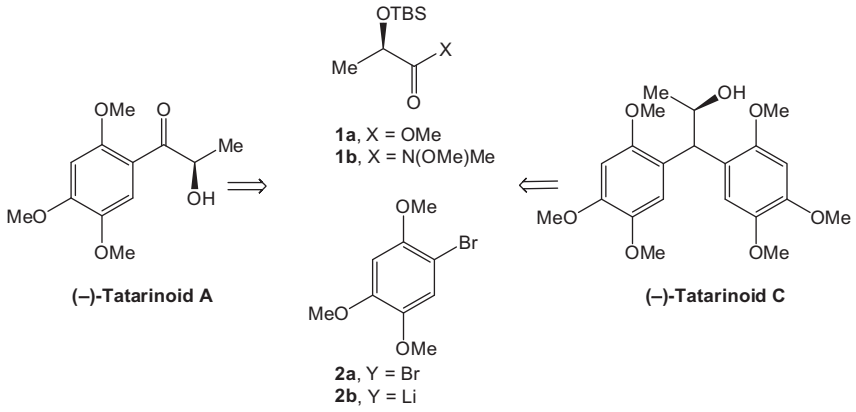
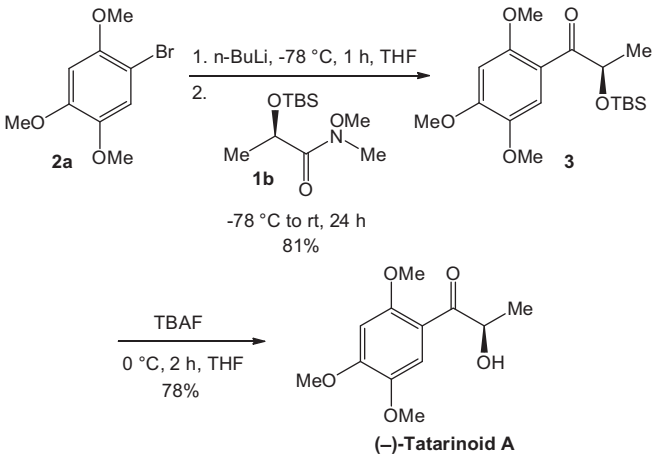


Scheme 1. Retrosynthesis of (−)-Tatarinoid A and (−)-Tatarinoid C.



Scheme 2. Synthesis of (−)-Tatarinoid A.

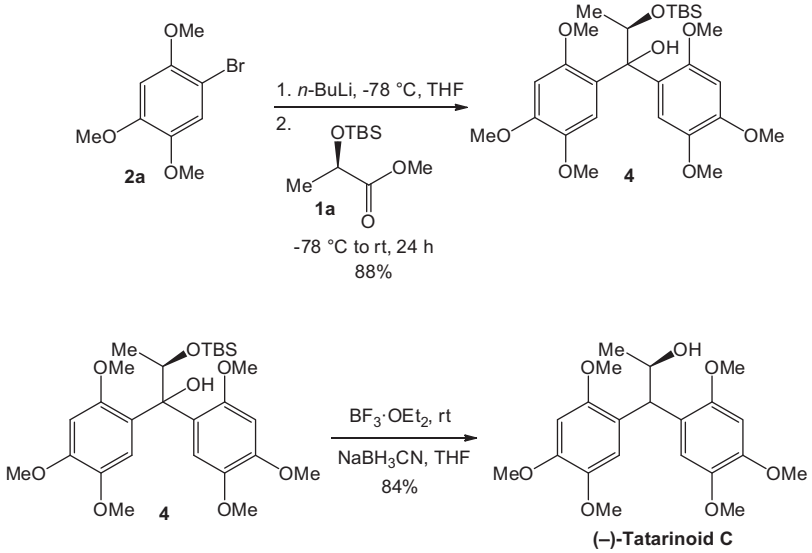
$NaBH_3CN$ at room temperature for 1 h was expected to only afford the desired deoxygenated product, which would then be treated with TBAF for the removal of the protecting group. However, the reaction afforded (−)-Tatarinoid C in 84% yield, suggesting that the excess $NaBH_3CN$ (3 equiv) permits for the reductive cleavage of the TBS group.[12,13] The resulting natural product, (−)-Tatarinoid C, was completed in three steps from 1-bromo-2,4,5-trimethoxybenzene (**2a**) and methyl (*R*)-2-(*tert*-butyldimethylsilyloxy)propionate (**1a**) with an overall yield of 74%.

