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A Morita–Baylis–Hillman adduct allows the diastereoselective synthesis of styryl lactones

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ABSTRACT

We disclosed herein a diastereoselective approach for the total syntheses of (±)-Leiocarpin A and (±)-Goniodiol. These biologically active styryl lactones were obtained from a common intermediate, prepared in five steps and 40% overall yield, using a simple synthetic sequence starting from a Morita–Baylis–Hillman adduct. The total syntheses of these styryl lactones were accomplished in nine steps. This is the first report on the total synthesis of this class of natural products starting from Morita–Baylis–Hillman adduct.

The plants of the Goniothalamus genus (*Annonaceae* family) provide multi-functionalized molecules known as styryl lactones. These molecules are associated with a wide variety of biological effects, such as anti-tumor,[1] anti-parasitic,[2] abortifacient[3], and as insect repellents.[4] Styryl lactones also display great structural variations usually classified into six main groups (Fig. 1).[1a]

The styrylpyrone skeleton is always present and the biochemical pathway for its synthesis is related to shikimic acid and acetylcoenzyme A.[5] The unique structural patterns exhibited by these molecules associated with their biological effects have attracted great attention.[6]

Leiocarpin A (**1**) presents a pyranopyrone skeleton and was isolated from the ethanolic extract of stem barks of the plant *Goniothalamus leiocapus* (Fig. 2).[7] Leiocarpin A showed excellent biological profile against some types of cancer cells.[8] Structurally, Leiocarpin A is a bicyclo[3.3.1]heptane having substituents on C7 and C8. In addition, Leiocarpin A has four stereogenic centers, three of them adjacent. Despite its promising biological profile, few efforts have been reported so far in developing a synthetic route to Leiocarpin A (Fig. 2).[9]

Goniodiol (**2**, Fig. 2) is a hydroxylated styrylpyrone isolated from leaves and twigs of *Goniothalamus sesquipedalis*[3a] and also from stem barks of *Goniothalamus giganteus*.[10] Goniodiol also showed biological profile as anti-tumor and selective cytotoxicity against A549 lung carcinoma cells[3a] and P-388 leukemia cells.[11] This lactone presents three adjacent stereogenic centers with relative stereochemistry 1,2-*anti*-1,3-*anti*.

Contrary to Leiocarpin A, many routes to the total synthesis of Goniodiol have been reported.[12]

Morita–Baylis–Hillman (MBH) is an organocatalyzed reaction which provides functionalized small molecules showing great potential as the starting material for organic synthesis.[13,14] This MBH reaction also presents high atom economy and may be performed with low environmental impacts.[15]

In a research program focused on finding relevant synthetic applications for MBH adducts associated with the need to obtain styryl lactones for biological assays led us to investigate the diastereoselective synthesis of (±)-Leiocarpin A using a suitably functionalized aldehyde as the key precursor, which was easily prepared from a MBH adduct. Additionally, we also describe herein a diastereoselective synthesis of (±)-Goniodiol.

Leiocarpin A can be synthesized according to the retrosynthetic analysis depicted in Scheme 1.

Leiocarpin A can be prepared according to Scheme 1 from alkene **3** using a classical sequence.[9b,16] Ring closing metathesis (RCM) of **3** gives, therefore, an α,β-unsaturated lactone, which after removal of the protecting group in basic medium cyclizes directly to Leiocarpin A. Alkene **3** can be promptly prepared from aldehyde **4** by stereoselective allylation followed by the acylation of the resulting allyl alcohol with an adequate acylating agent. Depending on the stereoselectivity achieved in the allylation step both natural products can be prepared using the same synthetic sequence. Finally, the key aldehyde **4** can be prepared using an original and diastereoselective sequence from a MBH adduct.

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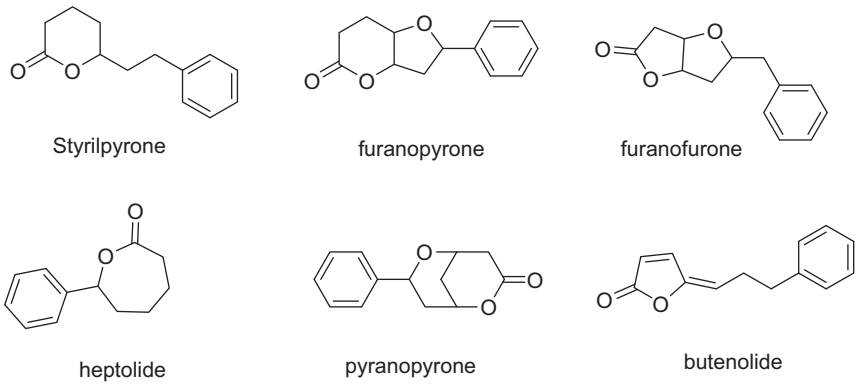


Figure 1. Main styryl lactones skeletons found in plants of Goniothalamus genus.

