Graphical Abstract

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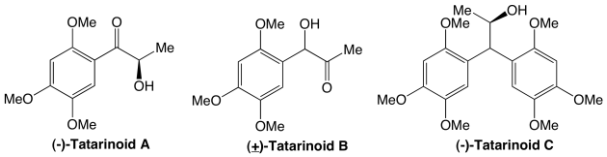

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Syntheses of (-)-Tatarinoid A, (±)-Tatarinoid B, and (-)-Tatarinoid C

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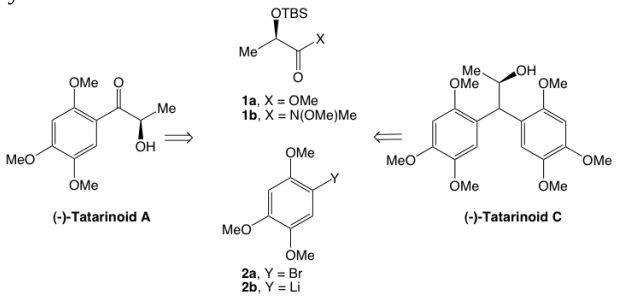
ABSTRACT

The syntheses of (–)-Tatarinoid A, (±)-Tatarinoid B, and (–)-Tatarinoid C in 1 to 3 steps are described herein. (–)-Tatarinoid A and (–)-Tatarinoid C are both constructed in 3 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 1 step in 97% yield.

(–)-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. Although (–)-Tatarinoids B and C have shown weak efficacy we continued our efforts towards 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 towards these natural products.

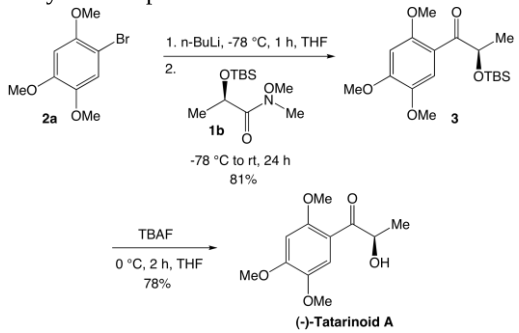
As illustrated in Scheme 1, (–)-Tatarinoid A, and Tatarinoid C can be accessed from 1-bromo-2,4,5-trimethoxybenzene (**2a**). The required organolithium **2b** would be accessed through a metal halogen exchange between the aryl bromide (**2a**) and *n*-butyllithium.



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

In the case of (–)-Tatarinoid A it would be necessary to convert the TBS protected methyl (*R*)–lactate (**1a**) to 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.[2]

Alternatively, the desired (–)-Tatarinoid C would employ the TBS protected methyl (*R*)–lactate (**1a**)[3], in order to allow for the over addition of the aryllithium (**2b**) and result in the formation of the tertiary alcohol precursor.



Scheme 2. Synthesis of (-)-Tatarinoid A

The synthesis of (–)-Tatarinoid A was shown to proceed in three steps from Weinreb amide **1b**[4,5] and aryl bromide **2a** (Scheme 2).[6] Formation of the aryllithium (**2b**) proceeded from the treatment of the aryl bromide (**2a**) with *n*-BuLi at —78 °C for

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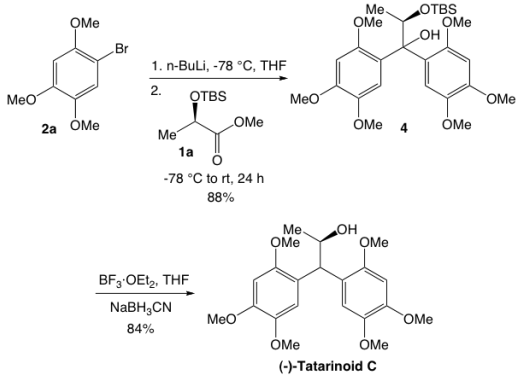
1 hour. Initial investigations towards the total synthesis of (–)-Tatarinoid A included the addition of aryllithium to the TBS protected ester **1a**. The mono addition product, ketone **3**, was observed as a minor product. As expected, the over addition of the aryllithium to yield the tertiary alcohol (**4**), the precursor to (–)-Tatarinoid C (Scheme 3), was the major product.

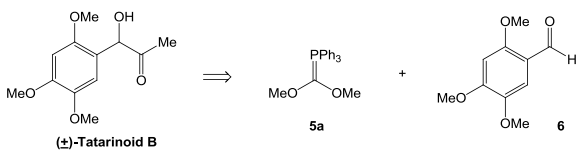
To avoid the formation of the tertiary alcohol, we turned our attention towards the derivatization of the TBS protected ester **1a** to the Weinreb amide **1b**, synthesized from the treatment of ester **1a** with *N,O*-dimethylhydroxylamine hydrochloride salt and *i*-PrMgCl in THF. The reaction proceeded smoothly in 99% yield without purification. As predicted, the mono addition of the aryllithium to the amide resulted in the desired ketone, **3**, in a 81% yield, without any of the overaddition product observed. Finally, removal of the TBS protecting group with TBAF (tetrabutylammonium fluoride)[7] in THF, at 0 °C for 2 hours, 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 equivalents 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 $NaBH_3CN$ at room temperature for 1 hour 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.[8,9] 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%.



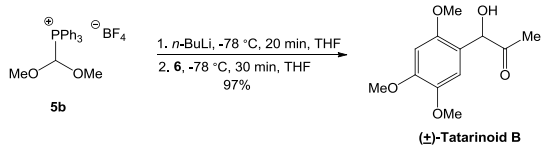
Scheme 3. Synthesis of (-)-Tatarinoid C

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 using ylide (**5a**) and 2,4,5-trimethoxybenzaldehyde (**6**).[10,11]



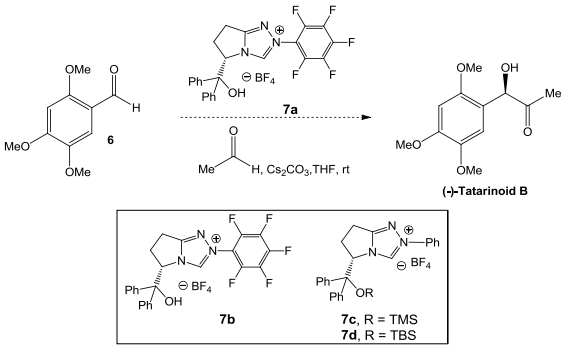
Scheme 4. Retrosynthesis of (±)-Tatarinoid B

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



Scheme 5. Synthesis of (±)-Tatarinoid B

Currently, we are turning our efforts toward the construction of (–)-Tatarinoid B in one step from a crossed acyloin condensation[12] between 2,4,5-trimethoxybenzaldehyde (**6**) and acetaldehyde using a chiral triazolium salt as a catalyst (Scheme 6, **7a-7d**).[13,14] 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.



Scheme 6. Synthesis of (-)-Tatarinoid B

In conlusion, we have described the first total syntheses of (–)-Tatarinoid 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 while (–)-Tatarinoid C was synthesized also in three steps with an overall yield of 74%.

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Supplementary Material

Supplementary data associated with this article may be found, in the online version, at.