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A Short Synthesis of (±)-Epiasarinin

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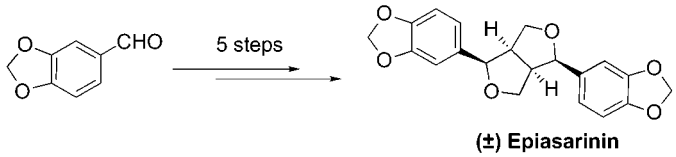
ABSTRACT



Epiasarinin, an endo-endo furofuran, has been synthesized from piperonal via a five-step route with good stereocontrol. The sequence involves Darzens condensation, alkenyl epoxide–dihydrofuran rearrangement, and a Lewis acid mediated cyclization.

Compounds containing the 2,6-diaryl-3,7-dioxabicyclo[3,3,0]-octane skeleton (furofurans) belong to the lignan family of natural products. There is considerable structural variation in this series, in both the nature and the stereochemistry of the aryl substituents, e.g., Epiasarinin, Praderin, or Kobusin, Figure 1.[1]

Due to their large range of biological properties, which include antioxidant, anticancer, antiviral, and immunosuppressant activities, these natural products represent very attractive synthetic targets. Since activity is dependent on stereochemistry, synthetic routes that can provide controlled but tuneable access to one particular class are very attractive. In this respect, we have been interested in developing efficient ways to synthesize the furofuran skeleton. Recently, we have reported a sequence based on the thermal rearrangement of alkenyl epoxides to dihydrofurans and the subsequent Lewis acid catalyzed cyclization to generate the furofuran nucleus with good stereocontrol, Scheme 1.[2] While many syntheses of Sesamin (exo-exo furofuran **3**) have been published, there have been no accounts of approaches to the less stable endo-endo furofuran diastereoisomer.[3−6] In this paper, we report an efficient stereoselective approach to a natural endo-endo furofuran represented by Epiasarinin.[7]

In our model studies, we had generated the alkenyl epoxide **8** through a Wadsworth−Emmons reaction of epoxide **7**.

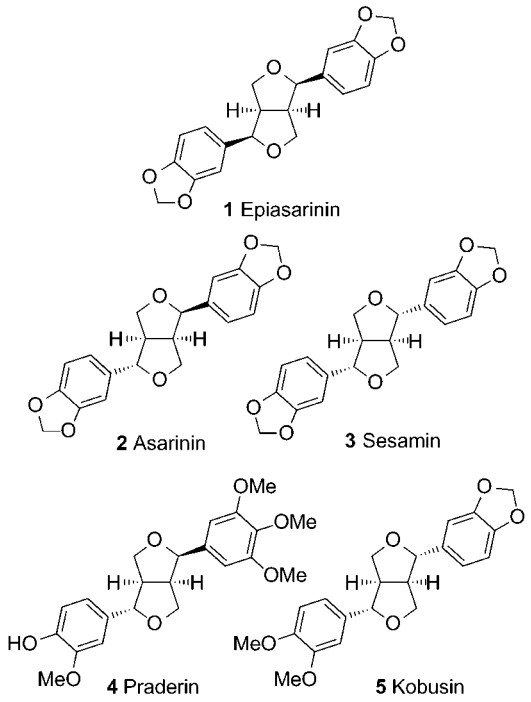


Figure 1. Typical natural furofuran lignans.

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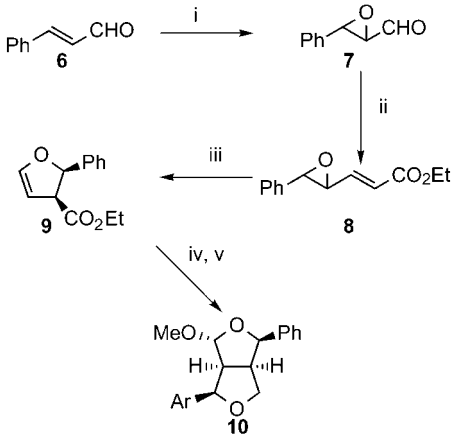
Scheme 1. Model Studies[a]

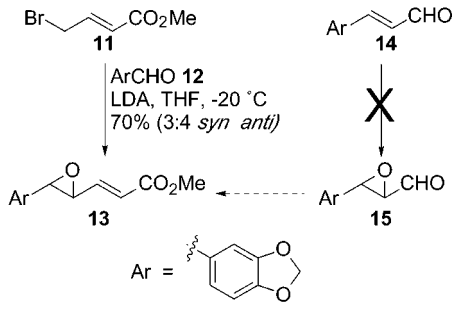


[a] Conditions: (i) ^{t}BuOOH, NaOH, 73%; (ii) $(EtO)_2P(O)CH_2CO_2Et$, NaH, PhMe, 68%; (iii) sealed tube, PhMe, 180 °C, 70%; (iv) $LiAlH_4$, Et_2O, 0 °C, 100%; (v) $ArCH(OMe)_2$, TMSOTf, DCM, −20 °C, 81%.

