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# Chirality in Diarylether Heptanoids: Synthesis of Myricatomentogenin, Jugcathanin, and Congeners

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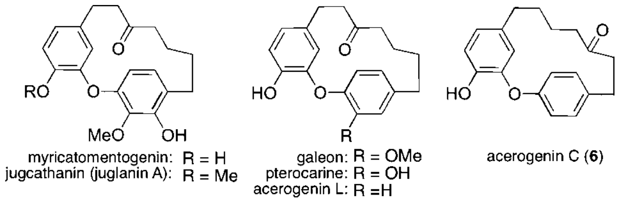
## ABSTRACT



**The syntheses of myricatomentogenin, jugcathanin, galeon, pterocarine, and acerogenin L are reported. Synthetic material was used to measure their optical activities and free energy of activation for racemization. The natural enantiomers of myricatomentogenin, jugcathanin, galeon, and pterocarine were determined to have the same p*R* absolute stereochemistry. Acerogenins L and C are achiral compounds.**

Chirality is of paramount importance to medicine, biology, and chemistry.[1] Substantial effort has been devoted to preparing molecules that are chiral because of the presence of $sp^3$ hybridized stereogenic centers. In contrast, less emphasis has been devoted to molecules that are chiral by virtue of their conformation. However, structures with restricted rotation of $\sigma$-bonds including biaryls, cyclophanes, and strained cyclic alkenes have attracted longstanding attention as chiral ligands, catalysts, and targets of total synthesis.[2]

It is our contention that conformational chirality is more prevalent than commonly believed and goes unnoticed in many natural products. The long-term goal is to develop the ability to predict the existence of conformational chirality in complex molecular architectures devoid of stereogenic centers. Toward this end, we sought for study a family of molecules with conserved molecular architectures, devoid of stereogenic centers, that sometimes (but not always) display chirality. The aim is to establish which members are chiral, measure their free energy of activation for racemization, and determine their absolute stereochemistry. The diarylether heptanoid natural products fit these criteria, and they were chosen for the preliminary studies documented herein.

Diarylether heptanoids (DAEHs)[3] are a class of natural products isolated from woody plants. These natural products display a range of biological activities[4] and have attracted interest from synthetic chemists.[5] DAEHs are characterized by an oxa[1.7]metaparacyclophane architecture. Fifteen DAEHs do not possess a stereocenter (Figure 1), but interestingly, some (not all) DAEHs were isolated as optically active compounds.[6] The relationship between DAEH structure and chirality has not been systematically investigated.

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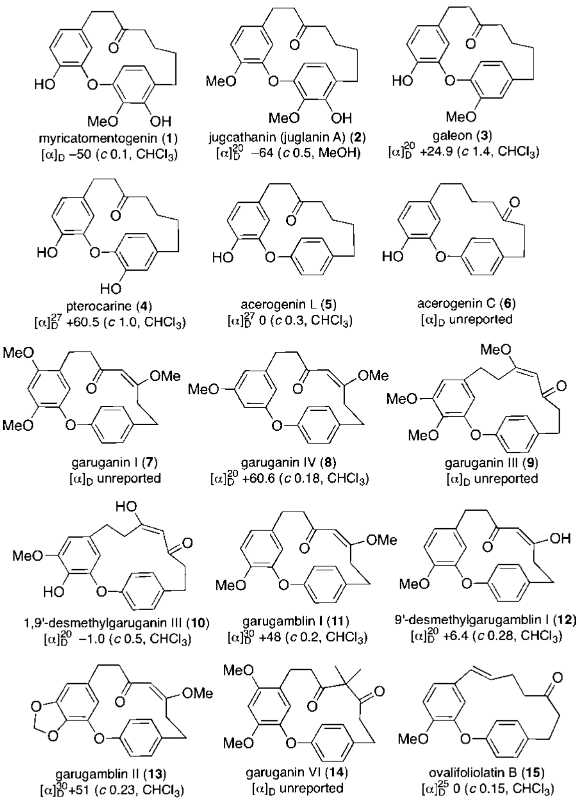


