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Stereocontrolled Synthesis of (+)-Plagiogyrin A

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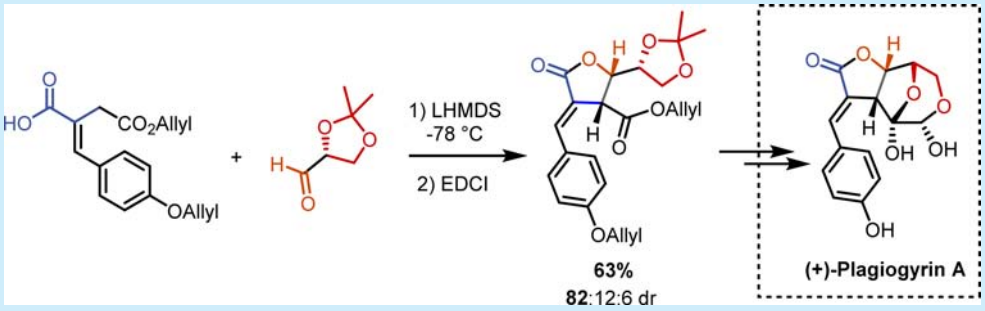
Supporting Information



ABSTRACT: Plagiogyrin A (**1**) was first isolated from the fronds of *Plagiogyria matsumureana*. Structurally, it features an α-ketoaldehyde functional group in its hemiacetal form, fused in a *cis*-substituted lactone ring. We have successfully synthesized the skeleton of this natural product by employing a stereocontrolled aldol reaction followed by the installation of the α-ketoaldehyde moiety derived from the mild oxidation of an α-diazoketone. Finally, anhydrous acidic conditions released the protected diol and provided the required cyclized hemiacetal.

Ferns of the genius Plagiogyria are mainly found in Asia, and select Plagiogyria species have been employed in traditional Chinese medicine to treat flu symptoms.[1] Studies have shown that *Plagiogyria maxima* and *Plagiogyria distinctissima* are rich sources of phenolic contents (0.62 and 0.95 wt %), and they display moderate radical scavenging ability (IC_{50} = 22.1 and 57.4 μg/mL, respectively).[2] Phenol-containing natural products plagiogyrin A (**1**), plagiogyrin B (**2**), and astragalin (**3**) were isolated from the fronds of *Plagiogyria matsumureana* by Murakami in 1983 (Figure 1).[3,4] Biosynthetically, **1** is proposed to derive from the hemiacetal rearrangement of plagiogyrin B (Figure 1);[4] however, to date no biosynthetic or synthetic studies toward **1** have been reported. Building on our interest in heavily oxidized heterocycles, we targeted an expedient and stereoselective synthesis of **1** and our successful efforts toward this goal are reported herein.

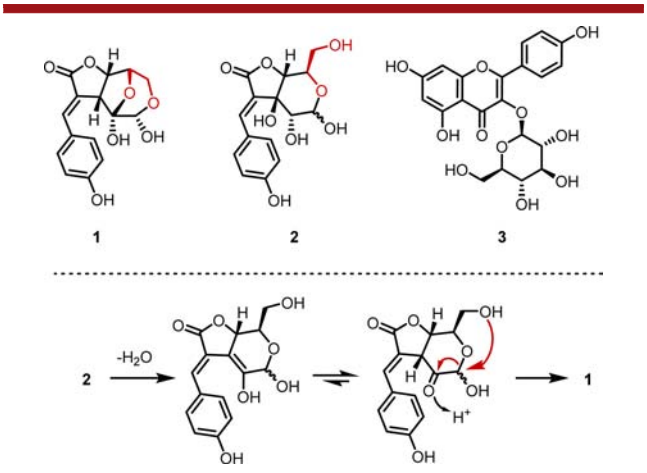


Figure 1. Structures of phenol-containing natural products from *Plagiogyria matsumureana*..

