

Total synthesis of ovalifoliolatin B, acerogenins A and C

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Abstract

A short and concise route for the synthesis of ovalifoliolatin B, a highly strained macrocyclic diaryl ether heptanoid natural product that also provides quick access to acerogenins A and C natural products has been reported.
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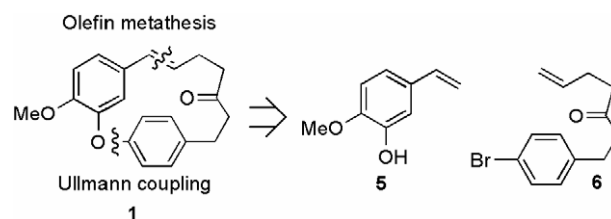
Macrocyclic diaryl ether heptanoid (MDEH) natural products form a subgroup of the diarylheptanoid family of natural products. Compounds of this class exhibit a wide range of biological activities that include, anti-cancer, anti-inflammatory, anti-fungal, and anti-bacterial effects.¹ The common structural core is a diaryl ether moiety connected by seven carbon atoms. The presence of a γ,δ trans-double bond and a *para*-substituted phenyl ring in the macrocycle makes ovalifoliolatin B a simple albeit challenging target.² The MDEH acerogenin C has the same structural core as ovalifoliolatin B except the γ,δ trans-double bond in the macrocycle.

In the first reported synthesis of acerogenin C, the linear diaryl heptanoid was constructed using the dianion chemistry of methyl acetoacetate followed by an intra-molecular hydrogen bond directed macrocyclization.³ This strategy was subsequently used for the synthesis of acerogenins A, B, L, and Aceroside.⁴ The need for 1-fluoro-2-nitro-4-alkyl substituted aryl moiety for the key macrocyclization step and the removal of the nitro group post macrocyclization increased the number of steps in this approach. A more direct route used Ullmann reaction to cyclize a linear diarylheptanoid to generate acerogenins C and A.⁵ The linear diarylheptanoid was generated through the selective reduction of the double bond in an α,β -unsaturated enone. In this approach, the selective reduction of the enone and

the cyclization proved challenging. In a recent report, acerogenins C and A were synthesized via a series of cross-aldol condensation reactions followed by the Ullmann macrocyclization.⁶ Herein we report the first total synthesis of ovalifoliolatin B in which a cross-metathesis reaction was used to set up the γ,δ trans-double bond, and the resulting linear diarylheptanoid was cyclized under Ullmann conditions.

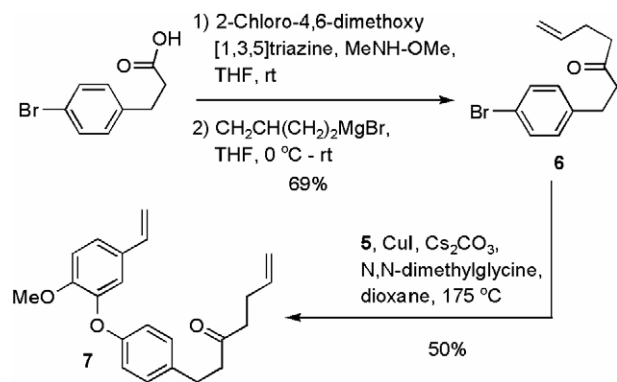
Ring closing metathesis (RCM) has emerged as a powerful tool for macrocyclization.⁷ The presence of a γ,δ trans-double bond in ovalifoliolatin B suggests that the use of RCM as the final macrocyclization step would be prudent. Therefore, our approach relied on generating ovalifoliolatin B from the two fragments **5** and **6** as outlined in Scheme 1.

Fragment **5** is a known compound⁸ and can be synthesized in three steps from isovanillin. Fragment **6** can be synthesized in a single step by the addition of butenylmagnesiumbromide to the Weinreb amide of 4-bromo-phenylpropanoic acid.⁹ Fragments **5** and **6** were



Scheme 1. Retrosynthesis of ovalifoliolatin B.

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Scheme 2. Synthesis of diarylether 7.

coupled using a CuI mediated Ullmann reaction to generate diarylether 7 (Scheme 2).¹⁰ Our attempts to carry out RCM on diarylether 7, under several conditions, were unsuccessful.¹¹ RCM was attempted with nearly all combinations with the following variations: catalysts (Grubbs I and II; Hoveyda–Grubbs I and II); solvents (DCM, THF, benzene, toluene); dilutions (2, 4 and 8 mM), and Temperature (rt, reflux and 150–170 °C in toluene).⁹

To probe the possible ring strain and electronic effects on the RCM, analogs 8–11 were synthesized (Fig. 1). Although we did observe the consumption of starting material under several RCM conditions, we were unable to isolate the corresponding macrocycle. At elevated temperatures the NMR signals that correspond to the γ,δ -olefin disappeared while the styrene signals remained. Therefore we decided to reverse the sequence of reactions viz., cross-metathesis followed by macrocyclization under Ullmann conditions.