**Figure 1.** Diarylether heptanoid natural products that lack stereogenic centers.

DAEHs can be divided into two distinct classes: (1) DAEHs with a heptanone *ansa* bridge (**1**−**6**); (2) DAEHs with multiple sp$^2$-hybridized carbons in the *ansa* bridge (**7**−**15**). Galeon (**3**) has been isolated on two separate occasions as both a levo- and dextrorotary compound.[7] Jugcathanin (**2**) was isolated without mention of optical activity or chirality, and it was later isolated as an optically active molecule and named juglanin A.[8] Seven other DAEHs were isolated as optically active compounds.[5a,7b,9]

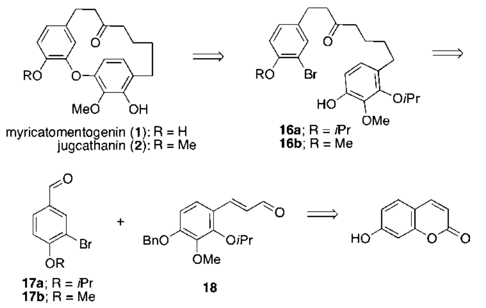
Two DAEHs were reported to be optically inactive,[10] and the remaining four DAEHs were isolated without mention of optical activity.[9b,11] It is unclear if the optically inactive members are achiral or are racemic. Similarly, it is unclear if the DAEHs with unreported optical activity are achiral, chiral racemic, or chiral nonracemic compounds. Although the more substituted members of this class are commonly optically active (e.g., myricatomentogenin, **1**), some molecules that have relatively little substitution (e.g., garuganin IV, **8**) are also optically active. In this report, we disclose the synthesis of the "heptanone-type" DAEHs (**1**−**6**), determination of their free energy of activation for racemization, and absolute stereochemistry.

DAEHs are commonly isolated by Soxhlet extraction using hot solvents for hours or days. Elevated temperatures could lead to racemization of these conformationally chiral molecules. We considered the possibility that the optically inactive members of this class had been racemized during isolation.

Insight into the chiral properties of the DAEHs can be gleaned from data presented in the isolation reports. Inspection of the $^1$H NMR data of **1**−**4** reveals that the geminal methylene hydrogens are chemical-shift inequivalent. This observation is consistent with the presence of an element of chirality on the NMR time scale. All geminal methylene protons of **5** and **6** are chemical-shift equivalent, suggesting the natural products are achiral at rt on the NMR time scale.

With these considerations in mind, the heptanone DAEHs (**1**−**6**) were prepared to investigate their chiral properties. Our retrosynthetic analysis of **1** and **2** simplifies the molecules by disconnection of the ether linkage to give achiral bromophenols **16** (Scheme 1). Positioning the phenolic functional group on the more electron-rich phenyl ring was anticipated to give a smoother cyclization than an alternative approach with an electron-rich bromide. Further simplification leads to aldehydes **17** and **18**. Differentially functionalized aldehyde **18** was envisioned to arise from commercially available 7-hydroxycoumarin.

**Scheme 1.** Retrosynthesis of Myricatomentogenin and Jugcathanin



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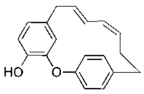
(6) During the preparation of this manuscript tedarene A was isolated. It has an estimated free energy of activation for interconversion of enantiomeric conformers of 14.0 kcal/mol at −40 °C. See: Costantino, V.; Fattorusso, E.; Mangoni, A.; Perinu, C.; Teta, R.; Panza, E.; Ianaro, A. *J. Org. Chem.* **2012**, ASAP. DOI: 10.1021/jo300295j.