The 1,4-dioxane ring of plagiogyrin A features two hemiacetals, retrosynthetically arising from an α-ketoaldehyde and a diol (**4**, Figure 2a). Due to the sensitive nature of α-ketoaldehydes and their precursors, methods to prepare these intermediates from 1,2-diols prove to be difficult on functionalized substrates.[5] Methods such as the Riley (selenium dioxide) oxidation[6] and oxidations of α-keto hemimercaptals[7]

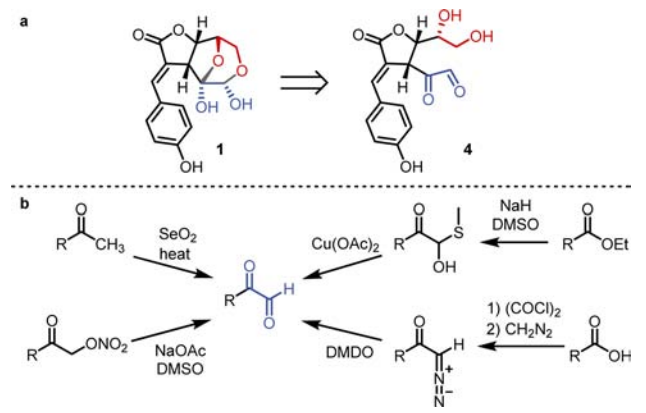


Figure 2. (a) Retrosynthesis of the cyclic bis-hemiacetal of **1**; (b) common methods to prepare α-ketoaldehydes.

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or nitrate esters[8] also provide access to α-ketoaldehydes (Figure 2b); however, these methods also tend to employ harsh conditions that can interfere with other functional groups and can provide overoxidized products in some cases. In our previous synthetic efforts toward the morpholinone fragment of monanchocidin A, we found the dimethyldioxirane (DMDO) oxidation of an α-diazoketone offered a mild and efficient way to prepare α-ketoaldehydes in complex settings;[9,10] therefore, we envisioned this approach for our synthesis of **1**. Retrosynthetically, this approach would require carboxylic acid **5** that we proposed could arise from lactonization of compound **6**, itself derived from a stereocontrolled aldol reaction of ester **7** and aldehyde **8** (Figure 3).

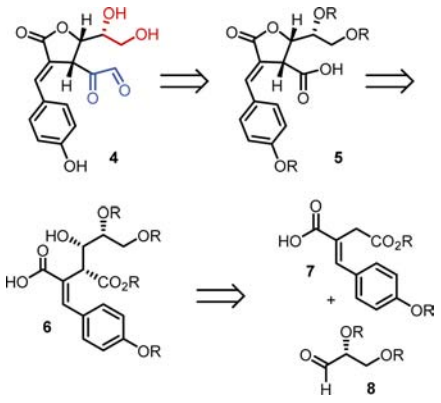


Figure 3. Retrosynthetic approach to diol **4**.

Our synthesis began with the Stobbe condensation of dimethyl succinate (**9**) and 4-anisaldehyde (**10**) (Figure 4a).