However, attempts to generate the corresponding piperonyl-derived epoxide **15** were not successful.

This problem was attributed to the electron-donating effect of the substituents on the aryl group promoting epoxide ring opening reactions. Since, despite considerable experimentation, we could not circumvent this difficulty, we sought an alternative route to the vinyl epoxide **13**. Recognizing that the Darzens condensation of bromocrotonate **11** was a possible method for preparing the vinyl epoxide **13**, we undertook a study of this transformation, Scheme 2.[8]

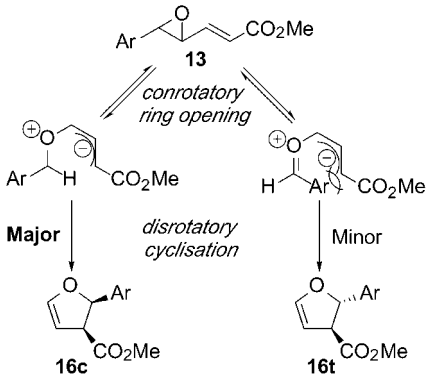
Scheme 2. Darzens Condensation



Although poor conversions and extensive decomposition complicated our initial efforts, an efficient method was developed. The optimized conditions involved addition of LDA at −20 °C to a solution of bromocrotonate (1 equiv) and piperonal (4 equiv). After a mild acidic quench (NH_4Cl), the excess of piperonal was scavenged as the bisulfite addition product and the resulting oil was purified by flash chromatography (1:3 ether/petrol). The desired alkenyl epoxide was obtained in 70% yield as a single alkene isomer (trans) and a 3:4 syn/anti mixture of epoxides. Since the stereochemical information is lost in the alkenyl epoxide−dihydrofuran rearrangement, this mixture was used directly in the next step with no further purification.

In our preliminary studies, alkenyl epoxide−dihydrofuran rearrangements were usually performed in an autoclave or a sealed tube, involving high temperatures for prolonged times (e.g., 180 °C for 20 h for the phenyl equivalent **8)**. However, with ester **13**, only traces of the desired piperonyl analogue **16** could be detected in the intractable crude product and we suspected either the product or the starting material to be thermally unstable under these conditions. Therefore, the rearrangement was carried out using flash vacuum pyrolysis (FVP) at 500 °C and 0.04 mbar. This method afforded the cis:trans dihydrofuryl ester **16** as a mixture of isomers (8:1). This ratio was independent of the stereochemistry of the starting epoxide and represents preferential disrotary ring closure of the less hindered ylid intermediate to afford the desired cis isomer, Scheme 3.[9,10] Following this protocol,

Scheme 3. Alkenyl Epoxide−Dihydrofuran Rearrangement



we isolated pure cis dihydrofuryl ester **16c** in 66% yield after flash column chromatography.

The reduction of the cis dihydrofuryl ester **16c** into the alcohol was performed with lithium aluminum hydride at −40 °C. The dihydrofuryl alcohol **17** could not be stored for more than a couple of hours at low temperatures under an inert atmosphere and, consequently, was used in the next step with no further purification (purity > 90% by NMR).

The alcohol **17** was then combined with piperonal dimethyl acetal **18a** in the presence of a Lewis acid (trimethylsilyl triflate) to generate the oxonium ion **19**, Scheme 4. Cycliza-

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(7) Hearon, W. M.; MacGregor, W. S. *Chem. Rev.* **1955**, *55*, 991−1001. A recent report (ref 14) has outlined the first selective synthesis of an endo-exo furofuran. In addition, a synthetic route to diaxial (endo-endo) 2,4-diarylfurofurans has been reported; see: Pelter, A.; Ward, R. S.; Collins, P.; Venkateswarlu, R.; Kamakshi, C. *Tetrahedron Lett.* **1992**, *33*, 4361−4364.

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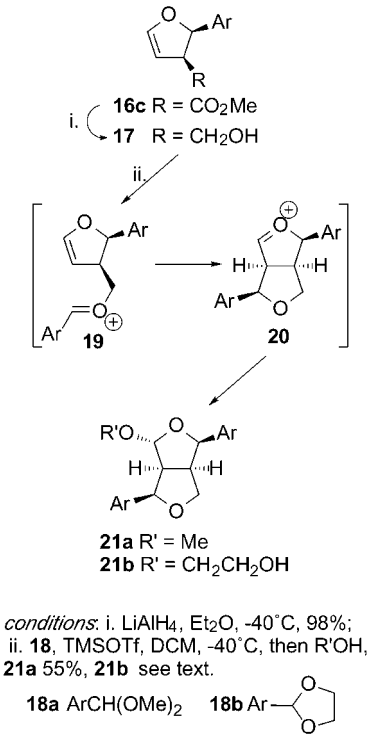
Scheme 4. Lewis Acid Catalyzed Cyclization



conditions: i. $LiAlH_4$, Et_2O, -40°C, 98%; ii. **18**, TMSOTf, DCM, -40°C, then R'OH, **21a** 55%, **21b** see text.

