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Total synthesis and conformational study of ovalifoliolatin B

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ABSTRACT

The diaryletherheptanoid natural product, ovalifoliolatin B, was synthesized. The synthesis features a regioselective reduction of a conjugated dienone and an intramolecular Ullmann etherification. The conformation of the natural product was studied by dynamic NMR methods and by X-ray crystallography. Although the natural product structure is strained, it has a relatively low barrier for interconversion of enantiomeric conformations.

Introduction

The diaryletherheptanoids (DAEHs) are a family of cyclophane natural products isolated from woody plants [1]. Their molecular architecture is characterized by a diphenylether and a heptanoid ansa bridge, exemplified by the core DAEH architecture **1** (Fig. 1). DAEH natural products have a wide variety of biological activities [2], and as a result, several groups have published syntheses and biological studies of various family members [3].

Our group became interested in these molecules because of their structural properties [4]. Specifically, many DAEHs lacked stereogenic carbon atoms; however, some were chiral molecules by virtue of having stable enantiomeric conformations. Moreover, despite a conserved molecular architecture, it was unclear which DAEHs exhibited conformational chirality, and what structural features led to restricted conformational mobility.

Some DAEHs, such as galeon (**2**), lacking stereogenic carbons were isolated as optically active compounds [5], and (unsurprisingly) we found them to have single enantiomer conformations stable at RT [4a]. At least one DAEH, juglanin (**3**), had been isolated without discussion of its chiral properties [6], and it was later found to have stable enantiomeric conformations [7]. Some DAEHs, such as acerogenin L (**4**) were isolated as optically inactive molecules [8], and we found them to be achiral molecules with rapidly interconverting enantiomeric conformations [4b]. We found that some DAEHs (e.g. garugamblin I, **5**) that were reportedly optically active were, in fact, achiral molecules [9,4b]. Finally, there are members with skipped-enone architectures, such as ovalifoliolatin B (**6**) [10], for which racemization barriers have not been measured.

The wide range of racemization energies in this class of compounds can be explained by consideration of the DAEH structure (Scheme 1). The mechanism of racemization requires complete inversion of the macrocycle, which in turn requires two distinct molecular motions: 180° rotation of the *para*-substituted B-ring and conformational reorganization of the *ansa* loop (Scheme 1) [11].

Rotation of the B-ring brings about *trans*-annular interaction of phenyl C–H bonds with the *ansa* loop; as a result, this rotation has a relatively high barrier (approx. 40 kcal/mol). This barrier is substantially higher than conformational changes to the *ansa* loop, and largely explains the racemization barrier. Thus, all DAEHs with hydroxy- or alkoxy-substituted B-rings (e.g. **2** and **3**) are chiral molecules with stable enantiomeric conformations at RT.

Those DAEH molecules with locally symmetric (i.e. unsubstituted) B-rings such as **4** *do not require* B-ring rotation for racemization. As a result, interconversion of enantiomeric conformations requires only movement of the *ansa* loop. Conformational rotation of the *ansa* loop has a relatively low barrier (<20 kcal/mol) for rotation, and as a result, all such DAEH natural products with locally symmetric B-rings (e.g., **4**–**6**) are achiral, that is, they have rapidly interconverting enantiomeric conformations.

Despite being achiral, the DAEHs with unsubstituted B-rings have a wide range of conformational half-lives. The rate of interconversion of enantiomeric conformations depends on the presence and position of C=C bonds in the *ansa* loop. Those DAEHs with simple heptanoid *ansa* loops have very low barriers of racemization and fast racemization kinetics. Compound **4** undergoes conformational enantiomerization at the NMR timescale at −60 °C.