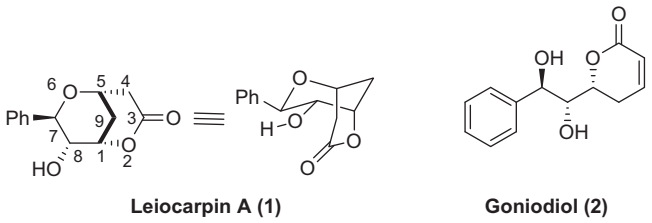
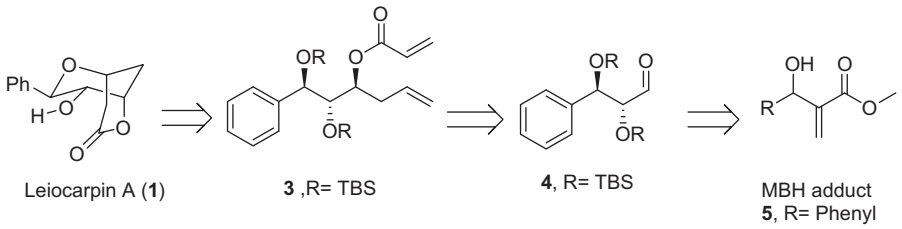


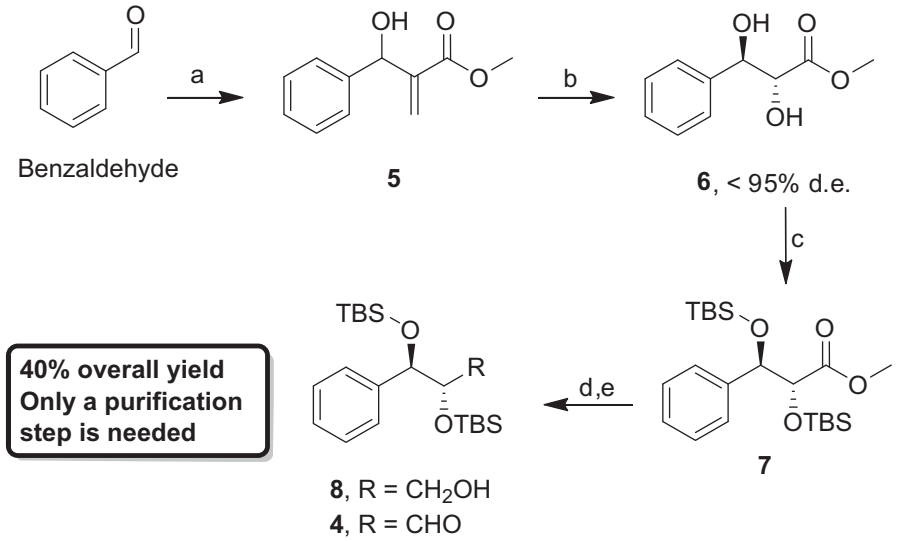
Figure 2. Structures of Leiocarpin A and Goniodiol.

We began our synthetic trial by preparing adduct **5**. The reaction between benzaldehyde and methyl acrylate gave the required adduct in 85% yield. Ozonolysis in methanol at −72 °C furnished after 15 min an ozonide, which was treated under reductive conditions with dimethylsulfide at the same temperature to give the corresponding carbonyl compound. The solvents were removed and the residue was dissolved in DCM and treated with $NaBH_4$ at −72 °C to give *anti*-dihydroxylated ester **6**, as the only product, and high diastereoisomeric purity (⩽95% de).[17] Ester **6** was obtained in 70% yield and was sufficiently pure to be used in the next step without purification (Scheme 2). The diastereoselectivity achieved in the reduction step could be rationalized by assuming the Cram-chelate model for 1,2-induction in acyloins.[18]

Following Scheme 1, ester **6** was treated with TBSCl in the presence of imidazole and DMF to provide the di-silylated ester **7**, in almost quantitative yield, even after chromatographic filtration. The silylated product was then reduced with DIBAl-H at −72 °C to give



Scheme 1. Retrosynthetic analysis for the synthesis of Leiocarpin A.

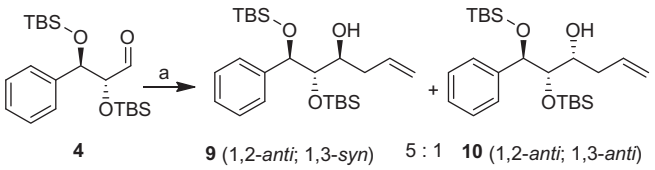


Scheme 2. Reagents and conditions: (a) methyl acrylate, rt, 96 h, 85%; (b) (i) O_3, MeOH, −72 °C, then $(CH_3)_2S$, 1 h; (ii) DCM, $NaBH_4$, −72 °C, 12 h, 70%; (c) TBSCl, Imidazole, rt, 12 h, 98%; (d) DIBAl-H, DCM, −72 °C, 1 h, 79%; (e) IBX, DMSO, rt, 1 h, 88%.