18a $ArCH(OMe)_2$ **18b** Ar

tion then occurred to generate the second oxonium ion **20**, which was quenched, by a molecule of methanol derived from the initial acetal, to provide the methyl furofuryl acetal **21a**. Attempts to use piperonal directly in this process failed, and while the more stable and convenient dioxolane acetal **18b** was a viable substrate, the resultant hydroxyethyl glycoside **21b** was relatively unstable and we were not able to isolate it in sufficient purity or yield. As in our preliminary report, the endo isomer was exclusively generated at low temperatures (kinetic product), whereas the exo isomer (thermodynamic) was favored when the reaction mixture was allowed to warm to room temperature for 48 h. To have access to the Epiasarinin skeleton (endo), the optimized conditions involved reaction at −40 °C overnight with, to avoid a mixture of furofuryl acetals, a methanol quench. Following this procedure, we obtained the endo methyl furofuryl acetal **21a** after purification by flash chromatography (4:1 petrol/ether) in 55% yield as a single diastereoisomer. To complete the synthesis of Epiasarinin, reduction of the methyl furofuryl acetal was required. Related transformations have been described in the literature.[11,12] However, using these conditions (Et_3SiH, $BF_3{\cdot}OEt_2$, DCM, 48 h), extensive decomposition resulted.

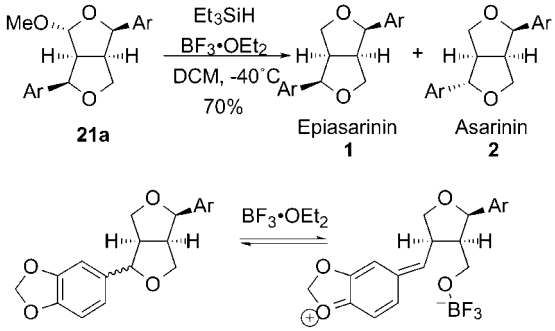
Following a detailed study of these conditions, it was found that the stereochemistry of the diaryl furofuran product depended on the temperature, with Epiasarinin and its two diastereoisomers, Asarinin (exo-endo **2**) and Sesamin (exo-exo **3**), being detected in different ratios, Table 1. The epimerization can be rationalized as Lewis acid promoted ring fragmentation and leads to the most stable exo-exo furofuran, Scheme 5.

Table 1. Ratio of Reduction Products Acetal **21a**:Epiasarinin **1**:Asarinin **2**:Sesamin **3**[a]

temp (°C)	time (h)	**21a**	**1**
−78	4	100	0
−40	4	90	10
−40	**15**	**10**	**67**
−78 to rt	4	0	0
0 to rt	48	0[b]	0[b]

[a] Percentage determined by ^1H NMR. [b] Decomposition.

Scheme 5 Reduction of the Methyl Acetal



After some experimentation, the conditions used to reduce the furofuryl acetal **21a** with a good conversion and a small rate of epimerization were Et_3SiH (10 equiv) and $BF_3{\cdot}OEt_2$ (1.1 equiv) at −40 °C for 15 h. This produced a mixture of starting acetal **21a**, Epiasarinin **1**, and Asarinin **2** in a 10:67:23 ratio, Scheme 5. After a difficult separation by flash chromatography (silica gel, 3:1:0.1 petrol/ether/triethylamine), pure samples of Epiasarinin **1** and Asarinin **2** were obtained. The structure of Epiasarinin was confirmed by detailed spectroscopic analysis (see Supporting Information). In particular, the NMR data reflected a symmetrical compound, that was clearly different from that reported for Sesamin **3**.[4,5] The sample of Asarinin was identical in all respects to that reported in the literature.[13,14] Attempts to enhance this reduction using different Lewis acids, $TiCl_4$, $Sc(OTf)_3$, or more powerful hydride sources, e.g., $Cl_3SiH/BF_3{\cdot}OEt_2$ or DIBAL, proved not to be viable.

In conclusion, a very concise stereoselective synthesis of the endo-endo furofuran Epiasaranin has been achieved for the first time (five steps, 20% overall yield). The route is amenable to considerable variation, and the preparation of

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structural and stereochemical analogues is in progress and will be reported in due course.

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Supporting Information Available: Experimental section containing procedures and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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