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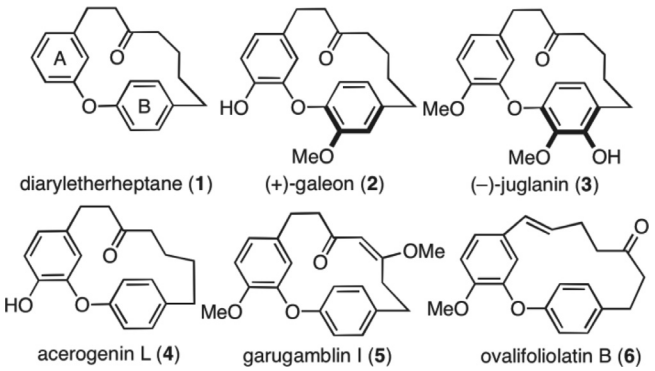
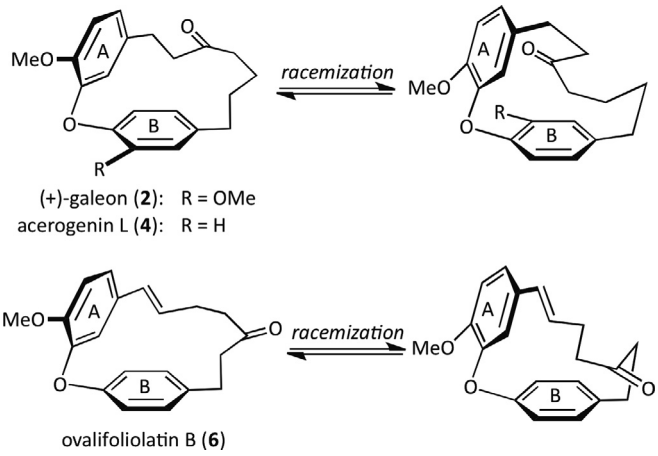
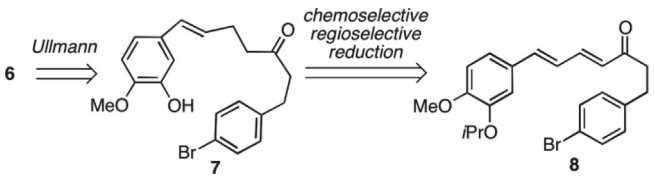


Fig. 1. Selected diaryletherheptanoid natural products.



Scheme 1. DAEH racemization.



Scheme 2. Retrosynthetic analysis of ovalifoliolatin B.

Adding unsaturation leads to slower racemization kinetics, and DAEHs with *ansa* loops containing a vinylogous acid group (e.g. **5**) have higher racemization barriers. For example, garugamblin I has a racemization half life of 0.3–0.5 s at RT, which results in slow conformational behavior on the NMR timescale (chemical-shift inequivalent methylene protons).

Aside from the garugamblin DAEHs, there are DAEH natural products that display unsaturation in their *ansa* loops, such as ovalifoliolatin B (**6**) [10] and tedarene [12]. The barriers for conformational racemization have not been determined for such molecules. Natarajan's inaugural synthesis of ovalifoliolatin B included a molecular modeling study to predict the ground state conformation and ring strain in the natural product [3b]. However, these computations have not been verified experimentally.

We decided to prepare ovalifoliolatin B in order to study its conformational behavior. Specifically, we determined the rate of interconversion of enantiomeric conformations, and we prepared crystals suitable for X-ray crystallographic studies in order to investigate the strain in the molecular structure.

Results and discussion

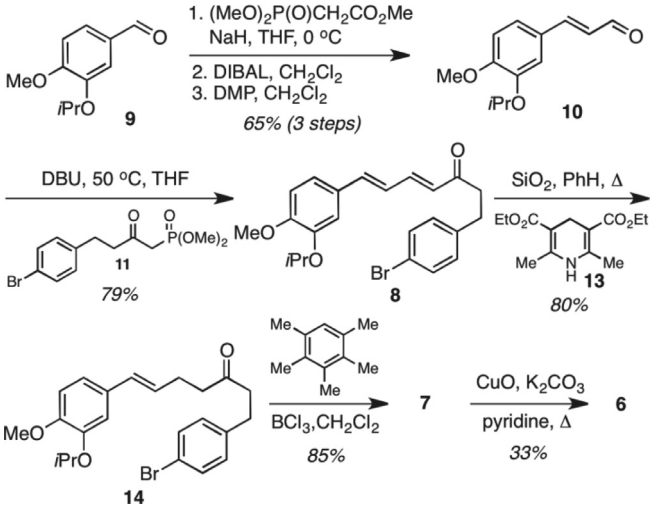
Retrosynthetically, we disconnected the macrocyclic ring in ovalifoliolatin B to give bromophenol **7** (Scheme 2). The skipped enone of **7** could arise from selective reduction of dienone **8**. Such a transformation would require regioselective reduction of the α,β-unsaturation of the conjugated dienone system, and it would require chemoselective reduction of the alkene in the presence of other functional groups prone to reduction, such as the carbonyl and the aryl bromide. We anticipated that this reduction (**8** to **7**) would require significant experimentation to find suitable reaction conditions; however, the preparation of dienone **8** would be quite expeditious using dependable transformations.