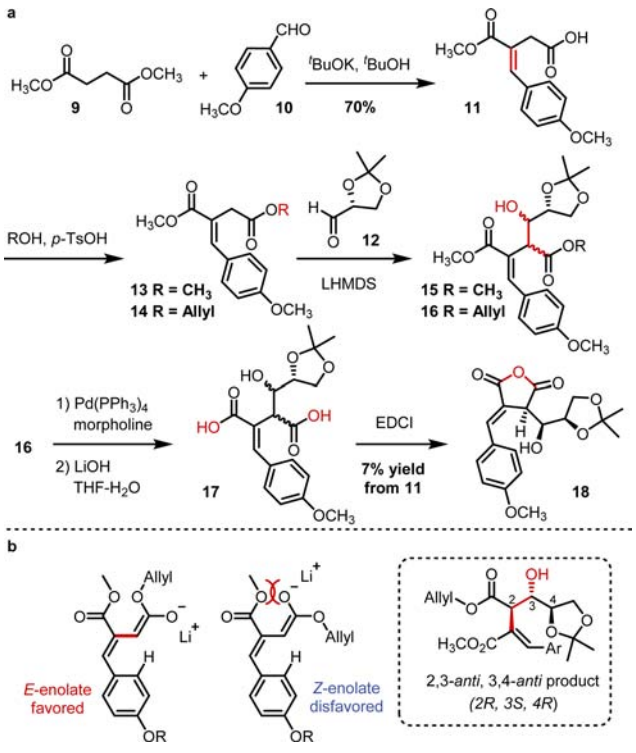


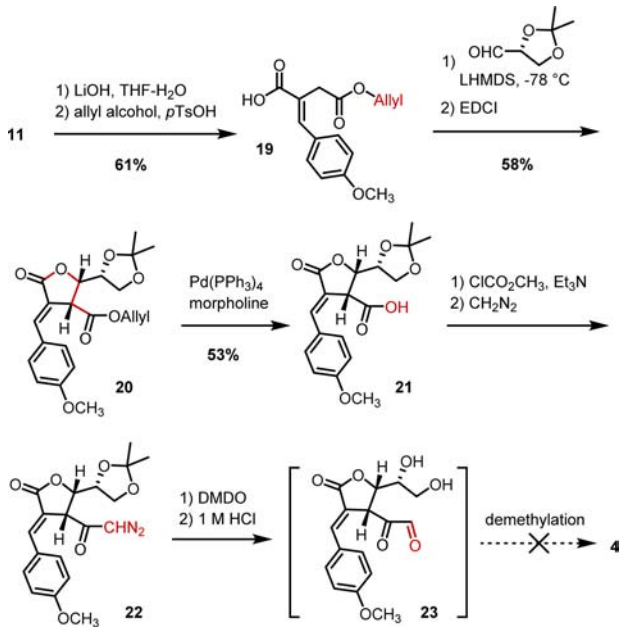
Figure 4. (a) Our initial synthetic attempts toward **4**; (b) proposed origin of the major diastereomer from the aldol addition to form **15**/**16**.

E-Alkene **11** was formed exclusively as anticipated;[11] unfortunately, the direct aldol reaction of **11** and aldehyde **12** failed due to the proximity of the carboxylate anion in our enolate substrate. Therefore, **11** was esterified and the resulting methyl ester **13** underwent aldol reaction smoothly.[12] Attempts to hydrolyze and lactonize ester **15** proved to be difficult, as elimination prevailed over hydrolysis when **15** was subjected to various basic conditions.

To circumvent ester hydrolysis issues, allyl ester **14** was prepared from acid **11**. Ally ester **14** was subjected to an aldol reaction, deallylation,[13] and ester hydrolysis sequence to yield bis-carboxylic acid **17** over three steps. At this stage compound **17** required cyclization of the secondary alcohol and conjugated carboxylic acid to obtain the lactone motif present in **1**. Surprisingly, **17** was not able to be lactonized under mild acidic conditions[14] although a rapid conversion to a compound with the desired mass was observed upon acid activation with EDCI. The diastereomers became separable after cyclization, and the major diastereomer **18** was obtained in 7% unoptimized overall yield (five steps from **11**). To our surprise, a crystal structure of **18** revealed an anhydride rather than the desired lactone (**5**). Although this result was disappointing, **18** possessed all three desired stereocenters found in plagiogyrin A (**1**).