Table 1
Allylation reaction with aldehyde **4**

Entry	Nucleophile	L. A.[c]	Solvent	Temperature (°C)	Time (min)	%,[d] dr[e]
1	allylMgBr[a]	—	THF	0	10	82 (1.2:1)
2	allylMgBr[a]	BF_3OEt	THF	−22	20	87 (2.5:1)
3	Allyl(Sn)^{n}Bu$_3$[b]	$TiCl_4$	CH_2Cl_2	−72	60	79 (5:1)

[a] 1.3 equiv were used.
[b] 1.5 equiv were used.
[c] 1.0 equiv was used.
[d] Yields refer to isolated and purified products. No chromatographic separation was possible at this stage.
[e] Diastereoisomeric ratio was determined by measuring the signals attributed to carbinolic hydrogen in NMR spectra.



Scheme 3. Reagents and conditions: (a) allylSn(^{n}Bu)$_3$, $TiCl_4$, CH_2Cl_2, −72 °C, 1 h, 79% (diastereoisomeric ratio 5: 1, **9**:**10**).

the triol di-silylated **8** in 79%. Finally, **8** was reacted with IBX in DMSO to give the required aldehyde **4** in 88% yield.[19] To increase the synthetic efficiency and to avoid the two-step transformation, we tried to reduce the ethyl ester directly to aldehyde **4** with DIBAL-H at −72 °C, but all attempts failed and only a mixture of aldehyde and alcohol was obtained.

The key aldehyde **4** was thus prepared with a high diastereoselectivity in five steps from a cheap and abundant commercially available aldehyde in 40% overall yield. The whole sequence is very easy to be performed. Analogs of this aldehyde having different protecting groups have already been used in the total synthesis of styryl lactones, but more complicated procedures have been used.

Allylation is a very relevant chemical transformation able to transfer three carbon atoms at once thus creating new stereogenic centers and a homoallyl alcohol that can be used for further chemical transformations.[20]

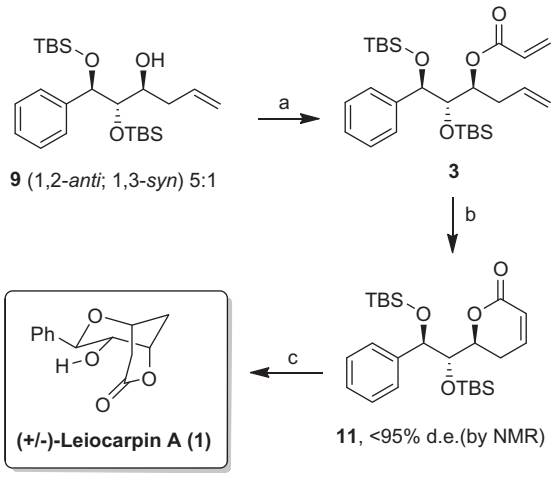
Initially aldehyde **4** was treated with phenylmagnesium bromide in THF at 0 °C to give after 5 min a mixture of diastereoisomeric compounds **9** and **10** in a poor ratio. We tested, therefore, some alternatives (Table 1).

Allylation using allyl tributylstanane in the presence of a Lewis acid at −72 °C gave the best diastereoselectivity (entry 3). Unfortunately, diastereoisomers are not separable by usual chromatographic techniques, but after purification we observed net diastereoisomeric enrichment in the reaction performed with allyl stannane (see Supplementary data for details).

By comparing our data with the reported data for allyl compounds **9** and **10**, it was possible to assume that the major isomer obtained was that having a 1,2-*anti*-1,3-*syn* stereochemical relationship (**9**, Scheme 3).[9b] The attained diastereoselectivity can be rationalized assuming the Felkin–Ahn model.[18,21]

The diastereoisomeric enriched mixture was used in the next step. So, allylic alcohol **9** (>90% de, after purification) was reacted with acryloyl chloride in the presence of Et_3N in DCM at 0 °C to provide alkene **3** in 83% yield. Ring closing metathesis of this olefin was performed using a first generation Grubb's catalyst to give α,β-unsaturated cyclohexenone **11** in 64% yield (Scheme 4).[22] After chromatographic purification the diastereoisomeric purity of **11** was superior to 95% (determined by NMR).

