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Total synthesis of (±)-epimagnolin A

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Abstract—The first total synthesis of (±)-epimagnolin A was achieved employing a C–H insertion reaction to generate selectively the bicyclic framework with the *exo*,*endo*-stereochemistry.

The crude Chinese drug from the flower buds of *Magnolia fargesii* known as shin-i has been a source of many natural products including biologically active lignans.[1–5] Recent bioassay-guided fractionation studies on shin-i yielded a new lignan epimagnolin A with growth inhibitory activity against the larvae of *Drosophila melanogaster*.[2] Structure **1** was assigned to the new lignan on the basis of mass spectroscopic evidence combined with ^{1}H and ^{13}C NMR data (Fig. 1).

The widespread occurrence of furofuran lignans combined with a variety of interesting biological activities has stimulated significant interest in their synthesis.[6–8] We recently reported an approach to *exo*,*endo*-furofuranones similar to **1** involving a highly diastereoselective C–H insertion reaction, and used the method to synthesise asarinin (**2**) (Fig. 1), which bears the same aryl substituents at the 2- and 6-positions.[9] A generally useful synthetic approach to lignans should be compatible with electron-rich aryl groups, but should also allow different oxygenated aryl groups to be installed at the 2- and 6-positions. To assess the utility of our C–H insertion approach in this regard we investigated the synthesis of epimagnolin A (**1**).

The synthesis commenced with a [2+2] cycloaddition reaction between amide **4** and allyl ether **11** (Scheme 1),[10] employing modified reaction conditions reported to allow the use of acid-sensitive substrates.[9] In the case of trimethoxy-substituted arylacetamides **4**, even with the precaution of adding anhydrous K_2CO_3 to the reaction mixture, the yield of the desired cyclobutanone **5** was disappointing. A modest improvement was obtained by careful temperature control, holding the reaction mixture at 0°C for 2 h. Separation of the *trans*-isomer **5** from the minor *cis*-isomer[†] was achieved by column chromatography prior to Baeyer–Villiger oxidation, which afforded the lactone **6** in 66% yield.

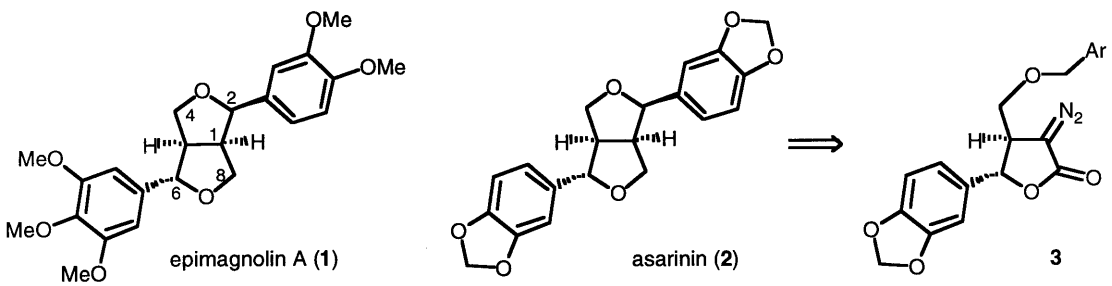

Figure 1.

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† We were unable to determine the ratio of isomers present in the crude reaction mixture by ^{1}H NMR. Only a trace of what was presumed to be the *cis*-isomer was present after flash chromatography.

