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A total synthesis of 11-*O*-methyldebenzoyltashironin

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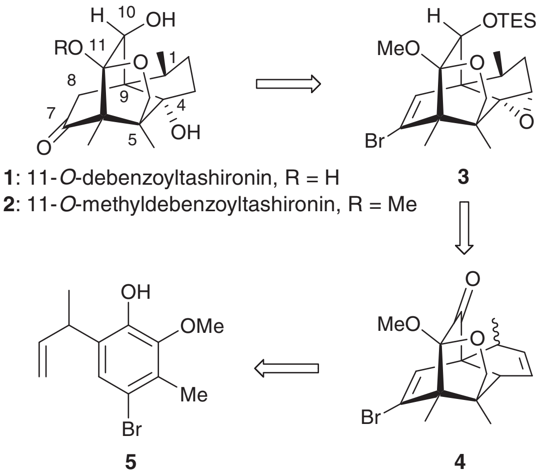
ABSTRACT

A concise total synthesis of 11-*O*-methyldebenzoyltashironin is reported in which oxidative dearomatization-IMDA-RCM triad constitutes the key ring forming steps, while an unorthodox DIBAL-H mediated stereo- and regioselective reductive epoxide openings and implementation of the vinyl bromide–carbonyl equivalency concept were pivotal to the success of this endeavor.

Tetracyclic and densely oxygenated neurotrophic agent 11-*O*-debenzoyltashironin **1**,[1a,b] isolated from the pericaps of North American species *Illicium merrillianum* exhibits impressive neurotrophic activity in cultured fetal rat cortical neurons at sub-micromolar concentration.[1a] This neurotrophic activity has implications in the maintenance of cognitive functions and neuronal repair that are relevant to several neurodegenerative disorders like Alzheimer's, Parkinson's, and Huntington's diseases, etc.[2] This uncommon but impressive biological activity profile and the intriguing structural intricacy of its tetracyclic framework, laced with oxygen functionalities and seven contiguous stereogenic centers, have stimulated interest in the total synthesis of 11-*O*-debenzoyltashironin **1** with the added intent of creating diversity around its bioactive scaffold.[3,4] As a part of our ongoing interest in the synthesis of neurotrophically active natural products,[5] we disclose here a concise total synthesis of 11-*O*-methyldebenzoyltashironin **2** wherein the tetracyclic core present in the natural product was assembled in just three steps from an appropriately crafted aromatic precursor.

As the target for a total synthesis endeavors, the natural product **1** presents quite a few significant challenges. Apart from its compact tetracyclic cage-like architecture, it also embodies tertiary α-hydroxyl and secondary hydroxy groups at C4 and C10, respectively, a β-methyl group at C1 and a carbonyl functionality at C7 position whose installation requires special attention. In order to conceptualize a viable roadmap toward **1**, we recognized the importance and centrality of a scalable and flexible strategy through which the tetracyclic core of the natural product could be constructed in a very short sequence. A retrosynthetic perspective that would lead to the total synthesis of **1** is unveiled in Scheme 1 which identified **3** as an advanced precursor with its vinyl bromide moiety as the masked equivalent of the C7 carbonyl group and a strategically positioned hydroxyl group at C10 to direct the regio- and stereoselective openings of the epoxide ring to deliver the C4 tertiary hydroxy functionality. The access to the advanced intermediate **3** was envisaged through functional group amplification/adjustment in the precursor **4** whose tetracyclic core could be assembled from an embellished aromatic precursor **5** via



Scheme 1. Retrosynthetic analysis of 1.