To finish the synthetic sequence the unsaturated lactone **11** was cyclized by treatment with TBAF in THF to (±)-Leiocarpin A (**1**) in 50% yield and high diastereoisomeric purity. (±)-Leiocarpin A (**1**)



Scheme 4. Reagents and conditions: (a) acryloyl chloride, NEt_3, CH_2Cl_2, 0 °C, 83%; (b) Grubbs I, CH_2Cl_2, reflux, 18 h, 64%; (c) TBAF, THF, 0 °C to rt, 12 h, 50%.

was thus synthesized in nine steps in 8.5% overall yield. This is the first approach to this natural product starting from a Morita–Baylis–Hillman adduct.

The spectral data of our synthetic Leiocarpin A were compared with those described both for natural and synthetic products and found fully compatible (see Supplementary data for details, page S18).[8,9]

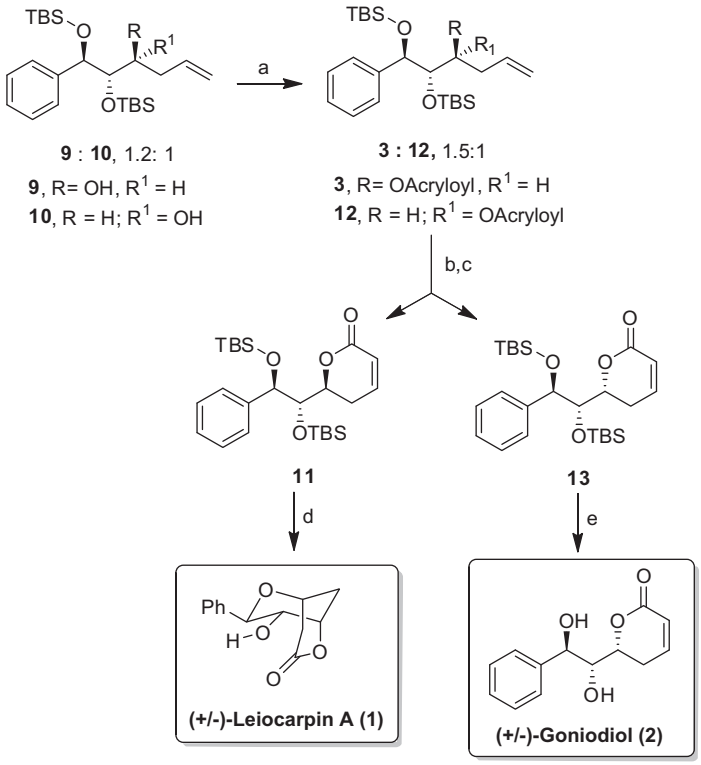
In the final steps of the total synthesis of Leiocarpin, we observed that diastereoisomeric lactones could be easily separable by silica gel column chromatography. We, therefore, decided to take advantage of this separation and accomplish also the total synthesis of (±)-Goniodiol.

The diastereoisomeric mixture of allylic alcohols **9** and **10** obtained when allylation was conducted without Lewis acid (see entry 1, Table 1) was used. Acylation with acryloyl chloride followed by ring closing metathesis using Grubbs I catalyst provided a mixture of diastereoisomeric lactones **11** (1,2-*anti*; 1,3-*syn*) and **13** (1,2-*anti*; 1,3-*anti*). (Scheme 5). The diastereoisomeric lactones were easily separated by silica gel chromatography providing **11** and **13**, as pure diastereoisomers.

An acetonitrile solution of the pure α,β-unsaturated lactone **13** was then treated with HF/pyridine at room temperature for 24 h to give (±)-Goniodiol (**2**) in 74% yield. Lactone **11** was also treated with TBAF in THF to give (±)-Leiocarpin A in 50% yield.

The spectral data of (±)-Goniodiol synthesized in this work were compared with those described for the natural and synthetic products and also found to be fully compatible (see Supplementary data for details, pages S29–30).[23]

In summary, we have described the diastereoselective total syntheses of (±)-Leiocarpin A and (±)-Goniodiol using a simple alternative approach. Both the molecules were prepared from the unique aldehyde **4**, which in turn can be easily synthesized via MBH reaction using a facile and scalable synthetic sequence.



Scheme 5. Reagents and conditions: (a) acryloyl chloride, NEt_3, CH_2Cl_2, 0 °C, 83%; (b) Grubbs I, CH_2Cl_2, reflux, 18 h, 64%; (c) chromatographic separation; (d) see Scheme 3; (e) HF, pyridine, CH_3CN, rt, 24 h, 74%.

This sequence can also allow the synthesis of these natural products in their enantiomeric forms simply starting with a chiral Morita–Baylis–Hillman adduct.

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Supplementary data

Supplementary data (Complete experimental synthetic descriptions and characterizations of all the compounds.) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.09.044.

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