The synthesis of ovalifoliolatin B began with isopropyl isovanillin **9** (Scheme 3) [13]. Horner–Wadsworth–Emmons olefination, followed by hydride reduction, and oxidation formed enal **10**. Another Horner–Wadsworth–Emmons olefination with known phosphonate **11** [14] gave dienone **8**.

With **8** in hand, we attempted the reduction of the dienone to give **14**. Note that the desired transformation is a regioselective partial reduction of a dieneone in the presence of an aryl bromide. Such regioselective reductions of dienones are quite rare in the literature [15], and we began investigating known reduction conditions developed on simple enones. Hydrogenation over standard metal catalysts (e.g. Pd/C, $Pd(OH)_2$, Pt/C, etc.) were not regioselective with respect to the diene, and both alkenes were reduced. Hydride reducing agents (e.g. L-Selectride, Stryker's reagent, etc.) gave reduction of the γ,δ-unsaturation, reduced the carbonyl group, or removed the aryl bromide.

Gratifyingly, we found that use of the Hansch ester (**13**) in combination with silica gel in hot benzene following Ohno's procedure gave smooth regioselective reduction of the dienone leading to formation of **14** in good yield [16]. No over-reduction of the alkene, carbonyl, or aryl bromide was observed. Presumably, these conditions could be used for regioselective reductions in other dienone-containing molecules. Selective removal of the isopropyl group was possible using BCl_3 in the presence of a cation scavenger to give **7** [17]. Finally, Ullmann ether formation completed the synthesis of ovalifoliolatin B. Overall, the synthesis was 6 steps and 12% yield from **9**.

With ovalifoliolatin B in hand, we began to study its conformation and barrier for interconversion of enantiomeric conformations. Natarajan and coworkers previously studied the structure of **6** using MM2 calculations [3b]. They predicted that the phenyl



Scheme 3. Synthesis of ovalifoliolatin B.

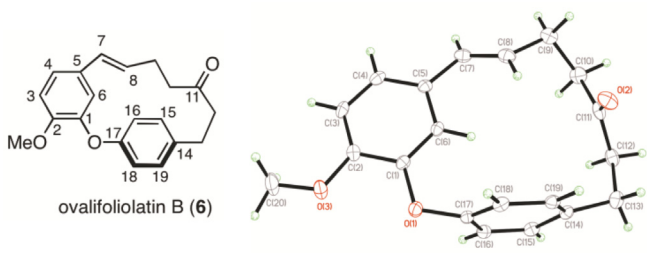


Fig. 2. ORTEP of ovalifoliolatin B.

rings of **6** would be positioned "almost perpendicular" to each other, the alkene carbons would have bond angles of 125°, and the ketone α-carbons would have bond angles of 115°.

We found that recrystallization of the natural product gave material suitable for x-ray crystallographic analysis (Fig. 2). The solid state conformation of **6** was similar to the conformation predicted by Natarajan. The two phenyl rings were approximately perpendicular. The torsion angles ∠C1–O1–C17–C16 and ∠C1–O1–C17–C18 were 89.2° and 83.9°, respectively (perpendicularity would lead to angles of 90°). The torsion angles ∠C2–C1–O1–C17 and ∠C6–C1–O1–C17 were −8.4° and 168.9°, respectively (perpendicularity would lead to angles of 0° and 180°, respectively). The ketone α-carbons (C10 and C12) showed angles ∠C11–C12–C13 of 114.9° and ∠C9–C10–C11 of 116.1°, quite close to the predicted angles of 115°. Bond angles of the alkene ∠C7–C8–C9 and ∠C5–C7–C8 were 127.5° and 121.7°, respectively, which reflects the structural distortion predicted by Natarajan; however, the angles at C8 deviated much more from standard alkene bond angles than C7.

Additional torsion angles further substantiate the overall strain in the molecule. The torsion angle of the alkene ∠C5–C7–C8–C9 is 165.2°, which is significantly different than unstrained planar alkenes (180°). Moreover, the alkene is twisted out of the plane of the adjacent benzene ring, as reflected by the torsion angle ∠C4–C5–C7–C8 of 158.3°, which indicates that the alkene is experiencing less conjugation with the benzene ring than a normal substituted styrene.