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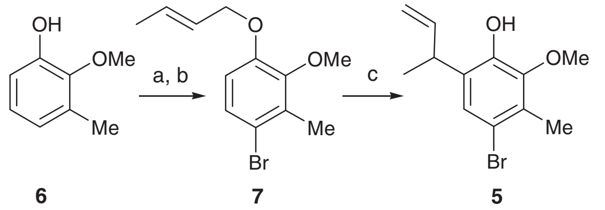


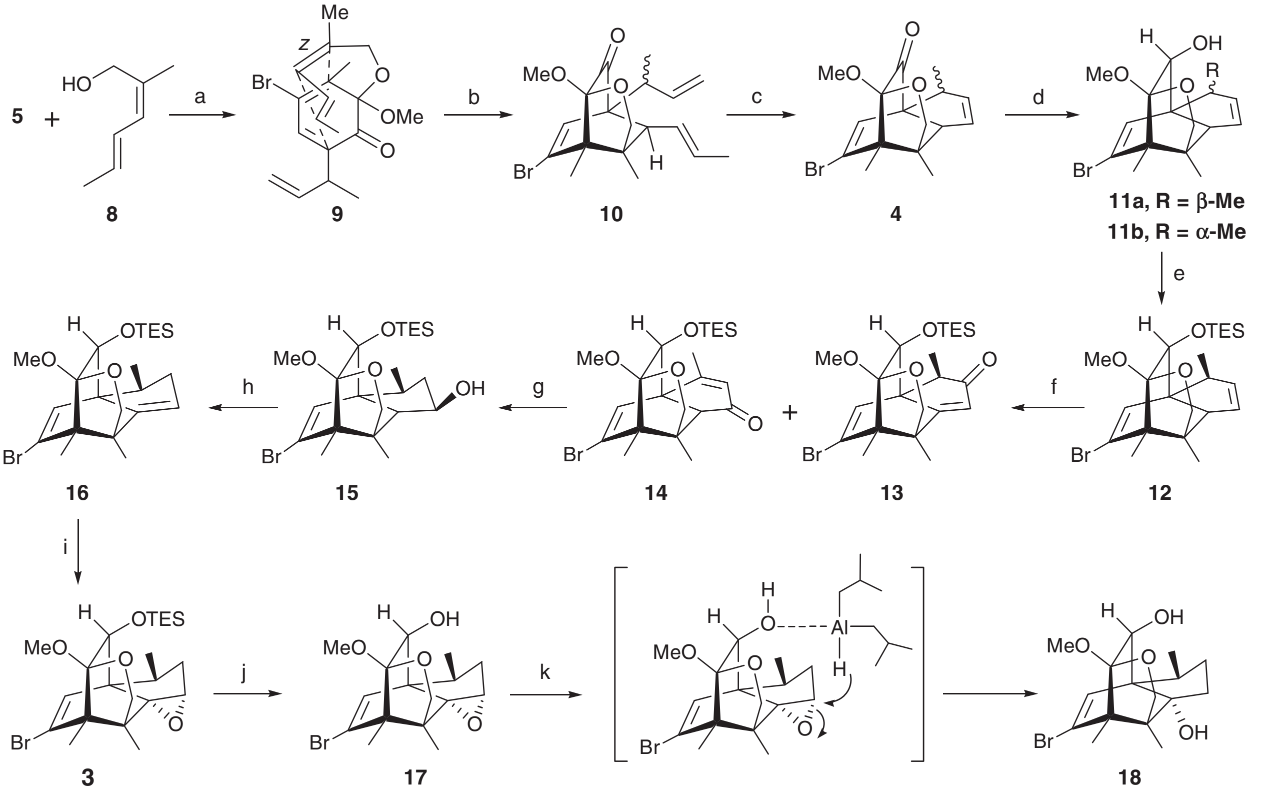
Scheme 2. Reagents and conditions: (a) $PyHBr_3$, DCM, 0 °C, 2 h, 90%; (b) K_2CO_3, crotyl bromide, acetone, reflux, 6 h, 92%; (c) $PhNEt_2$, 180 °C, 1 h, 67%.

a sequential orchestration of the oxidative dearomatization → intramolecular Diels–Alder reaction (IMDA) → ring closure metathesis (RCM) triad along the lines outlined earlier by us.[4] Appropriately substituted aromatic building block **5** could be crafted from readily available aromatic starting materials through routine maneuvers. It may be pointed out that the bromine substituent in aromatic precursor **5** was positioned to eventuate into a vinylic bromide functionality that served as a latent equivalent of the C7 carbonyl group.