tedarene A

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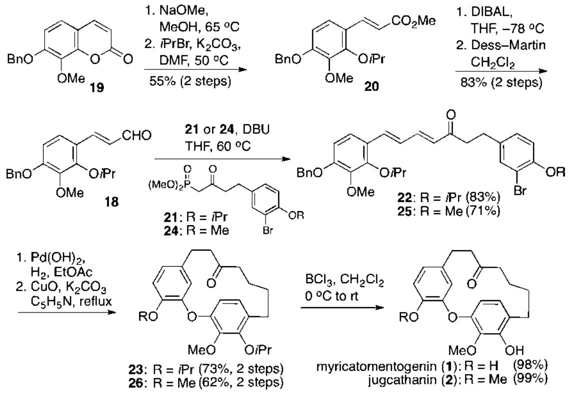
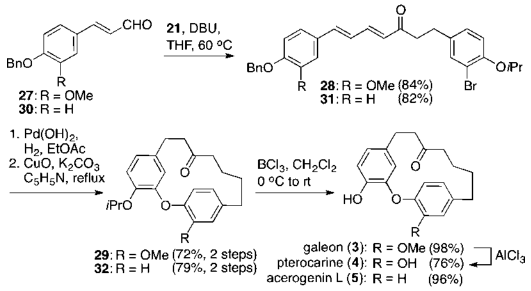
The synthesis begins with **19**, prepared in five steps from 7-hydroxycoumarin.[12] Methanolysis and alkylation of **19** give ester **20** (Scheme 2). Reduction of **20** produces aldehyde **18**. Horner–Wadsworth–Emmons reaction of **18** with phosphonate **21** yields ketone **22**. Subjection of **22** to hydrogen and $Pd(OH)_2$ leads to hydrogenation of both alkenes and hydrogenolysis of the benzyl ether. Intramolecular Ullmann reaction then gives cyclophane **23**.[13] Removal of the isopropyl ethers using $BCl_3$ completes the first synthesis of myricatomentogenin (**1**). A similar strategy was used for the synthesis of **2**. Olefination of **18** with phosphonate **24** gives ketone **25**. Hydrogenation and cyclization produce cyclophane **26**. Removal of the isopropyl ether using $BCl_3$ completes the first synthesis of jugcathanin (**2**).

**Scheme 2.** Synthesis of Myricatomentogenin and Jugcathanin



A related strategy was used in an improved synthesis of **3**, **4**, and **5** (Scheme 3). Vanillin derivative **27**[5e] undergoes condensation with phosphonate **21** to produce unsaturated ketone **28**. Reduction and cyclization give cyclophane **29** in good yield. Deprotection yields galeon (**3**). Removal of the methyl ether using $AlCl_3$ produces pterocarine (**4**). Benzyl coumaraldehyde (**30**)[14] is condensed with phosphonate **21** to produce **31**. Ketone **31** is reduced and cyclized to give **32**. Deprotection completes the acerogenin L (**5**) synthesis. Finally, acerogenin C was prepared using conditions from the literature.[5e] The syntheses of **1**–**5** shown in Schemes 2 and 3 had combined overall yields of 25–62% and provided up to gram quantities of the natural products for further studies.

**Scheme 3.** Syntheses of Galeon, Pterocarine, and Acerogenin L



The chiral properties of **1**–**6** were investigated. Some DAEHs have been isolated without optical activity data, and it has not been determined if optically inactive DAEHs are achiral or racemic. Compounds **1**–**4** were all found to be resolvable (i.e., chiral) by HPLC using a chiral stationary phase (Diacel, OD, hexanes/*i*PrOH). Analysis of **5** and **6** using chiral-phase HPLC showed a single sharp peak regardless of chiral columns or conditions. Moreover, geminal methylene protons of the acerogenins (**5** and **6**) were chemical shift equivalent in the $^1H$ NMR spectra. These observations suggest **5** and **6** are achiral molecules at rt.