A notable feature of the structure of **6** that was not discussed in the studies of Natarajan is the bent conformation of the *para*-substituted benzene ring. The solid state structure of **6** shows this ring is boat-shaped with torsion angles ∠O1–C17–C16–C15, ∠O1–C17–C18–C19, ∠C13–C14–C15–C16, and ∠C13–C14–C19-C18 all between 166° and 167°. Similar boat-shaped benzene rings have appeared in other strained cyclophane natural products such as haouamine [18] and cavicularin [19].

In addition to the solid state structure of **6**, we were interested in its conformational stability in solution. DAEH molecules that contain conjugated unsaturated carbonyls (e.g., **5**, Fig. 1) have enantiomeric conformations that interconvert sufficiently slowly at room temperature to appear as chiral molecules by NMR. Specifically, geminal methylene protons and symmetry-related arene protons in **5** are chemical shift inequivalent. However, ovalifoliolatin B, with its skipped enone structure, did not show chemical shift inequivalence in the methylene protons or arene protons. This indicates that the molecule is undergoing fast interconversion of enantiomeric conformations relative to the NMR timescale at RT. Presumably, the separation between the alkene and carbonyl π-systems leads to greater conformational flexibility, and in turn a lower barrier for racemization compared with **5**.

NMR spectra of ovalifoliolatin B were recorded at cryogenic temperatures to estimate its racemization barrier. We recorded the ^{1}H NMR spectrum of **6** at temperatures ranging from 25 °C to −90 °C (Fig. 3). At lower temperatures, methylene and arene protons became chemical shift inequivalent (decoalescence). The coalescence temperature was −30 °C.

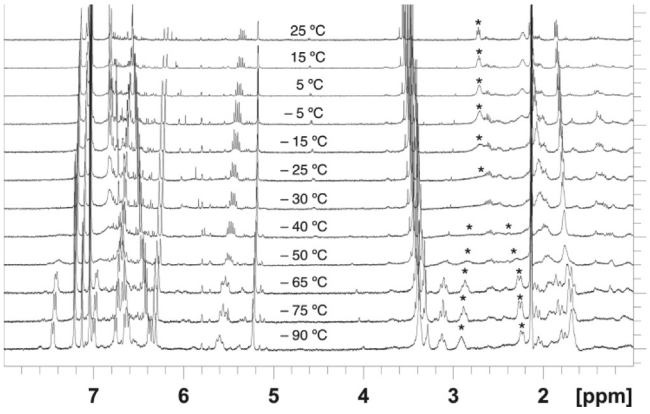


Fig. 3. VT-NMR study of **6** (toluene d_8, 400 MHz). *Indicates resonance used to determine T_C.

In two-site equally populated cases, the relationship k_C = 2.22-× Δν gives the rate constant for coalescence (k_C), where Δν is the separation in Hz of the coalescing peaks at temperatures below coalescence [20]. We used this relationship to estimate the rate of conformational exchange in **6**. At −90 °C the Δν = 268 Hz, which corresponds to a k_C = 121 s^{-1}. Using the coalescence temperature of −30 °C (243 K) gives an approximate $\Delta G^{\ddagger}_{rac}$ = 11.8 kcal/ mol at −30 °C, and a half-life ($t_{1/2}$) of 0.006 s. This data confirms that ovalifoliolatin is undergoing fast enantiomeric interconversion at temperatures above −30 °C. Thus, the barrier of racemization is between vinylogous ester-type DAEHs (e.g., **5**) and simple heptanone DAEHs such as acerogenin L. This data suggests that the unsaturation in the *ansa*-loop of ovalifoliolatin limits conformational degrees of freedom more than saturated loops, but not as much as when the π-systems are conjugated.

In summary, we have completed the total synthesis of the diaryletherheptanoid, ovalifoliolatin B, in 6 steps and 12% overall yield. Our synthesis featured an unusual regioselective reduction of a dienone to give a γ,δ-unsaturated ketone. Crystallographic studies show that ovalifoliolatin B exhibits significant distortion from normal bond angles at sp^2-hybridized carbons; in particular, there is significant deviation from planarity in the aromatic B-ring. In solution the molecule undergoes fast racemization above temperatures of −30 °C, which represents a racemization barrier between that of the simplest DAEHs (such as acerogenin L), and vinylogous ester DAEHs (such as garugamblin I).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A. Supplementary data

Crystallographic data (cif) for **6**, full experimental procedures, spectroscopic data, and depicted ^{1}H and ^{13}C NMR spectra for all new compounds. Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.151988.

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