To explain the observed stereoselectivity we modeled the geometry of the enolate generated from ester **14**. The flat nature of the enolate structure, along with the hindered rotation of this conjugated system, results in a preferred *E*-enolate to minimize repulsion (Figure 4b). The *E*-enolate, together with a Felkin addition model,[15] would result in the 2,3-*anti*, 3,4-*anti* product, which is what is observed. It has been reported that a similar aldol reaction lacking the aromatic moiety yielded a 2,3-*syn* product,[14] making the presence of the aromatic moiety essential for our selectivity and requiring its installation early in our synthetic sequence. Informed by the intrinsic reactivity of substrate **17**, we planned to protect the carboxylic acid group to avoid anhydride formation (Scheme 1). Hydrolysis of ester **11** to provide the bis-carboxylic acid followed by selective

Scheme 1. Synthesis of the Lactone 20 and Its Conversion to α-Ketoaldehyde 23



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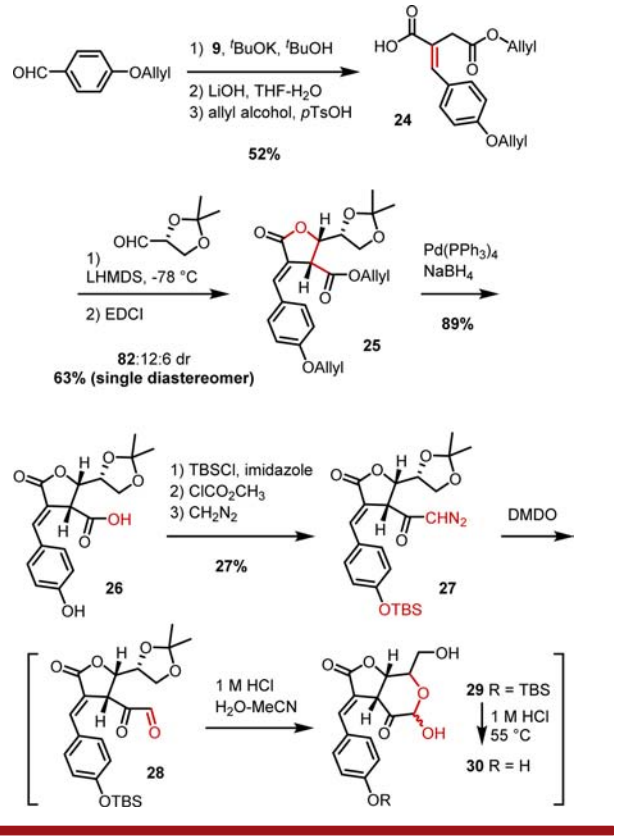
esterification of the nonconjugated acid furnished ester **19**.[16] The subsequent aldol reaction proceeded smoothly, and the carboxylic acid, now protected as an ester, underwent EDCI-mediated cyclization in good yield to provide lactone **20**. The major diastereomer of **20** was isolated by flash chromatography followed by deallylation to provide **21**. Satisfyingly, X-ray analysis of **21** confirmed the lactone structure along with all three desired stereocenters that are required for **1**.

With **21** in hand it was now time to employ our proposed α-ketoaldehyde synthesis. To this end, attempts to convert carboxylic acid **21** to an acyl chloride using oxalyl chloride were unsuccessful, possibly due to the generation of acidic byproducts. On the other hand, the mixed anhydride derived from methylchloroformate was prepared and subsequently converted to α-diazoketone **22** upon treatment with diazomethane.[17] The α-diazoketone moiety was then readily oxidized by DMDO to provide our key α-ketoaldehyde, and the acetonide protecting group was subsequently cleaved under acidic conditions; however, it was not clear by NMR analysis if the crude product **23** underwent cyclization to provide the acetal structures found in the natural product **1**. At this stage we planned to push this material to the end for final purification and characterization, and we therefore attempted various methods to deprotect the phenolic methyl ether of **23**. Unfortunately, Lewis acid promoted demethylation (Me_3SiI,[18] $AlBr_3$,[19] and BBr_3[20]) proved ineffective or decomposed our substrate under a variety of conditions. Given the oxygen-rich nature of **23**, along with the acid and base sensitivity of this intermediate, we required a more labile phenol protecting group at this late stage.