The racemization energies of the DAEHs were measured. To access enantiopure material, these compounds were simply resolved by preparative chiral HPLC. Enantiopure DAEHs were subjected to elevated temperatures in dichlorobenzene. Surprisingly, (+)-**3** and (+)-**4** did not undergo racemization with any appreciable rate at the temperatures of Soxhlet extraction (80–110 °C). Racemization of (+)-**3** occurred only slowly at 201 °C with a first-order rate constant ($k_{rac}$) of $5.20 \times 10^{-6}\ s^{-1}$ (approximate half-life of 8.5 h). This results in a free energy of activation for racemization ($\Delta G^{\ddagger}_{rac}$) of 39.6 ± 0.6 kcal/mol at 201 °C (Figure 2).[15] Decomposition of (+)-**4** occurred with no measurable racemization over a period of 9 h at 210 °C. Assuming first-order kinetics and a conservative half-life of at least 9 h gives a lower limit of $k_{rac} = 2.14 \times 10^{-5}\ s^{-1}$ and a $\Delta G^{\ddagger}_{rac}$ greater than 39.1 kcal/mol at 210 °C.

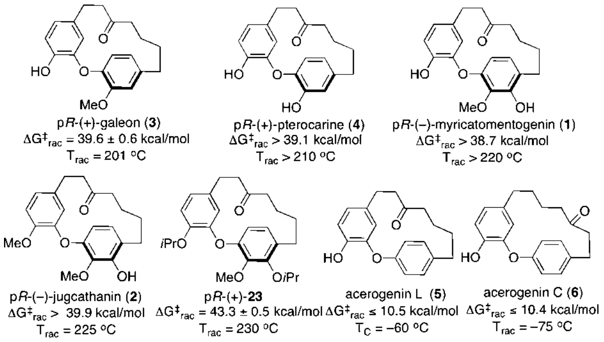


**Figure 2.** Free energies of racemization and absolute configuration of **1**–**6**.

We then investigated the racemization energies of (–)-**1** and (–)-**2**. Myricatomentogenin (**1**) decomposed without any measurable racemizaion at 220 °C over 6 h. Assuming a racemization half-life of more than 6 h gives a lower limit of $k_{rac} = 3.21 \times 10^{-5}\ s^{-1}$ and a $\Delta G^{\ddagger}_{rac}$ greater than 38.7 kcal/mol at 220 °C. Enantiopure (–)-**2** decomposed over 6 h with partial racemization (80% ee) at 225 °C. This gives a lower limit of $k_{rac} = 3.21 \times 10^{-5}\ s^{-1}$ and a $\Delta G^{\ddagger}_{rac}$ greater

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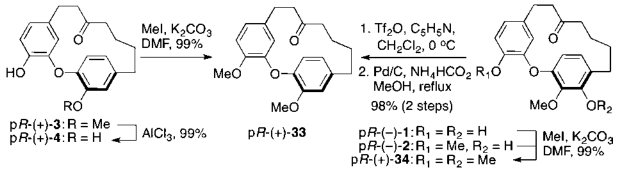
than 39.9 kcal/mol at 225 °C. We hypothesized that the decomposition of the DAEHs was attributable to oxidative processes of the phenol functional group. Without rigorous exclusion of oxygen the decomposition was more rapid. We then investigated the racemization of (+)-**23** (diisopropylmyricatomentogenin) which lacks phenols. Racemization occurs at 230 °C with a first-order rate constant of $k_{\mathrm{rac}} = 3.98 \times 10^{-6}\ \mathrm{s}^{-1}$ and a $\Delta G^{\ddagger}{}_{\mathrm{rac}}$ of 43.3 ± 0.5 kcal/mol at 230 °C.