As expected, cross-metathesis between styrene (5) and bromo olefin (6) led to the isolation of 12 as an inseparable mixture of stereoisomers (Scheme 3). A copper oxide

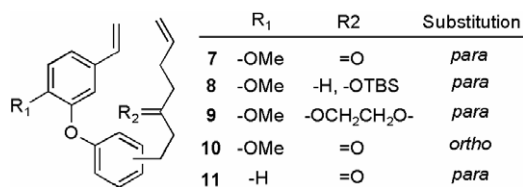
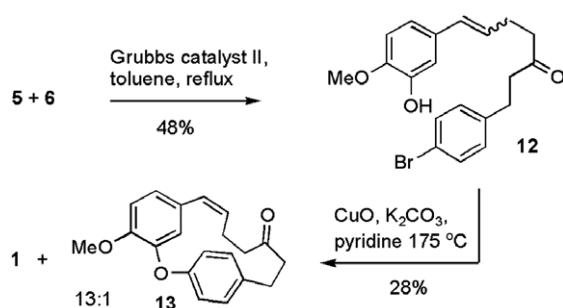


Fig. 1. RCM attempted intermediates.



Scheme 3. Synthesis of ovalifoliolatin B (1).

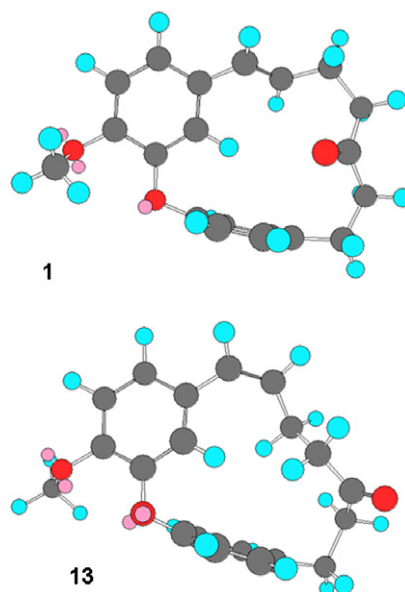
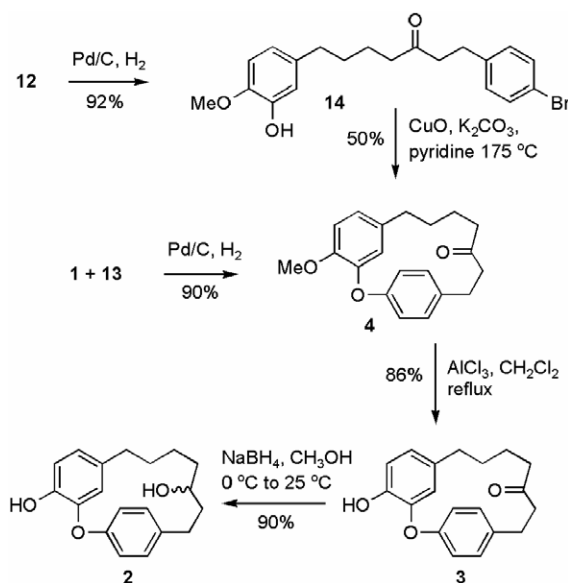


Fig. 2. MM2 minimized structures of 1 and 13.

mediated ring closure⁵ of 12 led to the isolation of ovalifoliolatin B (1) and its cis-isomer in 13:1 ratio. The stereochemistry of the double bond in the two isomers was defined by the coupling constants from ¹H NMR.

The MM2 minimized structures showed that the two aromatic rings in 1 and 13 are almost perpendicular to each other. The macrocyclic ring strain in 1 and 13 is exemplified by bond angles $\sim 125^\circ$ for the olefin carbons (sp^2) and bond angles $\sim 115^\circ$ for the carbons (sp^3) adjacent to the ketone (Fig. 2).

Synthesis of acerogenin C methyl ether (4) was accomplished by the reduction of the double bond (1 and 13).⁴ Alternatively, reduction of the double bond in 12 followed by ring closure also resulted in the isolation of 4 in higher



Scheme 4. Synthesis of acerogenins A and C.

yields (50% vs 28%). The higher yields during ring closure in the saturated system can be attributed to reduced strain. Acerogenin C (**3**) and acerogenin A (**2**) were synthesized following reported methods (Scheme 4).⁴

In summary, we report the first total synthesis of a strained MDEH natural product ovalifoliolatin B which was further elaborated to acerogenins C and A.

Acknowledgment

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Supplementary data

Experimental procedures and complete characterization of the natural products (**1–3**) and the intermediates are available. Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2008.01.135](https://doi.org/10.1016/j.tetlet.2008.01.135).

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