Having an established synthetic sequence developed, we revised the synthesis with 4-allyloxy benzaldehyde as the starting material (Scheme 2). Installation of the aryl group, ester hydrolysis, and allyl ester formation proceeded in 52% yield over three steps. With **24** in hand, we proceeded to conduct our key aldol reaction under the previously optimized conditions and observed three diastereomers with an 82:12:6 ratio by ^{1}H NMR.[21] At this point, both allyl groups in **25** were cleaved using $Pd(PPh_3)_4$ and $NaBH_4$,[22] and phenol **26** was reprotected with TBS, converted to α-diazoketone **27**, and oxidized with DMDO. The phenolic TBS ether was installed to provide a labile protecting group in the final stages of our synthesis. Surprisingly, **28** showed unusual stability under aqueous acidic conditions, but was eventually cleaved with 1 M HCl at 55 °C. With all protecting groups removed, we envisioned the product to rapidly undergo hemiacetal formation to afford **1**; however, crude ^{1}H NMR of our material did not match that reported for the natural product, most likely due to the formation of a regioisomer or partially cyclized material.[3] The acid and base sensitivity of these products limited our study on the interconversion of these materials, and we therefore sought alternate deprotection/cyclization conditions. It has been reported that subjection of tetra-acetate **31** to 3% HCl in dioxane under reflux provides plagiogyrin A in low yield (Figure 5).[4] Inspired by this report, we treated compound **28** with 3% HCl in dioxane at room temperature. The acetonide group was cleaved immediately, although the TBS group remained intact, even upon heating.[23] LC-MS analysis revealed product **32** had an identical mass with **29** (Scheme 2) but was less polar, likely revealing an alternate hemiacetal formation. Various fluoride sources were efficient at removing the TBS ether, but reagents such as TBAF, CsF, and HF·pyridine were unsatisfactory due to the α-ketoaldehyde

Scheme 2. Revised Synthesis of Plagiogyrin A Core



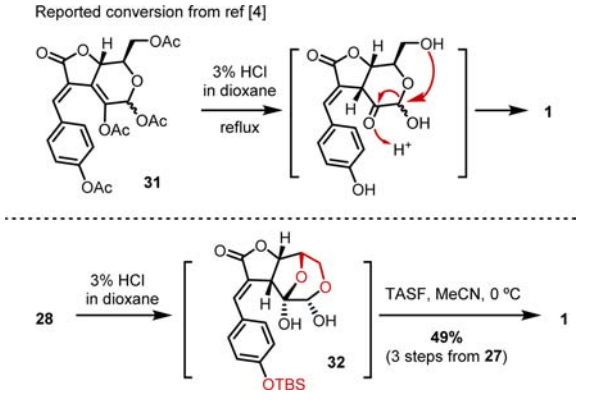


Figure 5. Acid-promoted hemiacetal formation.

moiety quickly decomposing even under mildly basic conditions. Finally, TASF,[24] known for its mild and anhydrous properties, removed the TBS ether without significant byproducts. With the fully deprotected and cyclized material in hand we were gratified to find that the ^{1}H and ^{13}C NMR data matched those reported for **1** (see Table S1). Further studies will be required to better understand the formation and possible interconversion of the hemiacetals related to plagiogyrin A (**1**) and related family members.

In conclusion, we have developed a stereocontrolled synthesis of the natural product plagiogyrin A (**1**) in 12 steps and 3.9% overall yield. Utilizing an intermediate poised to provide our required *E*-enolate, the key aldol reaction set two new stereocenters with good selectivity. Subsequent conversion of a carboxylic acid to an α-ketoaldehyde provided the required oxidation state of the natural product under mild conditions,

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and a final anhydrous acid promoted hemiacetal formation concluded the synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02629.