The initial task was to set-up the key IMDA reaction by accessing the aromatic precursor **5** and subjecting it to oxidative dearomatization in the presence of the partner diene. Regioselective mono-bromination of the known phenol[6] **6** using pyridinium tribromide ($PyHBr_3$) furnished a *para*-bromo derivative which was transformed in to the aryl–crotyl ether **7** on treatment with crotyl bromide/K_2CO_3 in excellent yield. Claisen rearrangement in **7** in the presence of $PhNEt_2$ was smooth and delivered the desired precursor **5**, Scheme 2. Concurrently, the oxidative dearomatization partner (2*Z*,4*E*)-2-methyl-2,4-hexadien-1-ol **8** was prepared from a commercially available crotonaldehyde in two steps adopting the Still–Gennari olefination protocol.[4,7] The choice of diene **8** to set-up the contemplated IMDA reaction was important to ensure the regio- and steroselectivities and to obtain the requisite orientation of the two alkene arms for the following RCM reaction.

Oxidative dearomatization of penta-substituted aromatic compound **5** with *bis*(trifluoroacetoxy)iodobenzene (BTIB)[8] in the presence of (2*Z*,4*E*)-2-methyl-2,4-hexadien-1-ol **8** led to the masked *o*-benzoquinone based pentaene **9**, which could be isolated and spectroscopically recognized. As predicted, when the crude pentaene **9** was refluxed in toluene, a single tricyclic [4+2]-adduct **10** was obtained in a decent yield, through the preferred *endo*-transition state (see **9**). The exclusive participation of the *Z*-double bond of **8** in the IMDA reaction ensured that the two alkenyl side arms in **10** were *syn*-disposed and well poised for effecting the RCM reaction. Initial attempts toward RCM reaction on **10** using Grubbs' catalyst I proved problematic and deployment of Grubbs' catalyst II, though encouraging, was plagued by low yields. It was reasonable to surmise that the presence of the additional methyl substituents on the alkene arms of **10** may be primarily responsible for its refractoriness toward the RCM reaction. Consequently, a switch to the Hoveyda–Grubbs' second generation catalyst[9] proved rewarding and under optimized conditions afforded tetracyclic **4** as an inseparable mixture (1:1) of diastereomers. In order to circumvent the problem of separation of the diastereomers **4** at this stage, the carbonyl group in **4** was first reduced with $NaBH_4$. Gratifyingly, the reduction of **4** was stereoselective and the anticipated epimeric alcohols **11a** (β-Me) and **11b** (α-Me) (ratio = 1:1) were amenable to chromatographic separation (SiO_2 gel), Scheme 3.[10]

The stereochemistry of the C10 hydroxyl group and C1 methyl group in **11a** was confirmed through X-ray crystal structure analysis (Fig. 1) and had the requisite attributes in the context of our objective.[11] Although both **11a** and **11b** were reckoned as



Scheme 3. Reagents and conditions: (a) BTIB, THF, rt, 5 h, 62%; (b) toluene, reflux, BHT, 20 h, 80%; (c) Hoveyda–Grubbs' catalyst-II (15 mol %), toluene, reflux, 48 h, 66%, 87% (borsm); (d) $NaBH_4$, DCM/MeOH (2:1), 0 °C, 8 h, 90%, (ratio = 1:1); (e) TESOTf, Et_3N, DCM, 0 °C, 2 h, 93%; (f) PDC, 70% aqueous TBHP, celite, benzene, rt, 5 h, 59% (**14**:**13** = 3:1); (g) Et_3BHLi, THF, 0 °C, 2 h, 81%; (h) $SOCl_2$, pyridine, 0 °C, 30 min, 91%; (i) *m*CPBA, DCM, 1.5 h, 0 °C, 97%; (j) 40% aqueous HF, THF, rt, 6 h, 73%; (k). DIBAL-H, DCM, 0 °C, 12 h, 87%.