A retrosynthetic overview of (±)-Tatarinoid B is illustrated in Scheme 4. It was expected that the racemic mixture of the natural product would be accessed in one step from an irregular Wittig reaction[14] using ylide (**5a**) and 2,4,5-trimethoxybenzaldehyde (**6**).[15]

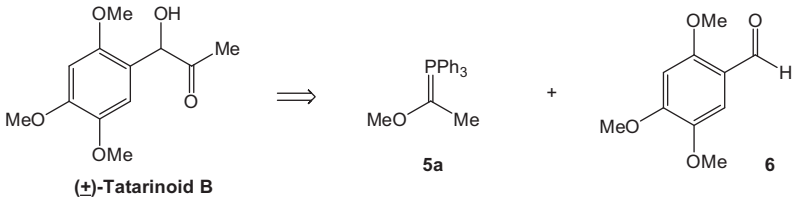
Indeed, treatment of (1-methoxyethyl)triphenylphosphonium salt (**5b**) with *n*-BuLi, for 20 min, provided the desired Wittig ylide **5a** that was then treated with 2,4,5-trimethoxybenzaldehyde (**6**) at −78 °C for 30 min to yield the racemic Tatarinoid B in 97% yield (Scheme 5). No sign of the typical Wittig product was observed.

Currently, we are turning our efforts toward the construction of (−)-Tatarinoid B in one step from a crossed acyloin condensation[16] between 2,4,5-trimethoxybenzaldehyde (**6**) and acetaldehyde using a chiral triazolium salt as a catalyst (Scheme 6, **7a**–**7e**).[17,18] These catalysts are not commercially available and are themselves constructed in five to six steps from methyl L-pyroglutamate. Our continued investigation on the total synthesis of (−)-Tatarinoid B, high yield and enantioselectivity, will be reported in due course.

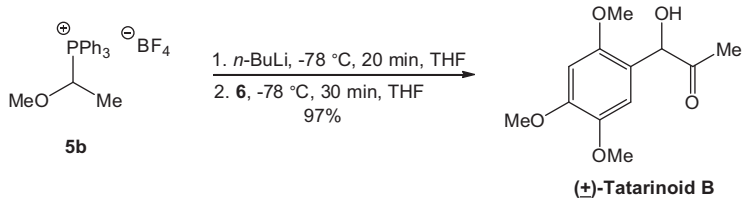
In conclusion, we have described the first total syntheses of (−)-Tatarinoids A and C and racemic Tatarinoid B. The synthesis of (−)-Tatarinoid A was accomplished in three steps with an overall yield of 63%. (±)-Tatarinoid B was constructed in one step in 97% yield



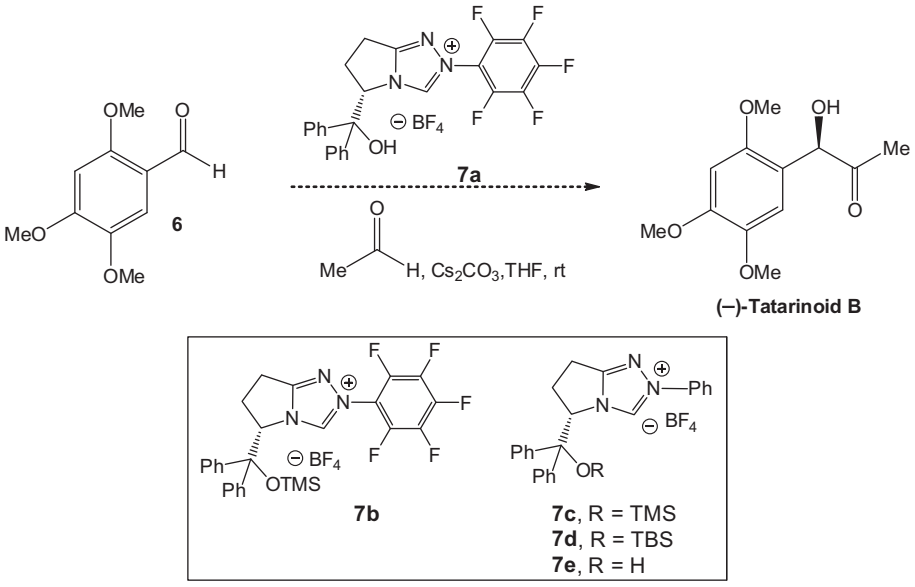
Scheme 3. Synthesis of (−)-Tatarinoid C.



Scheme 4. Retrosynthesis of (±)-Tatarinoid B.



Scheme 5. Synthesis of (±)-Tatarinoid B.



Scheme 6. Synthesis of (−)-Tatarinoid B.

while (−)-Tatarinoid C was also synthesized in three steps with an overall yield of 74%.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.10.104.

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