Experimental procedures, characterization of products, crystallographic information for compound **18** and **21**, and ^{1}H and ^{13}C NMR spectra (PDF)
Crystallographic data for **18** (CIF)
Crystallographic data for **21** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Zhou, J.; Xie, G.; Yan, X. *Encyclopedia of Traditional Chinese Medicines - Molecular Structures, Pharmacological Activities, Natural Sources and Applications. Vol. 4: Isolated Compounds N-S*, 1st ed.; Springer: Berlin, 2011.
(2) Ding, Z. T.; Fang, Y. S.; Tai, Z. G.; Yang, M. H.; Xu, Y. Q.; Li, F.; Cao, Q. E. *Fitoterapia* **2008**, *79*, 581.
(3) Murakami, T.; Tanaka, N.; Kimura, T.; Noguchi, T.; Saiki, Y.; Chen, C. *Chem. Pharm. Bull.* **1984**, *32*, 1808.
(4) Murakami, T.; Tanaka, N.; Noguchi, T.; Saiki, Y.; Chen, C. *Chem. Pharm. Bull.* **1984**, *32*, 1815.
(5) Tojo, G.; Fernandez, M. *Oxidation of alcohols to aldehydes and ketones: a guide to current common practice*, 1st ed.; Springer: New York, 2006.
(6) Riley, H. L.; Morley, J. F.; Friend, N. A. C. *J. Chem. Soc.* **1932**, 1875.
(7) (a) Mikol, G. J.; Russell, G. A. *Org. Synth.* **1968**, *48*, 109. (b) Hayashi, Y.; Yasui, Y.; Kojima, M.; Kawamura, T.; Ishikawa, H. *Chem. Commun.* **2012**, *48*, 4570.
(8) (a) Kornblum, N.; Jones, W. J.; Anderson, G. J. *J. Am. Chem. Soc.* **1959**, *81*, 4113. (b) Chen, F. Q.; Zheng, J. L.; Hirano, T.; Niwa, H.; Ohmiya, Y.; Ohashi, M. *J. Chem. Soc., Perkin Trans. 1* **1995**, *17*, 2129.
(9) Shi, Y.; Pierce, J. G. *Org. Lett.* **2015**, *17*, 968.
(10) For some applications of DMDO oxidation of α-diazoketones in complex molecule syntheses, see: (a) He, S.; et al. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 1529. (b) Kuse, M.; Doi, I.; Kondo, N.; Kageyama, Y.; Isobe, M. *Tetrahedron* **2005**, *61*, 5754. (c) Bernard, E.; Vanderesse, R. *Tetrahedron Lett.* **2004**, *45*, 8603. (d) Jiang, B.; Liu, J.-F.; Zhao, S.-Y. *Org. Lett.* **2001**, *3*, 4011.
(11) El-Abbady, A. M.; El-Assal, L. S. *J. Chem. Soc.* **1959**, *0*, 1024.
(12) The diastereomeric ratio of products was not carefully determined at this stage.
(13) Casy, G.; Sutherland, A. G.; Taylor, R. J. K.; Urben, P. G. *Synthesis* **1989**, *1989*, 767.
(14) Biel, M.; Kretsovali, A.; Karatzali, E.; Papamatheakis, J.; Giannis, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3974.
(15) Chérest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, *9*, 2205.
(16) Devi, A. R.; Rajaram, S. *Indian J. Chem., Sect. B* **2000**, *39B*, 294.
(17) Podlech, J.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 471.
(18) Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761.
(19) Node, M.; Nishide, K.; Fuji, K.; Fujita, E. *J. Org. Chem.* **1980**, *45*, 4275.
(20) McOmie, J. F. W.; West, D. E. *Org. Synth.* **1969**, *49*, 50.
(21) Determined by ^{1}H NMR.
(22) Beugelmans, R.; Bourdet, S.; Bigot, A.; Zhu, J. *Tetrahedron Lett.* **1994**, *35*, 4349.
(23) We cannot rule out silyl migration to an aliphatic alcohol under these reactions.
(24) Scheidt, K. A.; Chen, H.; Follows, B. C.; Chemler, S. R.; Coffey, D. S.; Roush, W. R. *J. Org. Chem.* **1998**, *63*, 6436.

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