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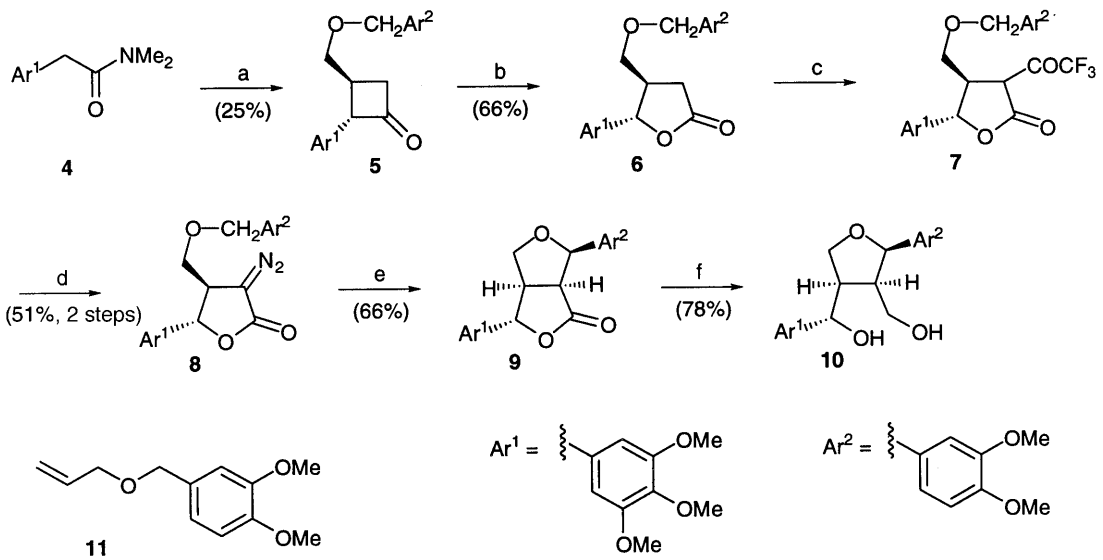
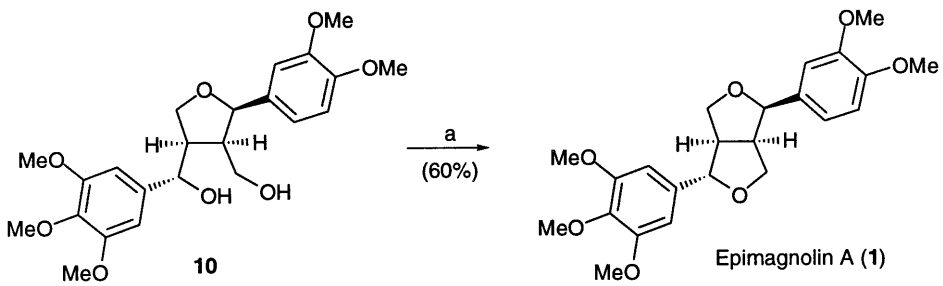


Scheme 1. *Reagents and conditions*: (a) i. Tf_2O, CH_2Cl_2, −25°C; ii. K_2CO_3, 2,6-di-*tert*-butylpyridine, **11**, −25 to 0°C; iii. $NaHCO_3$ (aq), rt; (b) H_2O_2, AcOH; (c) i. LiHMDS, THF, −78°C; ii. $F_3CCH_2OCOCF_3$, −78°C; (d) *p*-nitrobenzenesulfonylazide, Et_3N, CH_3CN; (e) $Rh_2(OAc)_4$, THF; (f) $LiAlH_4$, THF.



Scheme 2. *Reagents and conditions*: (a) MsCl, pyridine, CH_2Cl_2, rt.

A decarbonylative approach was employed to achieve the conversion of lactone **6** to the diazo-lactone **8**,[11] forming the trifluoroacylated lactone **7** prior to diazo-transfer. Diazo-lactone **8** was sufficiently stable to survive purification by flash chromatography on silica, although complete removal of the sulfonamide by-product, arising from the diazo-transfer reagent, was not possible. Fortunately, the presence of 4-nitrophenylsulfonamide did not appear to affect the subsequent C–H insertion reaction, which proceeded readily upon the addition of catalytic rhodium(II) acetate dimer. The formation of the *exo*,*endo*-furofuranone **9** was confirmed by means of GOESY experiments.

Conversion of **9** to (±)-epimagnolin A was achieved following the method employed during the synthesis of asarinin. However, the sensitivity of the methoxy substituted compounds was apparent during the reduction of lactone **9** using $LiAlH_4$, which afforded the desired 2° alcohol **10** and small quantities of by-products possibly arising from over reduction. Mesylation of **10** resulted in closure of the second tetrahydrofuran ring, affording the racemic natural product (Scheme 2), which displayed spectroscopic data consistent with those reported for epimagnolin A.[2]

In summary, a short and diastereoselective synthesis of (±)-epimagnolin A has been described employing a highly diastereoselective C–H insertion reaction of an α-diazo-γ-butyrolactone. We are currently investigating improved routes to α-diazo-γ-lactones and lactams and investigating the scope of their C–H insertion reactions in the synthesis of various bicyclic and tricyclic scaffolds.

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We extend our gratitude to The Royal Society (R.C.D.B.), The University of Southampton (J.D.H.) and AstraZeneca (unrestricted grant) for supporting this research. We also wish to acknowledge the use of the EPSRC's Chemical Database Service at Daresbury.[12]

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