**Scheme 4.** Absolute Stereochemistry Determination of **1**−**4**



Determination of $\Delta G^{\ddagger}{}_{\mathrm{rac}}$ for the interconversion of enantiomeric conformations of the acerogenins was accomplished using low-temperature NMR methods. Specifically, acquisition of $^1$H NMR spectra at cryogenic temperatures induced decoalescence of geminal methylene protons. The coalescence temperature ($T_{\mathrm{C}}$) was −60 and −75 °C for **5** and **6**, respectively. The relationship $k_{\mathrm{C}} = 2.22 \times \Delta\nu$ gives the rate constant for coalescence ($k_{\mathrm{C}}$) where $\Delta\nu$ is the separation in Hz of the coalescing peaks at temperatures below coalescence.[16] Acquisition of NMR spectra at temperatures below coalescence was not possible for the acerogenins. We approximated $\Delta\nu$ using the width at half-height of the peak at coalescence.[17] For **5**, our estimated $\Delta\nu = 33$ Hz giving an upper limit of $k_{\mathrm{C}} = 73\ \mathrm{s}^{-1}$ and a $\Delta G^{\ddagger}{}_{\mathrm{rac}}$ of 10.5 kcal/mol at −60 °C. For **6**, our estimated $\Delta\nu = 31$ Hz giving an upper limit of $k_{\mathrm{C}} = 93\ \mathrm{s}^{-1}$ and a $\Delta G^{\ddagger}{}_{\mathrm{rac}}$ of 10.4 kcal/mol at −75 °C. Thus, the relative rate of racemization of the acerogenins compared to **1**−**4** is approximately $10^7$. More importantly, **5** and **6** undergo racemization at temperatures above −60 °C and **1**−**4** do not undergo racemization with any appreciable rate up to temperatures of 200 °C.

With enantiopure DAEHs in hand, their absolute stereochemistry was determined (Scheme 4). The absolute stereochemistry of (+)-**3** (lit. $[\alpha]_{\mathrm{D}}^{24}$ + 24.9; *c* 1.4, CHCl$_3$) was determined through recrystallization of its bromobenzoate derivative.[7b] We find that (+)-**3** (% ee = >99 by HPLC analysis) has $[\alpha]_{\mathrm{D}}^{23}$ + 17.0 (*c* 1.4, CHCl$_3$). Demethylation of (+)-**3** leads to (+)-**4** (Scheme 4). Methylation of (+)-**3** gives (+)-**33** with no loss in enantiopurity by HPLC. Enantiopure (−)-**2** was deoxygenated[18] to give (+)-**33**, which matched (chiral HPLC) the sample prepared from (+)-**3**. Methylation of (−)-**1** and (−)-**2** gave the same enantiomer of (+)-**34** (methylmyricatomentogenin). Thus, all the natural enantiomers of DAEHs **1**−**4** have the same p*R* absolute stereochemistry as shown in Scheme 4 and Figure 2.

In summary, we have completed the first syntheses of myricatomentogenin (**1**) and jugcathanin (**2**). Our synthetic route was used in an improved synthesis of galeon (**3**), pterocarine (**4**), and acerogenin L (**5**). With synthetic DAEHs we determined definitively which of these compounds were chiral and measured their optical activities. We measured racemization energies of these natural products by heating synthetic material and using kinetics to determine their energies of racemization. Low-temperature NMR was used to determine the $\Delta G^{\ddagger}{}_{\mathrm{rac}}$ for interconversion of enantiomeric conformations of the acerogenins (**5** and **6**). We have found that the acerogenins were not racemized upon Soxhlet extraction, but rather they are achiral at rt. Furthermore, **1**−**4** were not racemized during isolation temperatures (80−110 °C). The natural enantiomers of **1**−**4** have the same p*R* absolute stereochemistry. Efforts to develop a predictive tool for chirality in the DAEHs are underway and will be reported shortly.

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**Supporting Information Available.** Experimental procedures, spectroscopic data, depiction of $^1$H and $^{13}$C NMR spectra for all new compounds. Chiral HPLC traces, CD spectra, and relevant VT-NMR spectral data for chiral DAEHs. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.